For the use of Oncologist and Rheumatologist only

TORITZ RA

For Injection (100 mg/10 ml and 500 mg/50 ml)

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 has a binding affinity for the CD20 antigen of approximately 8.0 nM.

Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. TORITZ RA is a sterile, clear, colorless, preservative free liquid concentrate for intravenous administration.

COMPOSITION

Each vial of **TORITZ RA** contains:

Component	**Quantity / ml**
Rituximab	10 mg
Sodium Citrate Dihydrate I.P.	7.35 mg
Sodium Chloride I.P.	9.0 mg
Polysorbate 80 I.P.	0.7 mg
Water for Injection I.P.	q.s. to 1 mL

Fill Volume 10 ml (100 mg), 50 ml (500 mg)

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies, ATC code: L01XC02.

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

CD20 is found on both normal and malignant B cells, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue. This antigen does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.

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

Possible mechanisms of effector-mediated cell lysis include complement dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells.

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

Peripheral B cell counts declined below normal following completion of the first dose of rituximab.

In patients treated for haematological malignancies, B cell recovery began within 6 months of treatment and generally returned to normal levels within 12 months after completion of therapy, although in some patients this may take longer (up to a median recovery time of 23 months post-induction therapy).

In rheumatoid arthritis patients, immediate depletion of B cells in the peripheral blood was observed following two infusions of 1000 mg rituximab separated by a 14 day interval. Peripheral blood B cell counts begin to increase from week 24 and evidence for repopulation is observed in the majority of patients by week 40, whether rituximab was administered as monotherapy or in combination with methotrexate. A small proportion of patients had prolonged peripheral B cell depletion lasting 2 years or more after their last dose of rituximab.

Pharmacokinetics

Non-Hodgkin's lymphoma (NHL)

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of rituximab as a 2 single agent or in combination with CHOP therapy (applied rituximab doses ranged from 100 to 500 mg/m^2), the typical population estimates of nonspecific clearance (CL1), specific clearance (CL2) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V1) were 0.14 l/day, 0.59 l/day, and 2.7 l, respectively.

The estimated median terminal elimination half-life of rituximab was 22 days (range, 6.1 to 52 days).

Baseline CD19-positive cell counts and size of measurable tumour lesions contributed to some of the variability in CL2 of rituximab in data from 161 patients given 375 mg/m^2 as an intravenous infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumour lesions had a higher CL2. However, a large component of inter-individual variability remained for CL2 after correction for CD19-positive cell counts and tumour lesion size. V1 varied by body surface area (BSA) and CHOP therapy. This variability in V1 (27.1% and 19.0%) contributed by the range in BSA (1.53 to 2.32 m2) and concurrent CHOP therapy, respectively, were relatively small.

Age, gender and WHO performance status had no effect on the pharmacokinetics of rituximab. This analysis suggests that dose adjustment of rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

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

Upon administration of rituximab at a dose of 375 mg/m^2 as an intravenous infusion at weekly intervals for 8 doses to 37 patients with NHL, the mean Cmax 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 rituximab when administered as 6 infusions of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone.

Rheumatoid Arthritis

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

Based on a population pharmacokinetic analysis of data from 2005 RA patients who received rituximab, the estimated clearance of rituximab was 0.335 l/day; volume of distribution was 3.1 l and mean terminal elimination half-life was 18.0 days (range, 5.17 to 77.5 days).

Age, weight and gender had no effect on the pharmacokinetics of rituximab in RA patients.

INDICATIONS

Non-Hodgkin's Lymphoma

TORITZ RA is indicated for the treatment of:

• Previously untreated patients with stage III- IV follicular lymphoma in combination with chemotherapy

• Follicular lymphoma responding to induction therapy

• Stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy

• Patients with CD20-positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (Cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy.

Rheumatoid Arthritis

• The treatment of adult patients with active rheumatoid arthritis who have an inadequate response or intolerance to one or more tumor necrosis factor (TNF) inhibitor therapies.

Chronic Lymphocytic Leukemia.

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

Granulomatosis with Polyangitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangitis (MPA)

Rituximab in combination with glucocorticoids, is indicated for the treatment of adult patients with Granulomatosis with Polyangitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangitis (MPA)

DOSAGE AND ADMINISTRATION

Administration

Administer only as an Intravenous Infusion. Do not administer as an intravenous push or bolus. Premedicate before each infusion. Rituximab should only be administered by a

healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur.

