RITUXIM®
(Rituximab)

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COMPOSITION:
Rituxim® 500mg/50ml
Active Ingredient:
Rituximab 10mg per 1ml

Rituxim® 100mg/10ml
Active Ingredient:
Rituximab 10mg per 1ml

Concentrate for solution for infusion
(As per innovator's specs.)

BLACK BOX WARNING

FATAL INFUSION-RELATED REACTIONS, SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Infusion-Related Reactions
Administration of rituximab products, including Rituxim®, can result in serious, including fatal, infusion-related reactions. Deaths within 24 hours of rituximab infusion have occurred. Approximately 80% of fatal infusion-related reactions occurred in association with the first infusion. Monitor patients closely. Discontinue Rituxim® infusion for severe reactions and provide medical treatment for Grade 3 or 4 infusion-related reactions [see Warnings and Precautions, Adverse Reactions].

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

Hepatitis B Virus (HBV) Reactivation
HBV reactivation can occur in patients treated with rituximab products, 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 Rituxim®. Discontinue Rituxim® 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 products [see Warnings and Precautions and Adverse Reactions].

DESCRIPTION
Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences. The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

CLINICAL PHARMACOLOGY

Mechanism of Action
Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). 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.

Pharmacodynamics
Non-Hodgkin's Lymphoma (NHL)
In NHL patients, administration of rituximab resulted in depletion of circulating and tissue-based B cells. Among 166 patients in NHL Study 1 (NCT000168740), circulating CD19-positive B cells were depleted within the first three weeks with sustained depletion for up to 6 to 9 months post treatment in 83% of patients. B-cell recovery began at approximately 6 months and 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; 14% of patients had IgM and/or IgG serum levels below the normal range.

Rheumatoid Arthritis
In RA patients, treatment with rituximab induced depletion of peripheral B lymphocytes, with the majority of patients demonstrating near complete depletion (CD19 counts below the lower limit of quantification, 20 cells/µl) within 2 weeks after receiving the first dose of rituximab. The majority of patients showed peripheral B-cell depletion for at least 6 months. A small proportion of patients (~4%) had prolonged peripheral B-cell depletion lasting more than 3 years after a single course of treatment.
Total serum immunoglobulin levels, IgM, IgG, and IgA were reduced at 6 months with the greatest change observed in IgM. At Week 24 of the first course of rituximab treatment, small proportions of patients experienced decreases in IgM (10%), IgG (2.8%), and IgA (0.8%) levels below the lower limit of normal (LLN). In the experience with rituximab in RA patients during repeated rituximab treatment, 23.3%, 5.5%, and 0.5% of patients experienced decreases in IgM, IgG, and IgA concentrations below LLN at any time after receiving rituximab, respectively. The clinical consequences of decreases in immunoglobulin levels in RA patients treated with rituximab are unclear.
Treatment with rituximab in patients with RA was associated with reduction of certain biologic markers of inflammation such as interleukin-6 (IL-6), C-reactive protein (CRP), serum amyloid protein (SAA), S100 A8/S100 A9 heterodimer complex (S100 A8/9), anti-citrullinated peptide (anti-CCP), and RF.

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis
In GPA and MPA patients, peripheral blood CD19 B-cells depleted to less than 10 cells/µl following the first two infusions of rituximab, and remained at that level in most (84%) patients through Month 6. By Month 12, the majority of patients (81%) showed signs of B-cell return with counts >10 cells/µL. By Month 18, most patients (87%) had counts >10 cells/µL.

Pharmacokinetics
Non-Hodgkin's Lymphoma (NHL)
Pharmacokinetics were characterized in 203 NHL patients receiving 375 mg/m^2 rituximab weekly by intravenous infusion for 4 doses. Rituximab was detectable in the serum of patients 3 to 6 months after completion of treatment.
The pharmacokinetic profile of rituximab when administered as 6 infusions of 375 mg/m^2 in
combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone.
Based on a population pharmacokinetic analysis of data from 298 NHL patients who received rituximab once weekly or once every three weeks, the estimated median terminal elimination half-life was 22 days (range, 6.1 to 52 days). Patients with higher CD19-positive cell counts or larger measurable tumor lesions at pretreatment had a higher clearance. However, dose adjustment for pretreatment CD19 count or size of tumor lesion is not necessary. Age and gender had no effect on the pharmacokinetics of rituximab.
Pharmacokinetics were characterized in 21 patients with CLL receiving rituximab according to the recommended dose and schedule. The estimated median terminal half-life of rituximab was 32 days (range, 14 to 62 days).

