For the use of an Oncologist or Hospital only

MABTAS

Rituximab 100 mg / 500 mg concentrate for solution for infusion

DECSRIPTION AND COMPOSITION

MABTAS is a genetically engineered chimeric murine/human monoclonal antibody consisting of a glycosylated IgG1 kappa immunoglobulin with murine light- and heavy-chain variable regions (Fab domain) and human kappa and gamma-1 constant regions (Fc domain). Rituximab is directed against the CD20 antigen and has a binding affinity for the CD20 antigen of approximately 8.0 nM.

Rituximab is a highly purified 1328-amino acid chimeric mouse/human antibody that is produced in mammalian cell culture using Chinese Hamster Ovary (CHO) cells. The molecular weight of Rituximab is ~145,000 Da where the light chain consists of 213 amino acids and heavy chain consists of 451 amino acids.

Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for solution for infusion. Rituximab is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-use vials.

Each 10 mL single use vial contains: Rituximab 100 mg (10 mg/mL)
Each 50 mL single use vial contains: Rituximab 500 mg (10 mg/mL)
The pH of the solution is 6.5±0.3.

Contents	Quantity
Rituximab	10 mg
Sodium Citrate Dihydrate	7.35 mg
Sodium Chloride	9.0 mg
Polysorbate-80	0.7 mg
Hydrochloric acid	q.s. to pH 6.5
Sodium Hydroxide	q.s. to pH 6.5
Water for injection (qs)	1.0 mL

DOSAGE FORM

Concentrate for solution for infusion, 100 mg/10 mL single-use vial
Concentrate for solution for infusion, 500 mg/50 mL single-use vial

PRECLINICAL PHARMACOLOGY

The relative potency of Rituximab was assessed in an in-vitro cell based assay. When compared with the reference standard, it was found comparable and equipotent.

Acute toxicity studies were conducted in mice by administering IV single doses of 230, 575 and 1150 mg/Kg of Rituximab and in rats by administering IV single doses of 116, 290, and 580 mg/kg. The animals were observed for mortality, clinical signs and gross organ examinations. There was no death or any other adverse effect in the animals at all the dose levels. In repeat dose sub acute toxicity studies in rats a doses of 58, 116 and 174 mg/Kg and in rabbits a doses of 29, 58 and 87 were administered for a period of 28 days by IV route. The animals were examined for body weight changes, food consumption, blood chemistry and histopathological examination of body organs. There was no abnormality detected in any of the parameters in the animals. Rituximab was well tolerated in low, medium and high dose levels.

CLINICAL PHARMACOLOGY

Mechanism of action

Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately 35 kDa located on pre-B and mature B lymphocytes. The antigen is expressed on > 90% of B-cell non-Hodgkin's lymphomas (NHL), but the antigen is not found on hematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissues. CD20 regulates an early step(s) in the activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion channel. CD20 is not shed from the cell surface and does not internalize upon antibody binding. Free CD20 antigen is not found in the circulation.

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

Mechanism of Action: The Fab domain of Rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis *in vitro*. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cell mediated cytotoxicity (ADCC). The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line.
Normal Tissue Cross-reactivity: Rituximab binding was observed on lymphoid cells in the thymus, the white pulp of the spleen, and a majority of B lymphocytes in peripheral blood and lymph nodes. Little or no binding was observed in the non-lymphoid tissues examined.

CLINICAL PHARMACODYANAMIC PROPERTIES

Administration of Rituximab resulted in a rapid and sustained depletion of circulating and tissue-based B-cells. Lymph node biopsies performed 14 days after therapy showed a decrease in the percentage of B-cells in seven of eight patients with NHL who had received single doses of Rituximab =100 mg/m^2. Among the 166 patients in the pivotal NHL study, circulating B-cells (measured as CD19-positive cells) were depleted within the first three doses with sustained depletion for up to 6 to 9 months post-treatment in 83% of patients. Of the responding patients assessed (n = 80), 1% failed to show significant depletion of CD19-positive cells after the third infusion of Rituximab as compared to 19% of the non responding patients. B-cell recovery began at approximately 6 months following completion of treatment. Median B-cell levels returned to normal by 12 months following completion of treatment.