• First Infusion:
Initiate infusion at a rate of 50 mg/hr. In the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

• Subsequent Infusions:
Standard infusion: Initiate infusion at a rate of 100 mg/hr. In the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.
For previously untreated follicular NHL and diffuse large B cell lymphoma (DLBCL) patients: If patients did not experience a Grade 3 or 4 infusion related adverse event during Cycle 1, a 90-minute infusion can be administered in Cycle 2 with a glucocorticoid-containing chemotherapy regimen.

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

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

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

Recommended Dose for Non-Hodgkin's Lymphoma (NHL)
The recommended dose is 375 mg/m^2 as an intravenous infusion according to the following schedules:

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

• Follicular lymphoma responding to induction therapy
Maintenance treatment for follicular lymphoma patients who respond to induction therapy:
375 mg/m^2 body surface area once every 2 months by intravenous infusion; starting 2 months after the last dose of induction therapy; treatment until disease progression or for a maximum period of two years.

• Stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy
Administer once weekly for 4 doses.

• **Patients with CD20-positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy.**
Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions.

Recommended Dose for Rheumatoid Arthritis (RA)
Administer rituximab as two-1000 mg intravenous infusions separated by 2 weeks.
Glucocorticoids administered as methylprednisolone 100 mg intravenous or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion reactions.

Subsequent courses should be administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks. Rituximab is given in combination with methotrexate.

Recommended Concomitant Medications
Premedicate before each infusion with acetaminophen and an antihistamine. For patients administered rituximab according to the 90-minute infusion rate, the glucocorticoid component of their chemotherapy regimen should be administered prior to infusion.

For RA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion.

Recommended Dose for Chronic Lymphocytic Leukemia(CLL)
The recommended dose is: 375mg/m^2 the day prior to the initiation of FC chemotherapy, then 500mg/m^2 on Day 1 of cycles 2-6(every 28 days).

Recommended Dose for Granulomatosis with Polyangitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangitis (MPA)
Administer Rituximab as a 375mg/m^2 intravenous infusion once weekly for 4 weeks.

Glucocorticoids administered as methylprednisolone 1000mg intravenously per day for 1 to 3 days followed by oral prednisone 1mg/kg/day (not to exceed 80mg/day and tapered per clinical need) are recommended to treat severe vasculitis symptoms. This regimen should begin within 14 days prior to or with the initiation of Rituximab and may continue during and after the 4 week course of Rituximab treatment.

Safety and efficacy of treatment with subsequent courses of Rituximab have not been established.

Preparation for Administration
Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use vial if particulates or discoloration is present.

Withdraw the necessary amount of rituximab and dilute to a final concentration of 1 mg/ml to 4 mg/ml in an infusion bag containing either 0.9 % Sodium Chloride, USP, or 5% Dextrose in Water, USP.

Gently invert the bag to mix the solution. Do not mix or dilute with other drugs. Discard any unused portion left in the vial.

Rituximab solutions for infusion may be stored at 2°C-8°C (36°F-46°F) for 24 hours. Rituximab solutions for infusion have been shown to be stable for an additional 24 hours at room temperature.

However, since rituximab solutions do not contain a preservative, diluted solutions should be stored refrigerated (2°C-8°C). No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

CLINICAL STUDY DATA

A prospective, multi-centric, open-label, two-arm, parallel group, active-control, randomized, comparative clinical study evaluated efficacy and safety of rituximab (biosimilar)/ innovator in patients with Non-Hodgkin's Lymphoma. After randomization (4:1), 86 subjects were enrolled in rituximab (biosimilar) arm and 22 subjects in comparator arm. A total of 66 subjects from rituximab (biosimilar) arm and 15 subjects from Comparator arm completed the 24 week evaluation phase of the study.

Both products were administered at a dose of 375 mg/m^2 as intravenous infusion on Day 1 of each cycle (21 Days) in combination with chemotherapy (CHOP), for Non-Hodgkin's Lymphoma during induction phase. A total of six cycles were given during induction phase. The maintenance dose was given at the investigator's discretion.