Rheumatoid Arthritis
Based on a population pharmacokinetic analysis of data from 2005 RA patients who received rituximab, the estimated clearance 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.

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis
Based on the population pharmacokinetic analysis of data in 97 GPA and MPA patients who received 375 mg/m^2 rituximab once weekly by intravenous infusion for four weeks, the estimated median terminal elimination half-life was 23 days (range, 9 to 49 days). Rituximab mean clearance and volume of distribution were 0. 312 L/day (range, 0.115 to 0.728 L/day) and 4.50 L (range, 2.21 to 7.52 L) respectively. Male patients and patients with higher BSA or positive HACA levels have higher clearance. However, further dose adjustment based on gender or HACA status is not necessary.

INDICATIONS

Non-Hodgkin's lymphoma (NHL)
Rituxim® (rituximab) is indicated for the treatment of adult patients with:
•Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent. •Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy.
•Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy +6.
•Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

Chronic lymphocytic leukaemia (CLL)
Rituxim®, in combination with fludarabine and cyclophosphamide (FC), is indicated for the treatment of adult patients with previously untreated and previously treated CD20-positive CLL.

Rheumatoid arthritis
Rituxim®, in combination with methotrexate, is indicated for the treatment of adult patients with moderately-to severely-active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

Granulomatosis with polyangiitis and microscopic polyangiitis
Rituxim®, in combination with glucocorticoids, is indicated for the treatment of adult and pediatric patients 2 years of age and older with Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA).

Pemphigus vulgaris
Rituxim® is indicated for the treatment of patients with moderate to severe pemphigus vulgaris (PV).

DOSAGE AND ADMINISTRATION

Adult dosage
1-Important Dosing Information
Administer only as an Intravenous Infusion
Do not administer as an intravenous push or bolus. Rituxim® should only be administered by a healthcare professional with appropriate medical support to manage severe infusion-related reactions that can be fatal if they occur. Premedicate before each infusion.

Prior to First Infusion: Screen all patients for HBV infection by measuring HBsAg and anti-
HBc before initiating treatment with Rituxim® [see Warnings and Precautions]. Obtain complete blood counts including platelets (CBC) prior to the first dose.

During Rituxim® Therapy: In patients with lymphoid malignancies, during treatment with Rituxim® monotherapy, obtain complete blood counts (CBC) with differential and platelet counts prior to each Rituxim® course. During treatment with Rituxim® and chemotherapy, obtain CBC with differential and platelet counts at weekly to monthly intervals and more frequently in patients who develop cytopenias [see Adverse Reactions].
• ***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 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^3 before Cycle 2 should not be administered the 90-minute infusion.

• Interrupt the infusion or slow the infusion rate for infusion-related reactions [see Box Warning, Warnings and Precautions]. Continue the infusion at one-half the previous rate upon improvement of symptoms.

2-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:
• Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL
Administer once weekly for 4 or 8 doses.
• Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL
Administer once weekly for 4 doses.
• Previously Untreated, Follicular, CD20-Positive, B-Cell NHL
Administer on Day 1 of each cycle of chemotherapy, for up to 8 doses. In patients with complete or partial response, initiate Rituxim® maintenance eight weeks following completion of a rituximab product in combination with chemotherapy. Administer Rituxim® as a single-agent every 8 weeks for 12 doses.
• Non-progressing, Low-Grade, CD20-Positive, B-Cell NHL, after first line CVP chemotherapy
Following completion of 6−8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses.
• Diffuse Large B-Cell NHL
Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions.

3-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).

4-Recommended Dose as a Component of Zevalin® for treatment of NHL
When used as part of the Zevalin therapeutic regimen, infuse 250 mg/m^2 in accordance with the Zevalin package insert. Refer to the Zevalin package insert for full prescribing information regarding the Zevalin therapeutic regimen.

5-Recommended Dose for Rheumatoid Arthritis (RA)
•Administer Rituxim® as two-1000 mg intravenous infusions separated by 2 weeks.
•Glucocorticoids administered as methylprednisolone 100 mg intravenous or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion-related reactions.
•Subsequent courses should be administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks.
•Rituxim is given in combination with methotrexate.

