For the use of Oncologist and Rheumatologist only 8103954-9093

TORITZ

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

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

Infusion-Related Reactions - Rituximab administration can result in serious, including fatal, infusion-related reactions. Deaths within 24 hours of rituximab infusion have occurred. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. Monitor patients closely. Discontinue rituximab infusion for severe reactions and provide medical treatment for Grade 3 or 4 infusion-related reactions.

Severe Mucocutaneous Reactions - Severe, including fatal, mucocutaneous reactions can occur in patients receiving rituximab [see Warnings and Precautions].

Hepatitis B Virus (HBV) Reactivation - HBV reactivation can occur in patients treated with rituximab, in some cases resulting in fulminant hepatitis, hepatic failure, and death. Screen all patients for HBV infection before treatment initiation, and monitor patients during and after treatment with rituximab. Discontinue rituximab and concomitant medications in the event of HBV reactivation [see Warnings and Precautions].

Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving rituximab.

GENERIC NAME
Rituximab Injection I.P.

DOSAGE FORM AND STRENGTH
Solution for injection in vial (100 mg and 500 mg).

DESCRIPTION
TORITZ (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.
TORITZ 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 is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous administration.

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each single dose vial contains

	Strength	
Composition	**100 mg in Vial**	**500 mg in Vial**
Rituximab I.P.	100 mg	500 mg
Sodium Citrate Dihydrate I.P.	73.5 mg	367.5 mg
Sodium Chloride I.P.	90.0 mg	450 mg
Polysorbate 80 I.P.	7.0 mg	35.0 mg
Water for injection I.P.	q.s. to 10.0 ml	q.s. to 50.0 ml

PHARMACOLOGICAL PROPERTIES
Mechanism of action
Rituximab targets B lymphocyte by attaching to CD 20 proteins on the cell surface.
Pharmacodynamic properties
Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies, ATC code: L01X C02

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 the phase III study, pharmacodynamic parameter (absolute B cell count in the peripheral blood) assessment was planned in 42 patients in 1:1 ratio {21 subjects in each arm: the first 21 subjects of manufacturer's rituximab (test arm) and all 21 subjects of reference rituximab arm}. For baseline B cell assessment, total 20 subjects who were administered test rituximab & 19 subjects who were administered reference rituximab were included for analysis. The pharmacodynamic assessment was based on change in absolute B cell count in the peripheral blood after first cycle, at 24 weeks and 2 years compared to baseline. Subjects presented with a wide range of B-cell counts at baseline ranging from 2.0 to 8337.0 for test arm & 3.0 to 11673.0 for reference arm.
The baseline mean B cell count observed for test arm was 520.4, which showed a decline after start of treatment with test rituximab. 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 test arm. The baseline mean B cell count observed for reference arm was 760.1, which showed a decline after start of treatment with reference rituximab. There was a marked change in B cell count data at each defined sampling point starting from baseline to week 24 with reference 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 reference arm. The difference between two treatments for % reduction at week 24 was non significant (p 0.560).

Pharmacokinetic properties
Rituximab has shown target (CD20)-mediated disposition where antibody-antigen binding influences the rate and extent of antibody distribution and elimination. After i.v. administration of rituximab, all the drug administered reaches the systemic circulation, while after s.c. administration only a fraction of rituximab dose (F = 60%) is absorbed, because, during the absorption phase, a portion of the drug undergoes proteolytic degradation or phagocytosis. In general, the absolute bioavailability reported varies from 50 to 100%. For both i.v. and s.c. administration of antibodies, FcRn plays an important role by reducing mAb catabolism and mediating mAb transport across endothelial cells, thus promoting the distribution of the antibodies across tissues. The volume of distribution of rituximab at steady-state is approximately 9.6 L. With increasing concentrations of rituximab, total clearance (CL) decreases markedly (and the elimination half-life increases), as soon as the target-mediated elimination pathway begins to become saturated, and approaches that of the linear process (CLL).

CLINICAL PARTICULARS
Therapeutic indications
Non-Hodgkin's Lymphoma (NHL)
TORITZ (rituximab) is indicated for the treatment of:
- Previously untreated patients with stage III- IV follicular lymphoma in combination with chemotherap
- 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 prednisone) chemotherapy.

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

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

Pemphigus Vulgaris (PV)
Rituximab is indicated for the treatment of adult patients with moderate to severe pemphigus vulgaris.

Posology and method of 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 prednisone) 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 ecommended 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 1 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 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: 375 mg/m^2 the day prior to the initiation of FC chemotherapy, then 500 mg/m^2 on Day 1 of cycles 2-6 (every 28 days).