The primary efficacy endpoint was the Objective Response Rate (Complete Response and Partial Response) assessed by RECIST 1.1 criteria at week 24. Secondary efficacy endpoints included proportion of patients with Objective Response Rate (Complete Response and Partial Response) assessed by RECIST 1.1 criteria at 10 weeks, 24 weeks, 1 year, 1.5 year and 2 years, and proportion of patients with Stable Disease (SD) and Progressive Disease (PD) at week 24. Apart from these, progression free survival (PFS) from time of randomization to progression, relapse or death from any cause at 2 years and overall survival (OS) rate at 5 years were the planned efficacy endpoints in this study.

The pharmacodynamic parameter (absolute B cell count in the peripheral lood) assessment was planned in 42 patients in 1:1 ratio (21 subjects in each arm: the first 21 subjects of arm and all 21 subjects of comparator arm). The pharmacodynamic assessment was based on change in absolute B cell count in the peripheral blood after rituximab (biosimilar)/ comparator drug administration after the first cycle, at 24 weeks and 2 years compared to baseline. Follow-up for safety reasons and for assessment of other secondary endpoint parameters at 1 year, 2 years and 5 years is ongoing. Total 81 subjects completed the 24 week evaluation phase of the study. In terms of the primary endpoint, the objective response rate was 87.87% in rituximab (biosimilar) arm. 45.45% subjects showed complete response and 42.42% subjects showed partial response in rituximab (biosimilar) arm. The objective response rate was 86.66% in Comparator arm. 33.33% showed complete response and 53.33% subjects showed partial response in Comparator arm. The analysis of primary efficacy endpoint i.e. ORR at week 24 shows comparable response for both rituximab (biosimilar) and Comparator arms (87.87% Vs. 86.66%, P= 0.89656).

The proportions of subjects showing ORR in each arm were compared for statistical significance and the difference was found to be non-significant. (P= 0.89656) The pharmacodynamic assessment was based on change in absolute B cell count in the peripheral blood after rituximab (biosimilar)/Comparator administration after first cycle, at 24 weeks

and 2 years compared to baseline. The last sample is planned at the 2-year follow up visit. The baseline mean B cell count observed for rituximab (biosimilar) arm was 520.4, which showed a decline after start of treatment with rituximab (biosimilar). There was a marked change in B cell counts from baseline at the endpoint of week 24.

At week 24, the mean B cell count was reduced to 3.4 with mean change of -129.1 from baseline B cell count. The % change from baseline values was 88.5% and 98.5% at week 4 and week 24, respectively in rituximab (biosimilar) arm. The baseline mean B cell count observed for Comparator arm was 760.1, which showed a decline after start of treatment with comparator. There was a marked change in B cell count data at each defined sampling point starting from baseline to week 24 with comparator arm also.

At week 24, the mean B cell count was reduced to 52.5 with mean change of -983.6 from baseline B cell count. The % change from baseline values was 53.0 % and 97.9 % at week 4 and week 24, respectively in Comparator arm. The difference between two treatments for % reduction at week 24 was non significant (P= 0.560).

The observed efficacy results in this study for rituximab (biosimilar) were comparable for primary efficacy endpoint (ORR at week 24) with innovator product comparator. The difference for proportions of subjects showing ORR in rituximab (biosimilar) and Comparator arms was found to be non-significant (87.87% Vs. 86.66%, P=0.89656). This is further supported with marked pharmacodynamic effect observed with both rituximab (biosimilar) and Comparator arm. Hence, we conclude that both the treatment arms are comparable in terms of efficacy.

In the study, all 105 subjects who were dosed were considered for the safety population. In the rituximab (biosimilar) arm, the most commonly reported TEAEs (treatment emergent adverse events) were related to blood and lymphatic system disorders (52.94%) followed by gastrointestinal disorders (50.59%), general disorders and administration site conditions (40.00%).

In the Comparator arm, the most commonly reported TEAEs were related to blood and lymphatic system disorders (70.00%) followed by general disorders and administration site conditions (65.00%), and gastrointestinal disorders (60.00%).