6-Recommended Dose for Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)Induction Treatment of Adult Patients with Active GPA/MPA
•Administer Rituxim® as a 375 mg/m^2 intravenous infusion once weekly for 4 weeks for patients with active GPA or MPA.
•Glucocorticoids administered as methylprednisolone 1000 mg intravenously per day for 1 to 3 days followed by oral prednisone as per clinical practice. This regimen should begin within 14 days prior to or with the initiation of Rituxim® and may continue during and after the 4 week induction course of Rituxim® treatment.

Follow up Treatment of Adult Patients with GPA/MPA who have achieved disease control with induction treatment
•Administer Rituxim® as two 500 mg intravenous infusions separated by two weeks, followed by a 500 mg intravenous infusion every 6 months thereafter based on clinical evaluation. If induction treatment of active disease was with a rituximab product, initiate follow up treatment with Rituxim® within 24 weeks after the last induction infusion with a rituximab product or based on clinical evaluation, but no sooner than 16 weeks after the last induction infusion with a rituximab product.
•If induction treatment of active disease was with other standard of care immunosuppressants, initiate Rituxim® follow up treatment within the 4 week period that follows achievement of disease control. Induction treatment of Pediatric Patients with Active GPA/MPA.
•Administer Rituxim® as a 375 mg/m^{2}intravenous infusion once weekly for 4 weeks.
•Prior to the first Rituxim® infusion, administer intravenous methylprednisolone 30 mg/kg (not to exceed 1g/day) once daily for 3 days.
•Following intravenous methylprednisolone administration, oral steroids should be continued per clinical practice.

Follow up Treatment of Pediatric Patients with GPA/MPA who have achieved disease control with induction treatment
•Administer Rituxim® as two 250 mg/m^2 intravenous infusions separated by two weeks, followed by a 250 mg/m^2 intravenous infusion every 6 months thereafter based on clinical evaluation.
•If induction treatment of active disease was with a rituximab product, initiate follow up treatment with Rituxim® within 24 weeks after the last induction infusion with a rituximab product or based on clinical evaluation, but no sooner than 16 weeks after the last induction infusion with a rituximab product.
•If induction treatment of active disease was with other standard of care immunosuppressants, initiate Rituxim® follow up treatment within the 4 week period following achievement of disease control.

7-Recommended Dose for Pemphigus Vulgaris (PV)
•Administer Rituxim® as two-1000 mg intravenous infusions separated by 2 weeks in combination with a tapering course of glucocorticoids.
•Maintenance treatment Administer Rituxim® as a 500 mg intravenous infusion at Month 12 and every 6 months thereafter or based on clinical evaluation.
•Treatment of relapse Administer Rituxim® as a 1000 mg intravenous infusion on relapse, and consider resuming or increasing the glucocorticoid dose based on clinical evaluation. Subsequent infusions of Rituxim® may be administered no sooner than 16 weeks following the previous infusion.

8-Recommended Dose for Premedication and Prophylactic Medications
Premedicate with acetaminophen and an antihistamine before each infusion of Rituxim®. For patients administered Rituxim® according to the 90-minute infusion rate, the glucocorticoid component of their chemotherapy regimen should be administered prior to infusion.
For RA, GPA and MPA, and PV patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion.
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 Rituxim® infusion. PCP prophylaxis should be considered for patients with PV during and following Rituxim® treatment.

Dosage adjustment (Renal/Hepatic impairment, elderly etc.)
No dosage adjustment required.

Administration and Storage
Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Rituxim® should be a clear to opalescent, colorless to pale yellow solution. Do not use vial if particulates or discoloration is present.

Administration
Withdraw the necessary amount of Rituxim® 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 Injection, 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.

Storage
Diluted Rituxim® solutions for infusion may be stored at 2°C to 8°C (36°F to 46°F) for 24 hours. Diluted Rituxim® solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since Rituxim® solutions do not contain a preservative, diluted solutions should be stored refrigerated (2°C to 8°C). No incompatibilities between Rituxim® and polyvinylchloride or polyethylene bags have been observed.

CONTRAINDICATIONS
Contraindications for use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia
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, granulomatosis with polyangiitis and microscopic polyangiitis
Hypersensitivity to the active substance or to murine proteins, or to any of the other excipients listed.
Active, severe infections
Patients in a severely immunocompromised state.
Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease.

WARNING AND PRECAUTIONS

Infusion-Related Reactions
Rituximab products can cause severe, including fatal, infusion-related reactions. Severe reactions typically occurred during the first infusion with time to onset of 30−120 minutes.
Rituximab product-induced infusion-related 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. Institute medical management (e.g. glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion-related reactions as needed. Depending on the severity of the infusion-related reaction and the required interventions, temporarily or permanently discontinue Rituxim®. 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 products. 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 Rituxim® in patients who experience a severe mucocutaneous reaction. The safety of re-administration of rituximab products to patients with severe mucocutaneous reactions has not been determined.