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

Glucocorticoids administered as methylprednisolone 1000 mg intravenously per day for 1 to 3 days followed by oral prednisone 1mg/kg/day (not to exceed 80 mg/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

Recommended Dose for Pemphigus Vulgaris (PV)
Administer Rituximab as two-1000 mg intravenous infusions separated by 2 weeks in combination with a tapering course of glucocorticoids.
Maintenance treatment
Administer Rituximab as a 500 mg intravenous infusion at Month 12 and every 6 months thereafter or based on clinical evaluation.
Treatment of relapse
Administer Rituximab as a 1000 mg intravenous infusion on relapse, and consider resuming or increasing the glucocorticoid dose based on clinical evaluation.

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).

Recommended Dose for Premedication and Prophylactic Medications
Premedicate with acetaminophen and an antihistamine before each infusion of Rituximab. 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 and PV patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion.
For GPA and MPA patients, glucocorticoids are given in combination with Rituximab. Provide prophylaxis treatment for Pneumocystis jirovecii pneumonia (PCP) and herpes virus infections for patients with CLL during treatment and for up to 12 months following treatment as appropriate. PCP prophylaxis is also recommended for patients with GPA and MPA during treatment and for at least 6 months following the last Rituximab infusion. PCP prophylaxis should be considered for patients with PV during and following Rituximab treatment.

Clinical study
A prospective, multi-centric, open-label, two-arm, parallel group, active-control, randomized, comparative clinical study was designed to evaluate efficacy and safety of manufacturer's rituximab / innovator in patients with Non-Hodgkin's Lymphoma. After randomization (4:1), 86 subjects were enrolled in manufacturer's rituximab arm and 22 subjects in comparator arm. A total of 66 subjects from manufacturer's rituximab arm and 15 subjects from Comparator arm completed the 24 week evaluation phase of the study.
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 blood) assessment was planned in 42 patients in 1:1 ratio (21 subjects in each arm: the first 21 subjects of manufacturer's rituximab 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 manufacturer's rituximab / comparator drug administration after the first cycle, at 24 weeks and 2 years compared to baseline.

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 manufacturer's rituximab arm. 45.45% subjects showed complete response and 42.42% subjects showed partial response in manufacturer's rituximab arm. The objective response rate was 86.66% in Comparator arm. 33.33% subjects 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 manufacturer's rituximab 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 manufacturer's rituximab / Comparator administration after first cycle, at 24 weeks and 2 years compared to baseline. The baseline mean B cell count observed for manufacturer's rituximab arm was 520.4, which showed a decline after start of treatment with manufacturer's rituximab.

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 manufacturer's rituximab 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).

A total of 101 evaluable subjects were considered for secondary efficacy analysis, 82 evaluable subjects from manufacturer's rituximab arm and nineteen from the Comparator arm. The Objective Response Rate was observed to be 81.71% in manufacturer's rituximab arm and 89.47% in Comparator arm. 23.17% and 5.26% subjects showed complete response where as 58.54% and 84.21% subjects showed partial response in test and comparator arms respectively at week 10. The proportion of non-responders at week 24 was comparable. The analysis of efficacy assessment ORR at 1 and 1.5 year showed comparable response for both manufacturer's rituximab and Comparator arms. Only one subject in the manufacturer's rituximab arm completed the radiological assessment at 2 years. Hence, no analysis was done for ORR at 2 years. Change in absolute B cell count in the peripheral blood after 2 years was not analysed since only one subject completed the 2 year assessment. The median OS at 5 years was 11.90 months in manufacturer's rituximab arm and 12.37 months in Comparator arm. The mean OS at 5 years was 23.66 months in manufacturer's rituximab arm and 23.30 months in Comparator arm, The difference between two arms at 5 years was statistically not significant (p>0.05).

In the study, all 105 subjects who were dosed were considered for the safety population. In the manufacturer's rituximab 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 manufacturer's rituximab arm and 16 SAEs were reported in 8 subjects in Comparator arm. Four were considered as related to the study drug manufacturer's rituximab by the investigators. There were 2 (2.35%) subjects from manufacturer's rituximab 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 manufacturer's rituximab or Comparator were included for antibody titre analysis. During analysis, three samples were found to be positive for manufacturer's rituximab 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 manufacturer's rituximab and Comparator arm.[Subjects with atleast one TEAE, 74 (87.06%) subjects in the manufacturer's rituximab arm and 18 (90.00%) in comparator]. The serious adverse events reported in both manufacturer's rituximab and Comparator arms were similar [37(43.53%) subjects in the manufacturer's rituximab arm and 8 (40.00%) in comparator]. No new safety concerns were identified during this study in either treatment arm.

Undesirable 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 manufacturer's rituximab 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 manufacturer's rituximab arm. Four study related deaths were reported in the manufacturer's rituximab arm of the clinical study and three in the comparator arm.
There were 2 (2.35%) subjects from manufacturer's rituximab 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 manufacturer's rituximab and Comparator arm.[Subjects with at least one TEAE, 87.06% subjects in the manufacturer's rituximab arm and 90.00% in comparator]. The serious adverse events reported in both manufacturer's rituximab and Comparator arms were similar [43.53% subjects in the manufacturer's rituximab arm and 40.00% in comparator]. No new safety concerns were identified during this study in either treatment arm.