There were a total of 82 SAEs reported in the study. Sixty six SAEs were reported in 37 subjects in rituximab (biosimilar) arm and 16 SAEs were reported in 8 subjects in Comparator arm. Four were considered as related to the study drug rituximab (biosimilar) by the investigators. There were 2 (2.35%) subjects from rituximab (biosimilar) arm and 2 (10.00%) subjects from Comparator arm who discontinued the study due to an adverse event.

Considering the toxicity profile of R-CHOP (Rituximab plus CHOP), population under study, type of tumor, stage of the disease, other age-associated complications, the observed serious adverse events cases reported in this study were comparable in both groups.

A total of 65 subjects receiving rituximab (biosimilar) or Comparator were included for antibody titre analysis. During analysis, three samples were found to be positive for rituximab (biosimilar) binding antibodies (out of 52 samples).

No apparent confirmed immunologically mediated safety or efficacy concern was reported with these subjects. No major differences in safety were observed in both the treatment arms. The most commonly reported adverse event were from similar SOCs (system organ class) in both treatment arms. The frequency and severity of adverse events were comparable for both rituximab (biosimilar) and Comparator arm. [Subjects with atleast one TEAE, 74 (87.06%) subjects in the rituximab (biosimilar) arm and 18 (90.00%) in comparator]. The serious adverse events reported in both rituximab (biosimilar) and Comparator arms were similar [37(43.53%) subjects in the rituximab (biosimilar) arm and 8 (40.00%) in comparator]. No new safety concerns were identified during this study in either treatment arm.

ADVERSE EFFECTS

Most common adverse reactions of rituximab in clinical trials:

• NHL (≥25%): infusion reactions, fever, lymphopenia, chills, infection, and asthenia

• RA (≥10%): upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis (other important adverse reactions include infusion reactions, serious infections, and cardiovascular events)

Serious adverse reactions: Infusion reactions, mucocutaneous reactions, Hepatitis B reactivation with fulminant hepatitis, progressive multifocal leukoencephalopathy, tumor lysis syndrome, Infections, cardiac arrhythmias, renal toxicity, bowel obstruction and perforation.

In the comparative clinical study, the most commonly reported treatment emergent adverse events (TEAEs) were related to blood and lymphatic system disorders (52.94%) followed by gastrointestinal disorders (50.59%), general disorders and administration site conditions (40.00%).

There were 74 (87.06%) subjects in the rituximab (biosimilar) arm who had at least one adverse event in the study. There were a total of 82 SAEs were reported in the study. Sixty six SAEs were reported in 37 subjects in rituximab (biosimilar) arm. Four study related deaths were reported in the rituximab (biosimilar) arm of the clinical study and three in the comparator arm.

There were 2 (2.35%) subjects from rituximab (biosimilar) arm who discontinued the study due to an adverse event.

Considering the toxicity profile of R-CHOP, population under study, type of tumor, stage of the disease, other age-associated complications, the observed severe and fatal cases reported in this study were comparable in both groups and consistent with the known safety profile observed with R-CHOP therapy.

No apparent confirmed immunologically mediated safety or efficacy concern was reported with these subjects. No major differences in safety were observed in both the treatment arms.

The frequency and severity of adverse events were comparable for both rituximab (biosimilar) and Comparator arm. [Subjects with at least one TEAE, 87.06% subjects in the rituximab (biosimilar) arm and 90.00% in comparator]. The serious adverse events reported in both rituximab (biosimilar) and Comparator arms were similar [43.53% subjects in the rituximab (biosimilar) arm and 40.00% in comparator]. No new safety concerns were identified during this study in either treatment arm.

WARNINGS AND PRECAUTIONS

WARNING : FATAL INFUSION REACTIONS, SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Infusion Reactions

Rituximab can cause severe, including fatal, infusion reactions. Deaths within 24 hours of Rituximab infusion have occurred.

Approximately 80% of fatal infusion reactions occurred in association with the first infusion. Severe reactions typically occurred during the first infusion with time to onset of 30 -120 minutes.

Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

Premedicate patients with an antihistamine and acetaminophen prior to dosing. For RA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion.

Institute medical management (e.g. glucocorticoids, epinephrine, broncho - dilators, or oxygen) for infusion reactions as needed.

Depending on the severity of the infusion reaction and the required interventions, temporarily or permanently discontinue rituximab. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior 3 cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (>25,000/mm^3).