There were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5 through 11 months following Rituximab administration. However, only 14% of patients had reductions in IgM and/or IgG serum levels, resulting in values below the normal range.

In Rheumatoid Arthritis(RA) patients, treatment with Rituximab induced depletion of peripheral B lymphocytes, with all patients demonstrating near complete depletion within 2 weeks after receiving the first dose of Rituximab. The majority of patients showed peripheral B-cell depletion for at least 6 months, followed by subsequent gradual recovery after that timepoint. A small proportion of patients (4%) had prolonged peripheral B-cell depletion lasting more than 3 years after a single course of treatment.

CLINICAL PHARMACOKINETIC PROPERTIES

Non-Hodgkin's Lymphoma (NHL)
In patients with NHL-given single doses at 10, 50, 100, 250 or 500 mg/m^2 as an IV infusion, serum levels and the half-life of Rituximab were proportional to dose. In 14 patients given 375 mg/m^2 as an IV infusion for 4 weekly doses, the mean serum half-life was 76.3 hours (range, 31.5 to 152.6 hours) after the first infusion and 205.8 hours (range, 83.9 to 407.0 hours); after the fourth infusion. The wide range of half-lives may reflect the variable tumor burden among patients and the changes in CD20-positive (normal and malignant) B-cell populations upon repeated administrations.

Rituximab 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 CD20 positive B cells and measures of disease burden. Median steady-state serum levels were higher for responders compared with nonresponders; however, no difference was found in the rate of elimination as measured by serum half-life. 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 treatment.

Rituximab 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 through the eight infusion. The mean C_{max} after 8 infusions was 550 µg/mL (range, 171 to 1177 µg/mL).
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(RA)
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 × 500 mg and 2 × 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.

CLINICAL TRIAL OF RITUXIMAB IN INDIAN PATIENTS

The efficacy and safety of Rituximab of Intas was evaluated in comparison with innovator's Rituximab in multi-centric, randomized phase III trial in patients with Non Hodgkin's Lymphoma (NHL).Objective of study was to compare the safety and efficacy of Rituximab manufactured by Intas plus cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) regimen against innovator's Rituximab plus CHOP in patients with CD20-positive diffuse large B-cell or follicular lymphoma.

Adult men and women with age ≥18 with previously untreated histologically confirmed diffuse large B-cell or follicular type of NHL, with a performance status of 0-2 according to the Eastern Cooperative Oncology Group (ECOG) and not having serious disease or medical condition that would interfere with compliance were included in the study.

A total of 101 patients were enrolled. Eligible patients were randomly allocated to receive either Rituximab of Intas or innovator's Rituximab. They received either Rituximab concentrate for solution for infusion manufactured by Intas (Arm A) at 375 mg/m^2 BSA or innovator's Rituximab of (Arm B) at the same dose. All the randomized patients additionally received CHOP regimen at the standard recommended dose of BSA. Patients were evaluated for Objective Response Rate (ORR) which was a primary efficacy endpoint and defined as the proportion of subjects with tumor size reduction of a predefined amount and for a minimum time period. It was measured as the sum of partial responses and complete responses (CR + PR). Safety evaluation included incidence of drug related adverse events as assessed by any clinical significant changes in physical examination, vitals and / or laboratory parameters during the study compared to baseline.

The main efficacy endpoint was the objective response rate. The result of the study indicated that objective response rate of 76.67% in treatment arm of Intas Rituximab as compared to 65.22% in treatment arm of innovator's Rituximab. Further detailed analysis of the result showed CR rate of 33.33% in patients of Intas Rituximab treatment arm as compared to response rate of 21.73% in patients of innovator's Rituximab arm (P value < 0.4453). Similarly, PR rate of 43.33% in Intas Rituximab treatment arm and 43.48% in innovator's Rituximab treatment (P value < 0.9905) was achieved. Result of the study indicated that Rituximab concentrate for solution for infusion manufactured by Intas is a safe and effective similar to innovator's Rituximab concentrate for solution for infusion along with CHOP regimen in treatment of patients with NHL.