Reporting of side effects
If you experience any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

Special 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

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ITEM / PACK :	Insert	**NO. OF COLORS :** 1	**REMARK :**				
DESIGN STYLE :	Front Side	**PANTONE SHADE NOS.:**	**SUBSTRATE :**				
CODE :	8103954-9093	Black	**Activities**	**Department**	**Name**	**Signature**	**Date**
DIMENSIONS (MM) :	230 x 380 mm		Prepared By	**Pkg.Dev**			
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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, bronchodilators, 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 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.

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 hypogammaglobulinemia >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.

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.

Embryo-Fetal Toxicity
Based on human data, rituximab can cause fetal harm due to B-cell lymphocytopenia in infants exposed to rituximab in-utero. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving rituximab and for at least 12 months after the last dose.

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.

Drug interactions
There have been no formal drug interaction studies performed with TORITZ. However, the existing data suggest that rituximab does not affect the pharmacokinetics of drugs which are used in combination with rituximab.
Drug-Drug Interactions
There have been no formal drug interaction studies performed with rituximab. The tolerability of simultaneous or sequential combination of rituximab with chemotherapy other than CHOP and CVP or agents which are liable to cause depletion of normal B cells is not well defined.
Renal failure requiring dialysis has been observed in patients treated with the combination of rituximab and cisplatin. If this combination is used, extreme caution should be exercised and renal function should be monitored closely.
Concomitant use with Biologic Agents and 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 patients exhibiting peripheral B cell depletion following treatment with rituximab. Patients should be closely observed for signs of infection if biologic agents and/or DMARDs are used concomitantly.

NONCLINICAL PROPERTIES
Animal toxicology or pharmacology
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 manufacturer's rituximab, did not reveal any toxic effects at the highest dose tested. manufacturer's rituximab 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 observed adverse effect level (NOAEL). Skin sensitization study results showed manufacturer's rituximab 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.

Effect on ability to drive and use machines
No studies done.
Use in special population
Pregnant women:

Pregnancy Category C
Risk Summary

Based on human data, rituximab can cause adverse developmental outcomes including B-cell lymphocytopenia in infants exposed to rituximab in-utero. 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.

Lactating women:
It is not known whether rituximab is secreted into 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 patients:
The safety and effectiveness of rituximab in pediatric patients have not been established.

Geriatric patients:
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.

Overdose
Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

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

PHARMACEUTICAL PARTICULARS
Incompatibilities
No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed. No other studies done.
Packaging information
TORITZ (rituximab) is available as 100 mg/10 ml in single-use vial and 500 mg/50 ml in single use vial

Storage and handling instructions
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
For details of product shelf life please refer to the Expiry date mentioned on the carton and label.

PATIENT COUNSELING 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 rituximab.
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 a pregnant woman of the potential risk to a fetus. Advise female patients that rituximab can cause fetal harm if taken during pregnancy and to use effective contraception during treatment with rituximab and for at least 12 months after the last dose of rituximab.
Advise patients to inform their healthcare provider of a known or suspected pregnancy.
Lactation
Advise women not to breastfeed during treatment with rituximab and for 6 months after the last dose.

TORRENT PHARMA
Marketed by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.

Reliance Life Sciences
Manufactured by :
Reliance Life Sciences Pvt. Ltd.
DALC, Plant 2 & 7, R-282, TTC Area of MIDC,
Thane-Belapur Road, Rabale, Navi Mumbai - 400 701, INDIA.

DETAILS OF PERMISSION AND/OR LICENCE NUMBER WITH DATE
MF-17/2015, dated 12 Feb 2015
License # KD/7

DATE OF REVISION
September 2024

PRODUCT NAME	: Toritz	**COUNTRY :** Domestic P2P	**LOCATION :** Reliance Life Science		**Supercedes A/W No. :**		
ITEM / PACK	: Insert	**NO. OF COLORS :** 1	**REMARK :**				
DESIGN STYLE	: Back Side	**PANTONE SHADE NOS.:**	**SUBSTRATE :**				
CODE	: 8103954-9093	Black	**Activities**	**Department**	**Name**	**Signature**	**Date**
DIMENSIONS (MM)	: 230 x 380 mm		Prepared By	**Pkg.Dev**			
ART WORK SIZE	: S/S		Reviewed By	**Pkg.Dev**			
DATE	: 30-10-2025		Reviewed By	**CR**			
			Approved By	**Quality**			
			Approved By	**Quality**			

This colour proof is not colour binding. Follow Pantone shade reference for actual colour matching.