Severe Mucocutaneous Reactions

Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with rituximab. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has been variable and includes reports with onset on the first day of rituximab exposure.

Discontinue rituximab in patients who experience a severe mucocutaneous reaction. The safety of readministration of rituximab to patients with severe mucocutaneous reactions has not been determined.

Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including rituximab.

Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive.

Reactivation also has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive and hepatitis B surface antibody [anti-HBs] positive).

HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases increase in bilirubin levels, liver failure, and death can occur.

Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with rituximab.

For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during rituximab treatment.

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following rituximab therapy. HBV reactivation has been reported up to 24 months following completion of rituximab therapy.

In patients who develop reactivation of HBV while on rituximab, immediately discontinue rituximab and any concomitant chemotherapy, and institute appropriate treatment.

Insufficient data exist regarding the safety of resuming rituximab in patients who develop HBV reactivation.

Resumption of rituximab in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing hepatitis B.

Progressive Multifocal Leukoencephalopathy (PML)
JC virus infection resulting in PML and death can occur in rituximab-treated patients with hematologic malignancies or with autoimmune diseases.

The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant.

The patients with autoimmune diseases had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab.

Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations.

Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue rituximab and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

Tumor Lysis Syndrome (TLS)
Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12-24 hours after the first infusion of rituximab in patients with NHL. A high number of circulating malignant cells (>25,000/mm^3) or high tumor burden, confers a greater risk of TLS.

Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

Infections
Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of rituximab - based therapy. Infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinaemia >11 months after rituximab exposure).

New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue rituximab for serious infections and institute appropriate anti-infective therapy.

Cardiovascular
Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of rituximab for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina.

Renal
Severe, including fatal, renal toxicity can occur after rituximab administration in patients with NHL. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and rituximab is not an approved treatment regimen.

Monitor closely for signs of renal failure and discontinue rituximab in patients with a rising serum creatinine or oliguria.

Bowel Obstruction and Perforation
Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving rituximab in combination with chemotherapy. In postmarketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1-77) days in patients with NHL.

Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur.

Immunization

The safety of immunization with live viral vaccines following rituximab therapy has not been studied and vaccination with live virus vaccines is not recommended. For RA patients, physicians should follow current immunization guidelines and administer non-live vaccines at least 4 weeks prior to a course of rituximab.

The effect of rituximab on immune responses was assessed in a randomized, controlled study in patients with RA treated with rituximab and methotrexate (MTX) compared to patients treated with MTX alone.

A response to pneumococcal vaccination (a T-cell independent antigen) as measured by an increase in antibody titers to at least 6 of 12 serotypes was lower in patients treated with rituximab plus MTX as compared to patients treated with MTX alone (19% vs. 61%).

A lower proportion of patients in the rituximab plus MTX group developed detectable levels of anti-keyhole limpet hemocyanin antibodies (a novel protein antigen) after vaccination compared to patients on MTX alone (47% vs. 93%).

A positive response to tetanus toxoid vaccine (a T-cell dependent antigen with existing immunity) was similar in patients treated with rituximab plus MTX compared to patients on MTX alone (39% vs. 42%).

The proportion of patients maintaining a positive Candida skin test (to evaluate delayed type hypersensitivity) was also similar (77% of patients on rituximab plus MTX vs. 70% of patients on MTX alone).

Most patients in the rituximab-treated group had B-cell counts below the lower limit of normal at the time of immunization.

The clinical implications of these findings are not known.

Laboratory Monitoring
In patients with lymphoid malignancies, during treatment with rituximab monotherapy, obtain complete blood counts (CBC) and platelet counts prior to each rituximab course. During treatment with rituximab and chemotherapy, obtain CBC and platelet counts at weekly to monthly intervals and more frequently in patients who develop cytopenias.

In patients with RA, obtain CBC and platelet counts at two to four month intervals during rituximab therapy.

The duration of cytopenias caused by rituximab can extend months beyond the treatment period.

Concomitant Use with Biologic Agents and Disease-modifying antirheumatic drugs (DMARDs) other than Methotrexate in RA
Limited data are available on the safety of the use of biologic agents or DMARDs other than methotrexate in RA patients exhibiting peripheral B-cell depletion following treatment with rituximab.