All the vital parameters were also within acceptable range during the study in both the treatment groups. Overall both the study drugs, Rituximab manufactured by Intas as well innovator's Rituximab, were found safe and well tolerated in the study population. The overall tolerability of Rituximab manufactured by Intas is comparable with innovator's Rituximab, at intended therapeutic doses in lymphoma patients. Rituximab manufactured by Intas demonstrated to be safe and well tolerated in the study population.

INDICATION

Rituximab is indicated for the treatment of:
Non–Hodgkin's Lymphoma (NHL)
· Patients with relapsed or chemo resistant indolent B cell Non- Hodgkin's Lymphoma.
· Previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy
· For patient with relapsed/ refractory follicular lymphoma as maintenance therapy after responding to induction therapy after with chemotherapy
· Patients with CD20 positive diffuse large B cell Non- Hodgkin's lymphoma in combination with CHOP (Cyclophosphamide, doxorubicin, vineristinc, prednisolone) chemotherapy
Chronic Lymphocytic Leukemia
· Rituximab in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/ refractory Chronic Lymphocytic Leukemia
Rheumatoid Arthritis
· Adult patients with active rheumatoid arthritis who have had an inadequate response or intolerance to one or more Tumor Necrosis Factor inhibitor therapies

DOSE AND METHOD OF ADMINISTRATION

Administer prepared Rituximab as IV infusion through a dedicated line, with full resuscitation facilities immediately available and under supervision of an experienced physician. Do not administer as IV push or bolus. Administer premedication consisting of an anti-pyretic and an antihistamine, e.g paracetamol and diphenhydramine before each infusion of Rituximab. Consider premedication with glucocorticoids, if not given in combination with a glucocorticoid containing chemotherapy.

Patients should be closely monitored for the onset of cytokine release syndrome (CRS). Severe reactions, especially e.g. severe dyspnoea, bronchospasm or hypoxia require immediate interruption of infusion. Patients with NHL should than be evaluated for evidence of tumor lysis syndrome including appropriate laboratory tests and, for pulmonary infiltration, with chest x-ray. In all patients, the infusion should not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest x-ray findings. At this time, the infusion can be initially resumed at not more than one half the previous rate. If the same severe adverse reactions occur for a second time, the decision to stop the treatment should be seriously considered on a case by case basis.
First infusion
The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
Subsequent infusions
Subsequent doses of Rituximab can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minutes intervals, to a maximum of 400 mg/hr.
Mild or moderate infusion-related reactions usually respond to a reduction in the rate of infusion.

Non–Hodgkin's Lymphoma (NHL)
Dosage adjustments during treatment
No dose reductions of Rituximab are recommended. When Rituximab is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied.

A. Diffuse large B-cell non-Hodgkin's lymphoma:
Rituximab should be used in combination with CHOP chemotherapy. The recommended dosage is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP.

B. Follicular non-Hodgkin's lymphoma:
Combination therapy
The recommended dose of Rituximab in combination with chemotherapy for induction treatment of previously untreated or relapsed/ refractory patients with follicular lymphoma is: 375 mg/m^2 body surface area per cycle, for up to 8 cycles. Rituximab should be administered on day 1 of each chemotherapy cycle, after intravenous administration of the glucocorticoid component of the chemotherapy if applicable.
Maintenance therapy
Previously untreated follicular lymphoma
The recommended dose of Rituximab used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.
Relapsed/refractory follicular lymphoma
The recommended dose of Rituximab used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.
Monotherapy
Relapsed/refractory follicular lymphoma

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

Chronic lymphocytic leukaemia
Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are > 25 x 10^9/L it is recommended to administer prednisone/prednisolone 100 mg intravenous shortly before infusion with Rituximab to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.
The recommended dosage of Rituximab in combination with chemotherapy for previously untreated and relapsed/refractory patients is 375 mg/m^2 body surface area administered on day 0 of the first treatment cycle followed by 500 mg/m^2 body surface area administered on day 1 of each subsequent cycle for 6 cycles in total. The chemotherapy should be given after Rituximab infusion.

Rheumatoid Arthritis
Patients should receive treatment with 100 mg intravenous methylprednisolone to be completed 30 minutes prior to Rituximab infusions to decrease the incidence and severity of infusion related reactions. Premedication consisting of an analgesic/anti-pyretic (e.g. paracetamol) and an anti-histaminic drug (e.g. diphenhydramine) should always be administered before each infusion of Rituximab .
A course of Rituximab consists of two 1000 mg intravenous infusions. The recommended dosage of Rituximab is 1000 mg by intravenous infusion followed by a second 1000 mg intravenous infusion two weeks later.
The need for further courses should be evaluated 24 weeks following the previous course. Retreatment should be given at that time if residual disease activity remains, otherwise retreatment should be delayed until disease activity returns.Available data suggest that clinical response is usually achieved within 16 - 24 weeks of an initial treatment course. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

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

Second infusion of each course
Subsequent doses of Rituximab can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minutes intervals, to a maximum of 400 mg/hr.

PREPARATION FOR ADMINISTRATION

Use appropriate aseptic technique. Withdraw the necessary amount of Rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

CONTRAINDICATIONS

Contraindications for use in non-Hodgkin's lymphoma
· Hypersensitivity to the active substance or to any of the excipients or to murine proteins
- Active, severe infections
Contraindications for use in rheumatoid arthritis
· Hypersensitivity to the active substance or to any of the excipients or to murine proteins
· Active, severe infections
· Severe heart failure (NYHA class IV) or severe, uncontrolled cardiac disease.

WARNINGS

Severe Infusion Reactions:
Rituximab has caused severe infusion reactions. In some cases, these reactions were fatal. These severe reactions typically occurred during the first infusion with time to onset of 30 to 120 minutes. Signs and symptoms of severe infusion reactions may include hypotension, angioedema, hypoxia or bronchospasm, and may require interruption of Rituximab administration. The most severe manifestations and sequel include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Management of severe infusion reactions: The Rituximab infusion should be interrupted for severe reactions and supportive care measures instituted as medically indicated (e.g., intravenous fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen). In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Patients requiring close monitoring during first and all subsequent infusions include those with pre-existing cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events and those with high numbers of circulating malignant cells (≥25,000/mm^3) with or without evidence of high tumor burden.

Tumor Lysis Syndrome [TLS]:
Rapid reduction in tumor volume followed by acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia or hyperphosphatasemia have been reported within 12 to 24 hours after the first Rituximab infusion. Rare instances of fatal outcome have been reported in the setting of TLS following treatment with Rituximab. Correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis, should be initiated as indicated. Following complete resolution of the complications of TLS, Rituximab has been tolerated when re-administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

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.

Hypersensitivity Reactions:
Rituximab has been associated with hypersensitivity reactions (non-IgE-mediated reactions) which may respond to adjustments in the infusion rate and in medical management. Hypotension, bronchospasm, and angioedema have occurred in association with Rituximab infusion. Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and corticosteroids, should be available for immediate use in the event of a reaction during administration.

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

Infection:
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.

Severe cytokine release syndrome:
Severe cytokine release syndrome is characterised by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphaetemia, acute renal failure, elevated Lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome frequently manifests itself within one or two hours of initiating the first infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution.

Cardiovascular:
Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of Rituximab.

Renal:
Rituximab administration has been associated with severe renal toxicity including acute renal failure requiring dialysis and in some cases, has led to a fatal outcome.