Observe patients closely for signs of infection if biologic agents and/or DMARDs are used concomitantly.

Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis Factor (TNF) Antagonists
While the efficacy of rituximab was supported in four controlled trials in patients with RA with prior inadequate responses to nonbiologic DMARDs, and in a controlled trial in MTX-naïve patients, a favorable risk-benefit relationship has not been established in these populations.

The use of rituximab in patients with RA who have not had prior inadequate response to one or more TNF antagonists is not recommended.

Nonclinical Toxicology
Single dose toxicology studies in rats and mice by intravenous route, repeated dose toxicity in rats and rabbits and skin sensitization studies have been done.
The reports of toxicology studies conducted on rituximab (biosimilar) did not reveal any toxic effects at the highest dose tested. Rituximab (biosimilar) did not cause any adverse acute toxicity in Wistar Rats at a dose level of 200 mg/kg body weight and in Swiss Albino Mice at 400 mg/kg.

These doses are equal to 20X and 40X of human dose respectively. In repeated dose studies conducted in rats and rabbits, the highest dose administered (186 mg/Kg for rats and 77.50 mg/kg for rabbits) was the No TM observed adverse effect level (NOAEL). Skin sensitization study results showed rituximab (biosimilar) is “Not Considered as Positive”.

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

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

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

Nursing Mothers
It is not known whether rituximab is secreted into human milk. However, rituximab is secreted in the milk of lactating cynomolgus monkeys, and IgG is excreted in human milk.

Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts.

The unknown risks to the infant from oral ingestion of rituximab should be weighed against the known benefits of breastfeeding.

Pediatric Use
FDA has not required pediatric studies in polyarticular juvenile idiopathic arthritis (PJIA) patients ages 0 to 16 due to concerns regarding the potential for prolonged immunosuppression as a result of B-cell depletion in the developing juvenile immune system. Hypogammaglobulinemia has been observed in pediatric patients treated with rituximab.

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

Geriatric Use
Diffuse Large B-Cell NHL
In International rituximab studies, no overall differences in effectiveness were observed between these patients and younger patients.

Cardiac adverse reactions, mostly supraventricular arrhythmias, occurred more frequently among elderly patients.

Serious pulmonary adverse reactions were also more common among the elderly, including pneumonia and pneumonitis.

Low-Grade or Follicular Non-Hodgkin's Lymphoma
One of the International Rituximab study, no overall differences in safety or effectiveness were observed between these patients and younger patients.

Other clinical studies of rituximab in low-grade or follicular, CD20- positive, B-cell NHL did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects.

Rheumatoid Arthritis
In International Rituximab studies, the incidences of adverse reactions were similar between older and younger patients. The rates of serious adverse reactions, including serious infections, malignancies, and cardiovascular events were higher in older patients.

OVERDOSAGE
There has been no experience of overdosage with rituximab.

CONTRAINDICATIONS
Contraindications for use in non-Hodgkin's lymphoma
- Hypersensitivity to the active substance or to murine proteins, or to any of the other excipients
- Active, severe infections
- Patients in a severely immunocompromised state

Contraindications for use in rheumatoid arthritis

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

PREPARATION AND STORAGE
TORITZ RA is available as 100 mg/10 ml in single-use vial and 500 mg/50 ml in single use vial

Special precautions for storage
Store in a refrigerator (2°C-8°C). Keep the container in the outer carton in order to protect from light.

DO NOT FREEZE. DO NOT SHAKE.

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

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

Special precautions for disposal and other handling
Rituximab is provided in sterile, preservative-free, non-pyrogenic, single use vials. Aseptically withdraw the necessary amount of rituximab, and dilute to a calculated concentration of 1 to 4 mg/ml rituximab into an infusion bag containing sterile, pyrogen-free sodium chloride 9 mg/ml (0.9%) solution for injection or 5% D-Glucose in water.

For mixing the solution, gently invert the bag in order to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed.

Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration.

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

Shelf Life
24 months.

REFERENCES:
• FDA label Reference ID: 3608873; Revised: xx/2014
• SPC, EMEA; 2014
• Data on file

Marketed by:

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Manufactured by:
Reliance Life Sciences Pvt. Ltd.
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