Severe Mucocutaneous Reactions:
Mucocutaneous reactions, some with fatal outcome, have been reported in patients treated with Rituximab. These reports include paraneoplastic pemphigus (an uncommon disorder which is a manifestation of the patient's underlying malignancy), Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of the reaction in the reported cases has varied from 1 to 13 weeks following Rituximab exposure. Skin biopsy may help to distinguish among different mucocutaneous reactions and guide subsequent treatment.

PRECAUTIONS

Laboratory Monitoring:
Because Rituximab targets all CD20-positive B lymphocytes, malignant and nonmalignant, complete blood counts (CBC) and platelet counts should be obtained at regular intervals during Rituximab therapy 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 well beyond the treatment period.

Drug/Laboratory Interactions:
There have been no formal drug interaction studies performed with Rituximab. However, renal toxicity was seen with this drug in combination with cisplatin in clinical trials. HACA Formation: Human antichimeric antibody (HACA) was detected in 4 of 356 patients and 3 had an objective clinical response. The data reflect the percentage of patients whose test results were considered positive for antibodies to Rituximab using an enzyme-linked immunosorbant assay (limit of detection = 7 ng/mL).The observed incidence of antibody positivity in an assay is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Rituximab with the incidence of antibodies to other products may be misleading.

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 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 non-biologic 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.

Immunization:
The safety of immunization with live viral vaccines following Rituximab therapy has not been studied. The ability to generate a primary or anamnestic humoral response to vaccination is currently being studied. For RA patients, physicians should follow current immunization guidelines and administer non-live vaccines at least 4 weeks prior to a course of Rituximab.

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 its effects on fertility in males or females. Individuals of childbearing potential should use effective contraceptive methods during treatment and for up to 12 months following Rituximab therapy.

Pregnancy Category C:
Animal reproduction studies have not been conducted with Rituximab. It is not known whether Rituximab can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. Human IgG is known to pass the placental barrier, and thus may potentially cause fetal B-cell depletion; therefore, Rituximab should be given to a pregnant woman only if clearly needed.

Nursing Mothers:
It is not known whether Rituximab is excreted in human milk. Because human IgG is excreted in human milk and the potential for absorption and immunosuppression in the infant is unknown, women should be advised to discontinue nursing until circulating drug levels are no longer detectable.

Paediatric Use:
The safety and effectiveness of Rituximab in paediatric patients have not been established.

Geriatric Use:
Among the 331 patients enrolled in clinical studies of single agent Rituximab, 24% were 65 to 75 years old and 5% were 75 years old and older. The overall response rates were higher in older (age > 65 years) vs. younger (age < 65 years) patients (52% vs. 44%, respectively). However, the median duration of response, based on Kaplan-Meier estimates, was shorter in older vs. younger patients: 10.1 months (range, 1.9 to 36.5+) vs.11.4 months (range, 2.1 to 42.1+),respectively. This shorter duration of response was not statistically significant. Adverse reactions, including incidence, severity and type of adverse reaction were similar between older and younger patients.

USE IN SPECIAL POPULATIONS
Pregnancy
Pregnancy Category C
There are no adequate and well-controlled studies of Rituximab in pregnant women. 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.

Non-Hodgkin's lymphoma is serious condition that requires treatment. Rituximab should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. Reproduction studies in cynomolgus monkeys at maternal exposures similar to human therapeutic exposures showed no evidence of teratogenic effects. However, B-cell lymphoid tissue was reduced in the offspring of treated dams. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months of birth.

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

Front

Reason for Revision: addtional inforrmations from Medical Services **Artwork No.:** AW-QA-812-04

Supersedes No.: AW-QA-812-03

	Prepared by	Approved by					Authorised by
Department	**PPMC**	**Packing (FP)**	**Regulatory**	**Marketing**	**Medical Services**	**QA**	**QA**
Signature							
Date							
Name							
Designation							

Product Name : Mabtas - Domestic - Pack Insert
Size : 520 x 300 (mm)
No. of Col. : 1
Colour Shade No. : Black
No. of fold : 5
Fold size : ~130 mm X ~37.5 mm
Type of Paper / Board : Bible paper
GSM of Paper : 40 gsm ± 5 gsm

Rituximab should be weighed against the known benefits of breastfeeding.

Pediatric Use
Safety and effectiveness of Rituximab in pediatric patients have not been established.

Geriatric Use
No overall differences in safety or effectiveness were observed between patients aged 65 and older and younger patients.

Renal Impairment
Rituximab dose adjustment in patients with renal dysfunction is not necessary.

DRUG INTERACTIONS
There has been no formal drug interaction studies performed with Rituximab. However, renal toxicity was seen with this drug in combination with cisplatin in clinical trials. In patients with CLL, rituximab did not alter systemic exposure to fludarabine or cyclophosphamide. In clinical trials of patients with RA, concomitant administration of methotrexate or cyclophosphamide did not alter the pharmacokinetics of Rituximab.

UNDESIRABLE EFFECTS
The most serious adverse reactions caused by Rituximab include infusion reactions, tumor lysis syndrome, mucocutaneous reactions, hypersensitivity reactions, cardiac arrhythmias and angina, and renal failure. Infusion reactions and lymphopenia are the most commonly occurring adverse reactions.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Additional adverse reactions have been identified during postmarketing use of Rituximab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Rituximab exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to Rituximab.

Experience from non-Hodgkin's lymphoma and chronic lymphocytic leukaemia
The most frequently observed adverse drug reactions (ADRs) in patients receiving rituximab were infusion-related reactions which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1% after eight doses of rituximab.

Infectious events (predominantly bacterial and viral) occurred in approximately 30-55 % of patients during clinical trials in patients with NHL and in 30-50 % of patients during clinical trials in patients with CLL.

The most frequent reported or observed serious adverse drug reactions were infusion related reactions (including cytokine-release syndrome, tumour-lysis syndrome), infections and cardiovascular events.

Other serious ADRs reported include hepatitis B reactivation and PML.
The frequencies of ADRs reported with rituximab alone or in combination with chemotherapy are summarised in Table 1. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1000) and very rare (< 1/10,000). The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under "not known".

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

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	bacterial infections, viral infections, bronchitis	sepsis, pneumonia, febrile infection, herpes zoster, respiratory tract infection, fungal infections, infections of unknown aetiology, acute bronchitis, sinusitis, hepatitis B		serious viral infection Pneumo-cystis jirovecii	PML	
Blood and lymphatic system disorders	neutropenia, leucopenia, febrile neutropenia, thrombo-cytopenia	anaemia, pancytopenia, granulo-cytopenia	coagulation disorders, aplastic anaemia, haemolytic anaemia, lymph-adenopathy		transient increase in serum IgM levels	late neutropenia
Immune system disorders	infusion related reactions, angioedema	hypersensitivity		anaphylaxis	tumour lysis syndrome, cytokine release syndrome, serum sickness	infusion-related acute reversible thrombo-cytopenia
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia				
Psychiatric disorders			depression, nervousness,			
Nervous system disorders		paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia		peripheral neuropathy, facial nerve palsy	cranial neuropathy, loss of other senses
Eye disorders		lacrimation disorder, conjunctivitis			severe vision loss	
Ear and labyrinth disorders		tinnitus, ear pain				hearing loss
Cardiac disorders		myocardial infarction , arrhythmia, atrial fibrillation, tachycardia, cardiac disorder	left ventricular failure, supra-ventricular tachycardia, ventricular tachycardia, angina, myocardial ischaemia, bradycardia	severe cardiac events	heart failure	
Vascular disorders		hypertension, orthostatic hypotension, hypotension			vasculitis (predominately cutaneous), leukocytoclastic vasculitis	

Respiratory, thoracic and mediastinal disorders		Bronchospasm, respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia	interstitial lung disease	respiratory failure	lung infiltration
Gastrointestinal disorders	nausea	vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation	abdominal enlargement		gastro-intestinal perforation	
Skin and subcutaneous tissue disorders	pruritus, rash, alopecia	urticaria, sweating, night sweats, skin disorder			severe bullous skin reactions, Stevens-Johnson Syndrome toxic epidermal necrolysis (Lyell's Syndrome)	infusion-related acute reversible thrombo-cytopenia
Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					renal failure	
General disorders and administration site conditions	fever, chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome, fatigue, shivering, multi-organ failure	infusion site pain			
Investigations	decreased IgG levels					

Experience from rheumatoid arthritis
The most frequent adverse reactions considered due to receipt of rituximab were infusion related reactions. The overall incidence of IRRs in clinical trials was 23% with the first infusion and decreased with subsequent infusions. Serious IRRs were uncommon (0.5% of patients) and were predominantly seen during the initial course. In addition to adverse reactions seen in RA clinical trials for rituximab, progressive multifocal leukoencephalopathy (PML) and serum sickness-like reaction have been reported during post marketing experience.
Events are listed in Table 2. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), and very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	upper respiratory tract infection, urinary tract infections	Bronchitis, sinusitis, gastroenteritis, tinea pedis				PML, reactivation of hepatitis B
Blood and lymphatic system disorders		neutropenia			late neutropenia	Serum sickness-like reaction
Cardiac Disorders	neutropenia, leucopenia, febrile neutropenia, thrombo-cytopenia				Angina pectoris, atrial fibrillation, heart failure, myocardial infarction	Atrial flutter
Immune system disorders **General disorders and administration site conditions**	Infusion related reactions (hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension, rhinitis, rigors, tachycardia, fatigue, oropharyngeal pain, peripheral oedema, erythema)		Infusion related reactions (generalized oedema, bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalized pruritis, anaphylaxis, anaphylactoid reaction)			
Metabolism and Nutritional Disorders		hyper-cholesterolemia				
Nervous System disorders	headache	paraesthesia, migraine, dizziness, sciatica				
Skin and Subcutaneous Tissue Disorders		alopecia				Toxic Epidermal Necrolysis (Lyell's Syndrome), Stevens-Johnson Syndrome
Psychiatric Disorders		depression, anxiety				
Gastrointestinal Disorders		Dyspepsia, diarrhoea, gastro-oesophageal reflux, mouth ulceration, upper abdominal pain				
Musculo skeletal disorders		arthralgia / musculoskeletal pain, osteoarthritis, bursitis				
Investigations	decreased IgM levels	decreased IgG levels				

Immunogenicity
The incidence of antibody development in patients receiving Rituximab has not been determined. As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Rituximab with the incidence of antibodies to other products may be misleading.

Using an ELISA assay, anti-human anti-chimeric antibody (HACA) was detected in 4 of 356 (1.1%) patients with low-grade or follicular NHL receiving single-agent Rituximab. Three of the four patients had an objective clinical response.

OVERDOSE
There has been no experience with over dosage in human clinical trials. Single doses of up to 500 mg/m^2 have been given in controlled clinical trials.

INCOMPATIBILITIES
This medicinal product must not be mixed with other medicinal products.

SHELF LIFE: 24 Months

PACKING INFORMATION
MABTAS is supplied in a 10 mL single-use vial containing 100 mg Rituximab and 50 mL single-use vial containing 500 mg Rituximab.

STORAGE AND HANDLING INSTRUCTION
Store refrigerated between 2 °C to 8 °C (36 °F to 46 °F) in the carton to protect from light. Do not shake. The preparation should not be allowed to freeze. Keep out of reach and sight of children.

AW-QA-812-04

Manufactured and Marketed by:
INTAS
INTAS PHARMACEUTICALS LTD.
Plot No. 423/P/A, Sarkhej - Bavla Highway,
Village - Moraiya, Taluka - Sanand,
District - Ahmedabad-382 213, Gujarat, INDIA.

Back