Hepatitis B Virus (HBV) 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 products. 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 levels 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 Rituxim®. 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 Rituxim® 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 Rituxim® therapy. HBV reactivation has been reported up to 24 months following completion of rituximab therapy.
In patients who develop reactivation of HBV while on Rituxim®, immediately discontinue Rituxim® and any concomitant chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming Rituxim® treatment in patients who develop HBV reactivation. Resumption of

Rituxim® treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing HBV.

Progressive Multifocal Leukoencephalopathy (PML)
JC virus infection resulting in PML and death can occur in rituximab product-treated patients with hematologic malignancies. 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. 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 Rituxim® 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, sometimes fatal, can occur within 12−24 hours after the first infusion of rituximab products in patients with NHL.A high number of circulating malignant cells (≥25,000/mm3) 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 product-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 Rituxim® for serious infections and institute appropriate anti-infective therapy.Rituxim® is not recommended for use in patients with severe, active infections.

Cardiovascular Adverse Reactions
Cardiac adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock may occur in patients receiving rituximab products. Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of Rituxim® for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina.

Renal Toxicity
Severe, including fatal, renal toxicity can occur after rituximab product 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 Rituxim® is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue Rituxim® 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 products in combination with chemotherapy. In post marketing 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 product therapy has not been studied and vaccination with live virus vaccines is not recommended before or during treatment.
For patients treated with Rituxim®, physicians should review the patient's vaccination status and patients should, if possible, be brought up-to-date with all immunizations in agreement with current immunization guidelines prior to initiating Rituxim® and administer non live vaccines at least 4 weeks prior to a course of Rituxim®.

Embryo-Fetal Toxicity
Based on human data, rituximab products can cause fetal harm due to B-cell lymphocytopenia in infants exposed in-utero. Advise pregnant women of the risk to a fetus. Females of childbearing potential should use effective contraception while receiving Rituxim® and for 12 months following the last dose of Rituxim®.

Concomitant Use with Other Biologic Agents and DMARDS other than Methotrexate in RA, GPA and MPA, PV
Limited data are available on the safety of the use of biologic agents or disease modifying antirheumatic drugs (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 of concomitant immunosuppressants other than corticosteroids has not been studied in GPA or MPA or PV patients exhibiting peripheral B-cell depletion following treatment with Rituxim®.

Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis Factor (TNF) Antagonists
While the efficacy of Rituxim® 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 Rituxim® in patients with RA who have not had prior inadequate response to one or more TNF antagonists is not recommended.

Effects on ability to drive and use machines
Rituximab may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of rituximab.

ADVERSE REACTIONS

Infections and infestations
Very Common: Bacterial infections, viral infections, bronchitis
Common: Sepsis, pneumonia, febrile infection, herpes zoster, respiratory tract infection, fungal infections, infections of unknown aetiology, acute bronchitis, sinusitis, hepatitis B1
Rare: Serious viral infection, Pneumocystis jirovecii
Very Rare: PML

Blood and lymphatic system disorders
Very Common: Neutropenia, leucopenia, febrile neutropenia, thrombocytopenia
Common: Anaemia, pancytopenia, granulocytopenia
Uncommon: Coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy
Very Rare: Transient increase in serum IgM levels
Not known: Late neutropenia

Immune system disorders
Very Common: Infusion related reactions, angioedema
Common: Hypersensitivity
Rare: Anaphylaxis
Very Rare: Tumour lysis syndrome, cytokine release syndrome, serum sickness
Not known: Infusion-related acute reversible thrombocytopenia

Metabolism and nutrition disorders
Common: Hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia

Psychiatric disorders
Uncommon: Depression, nervousness

Nervous system disorders
Common: Paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety
Uncommon: Dysgeusia
Very Rare: Peripheral neuropathy, facial nerve palsy
Not known: Cranial neuropathy, loss of other senses

Eye disorders
Common: Lacrimation disorder, conjunctivitis
Very Rare: Severe vision loss

Ear and labyrinth disorders
Common: Tinnitus, ear pain
Not known: Hearing loss

Cardiac disorders
Common: Myocardial infarction and arrhythmia, atrial fibrillation, tachycardia, cardiac disorder
Uncommon: Left ventricular failure, supraventricular tachycardia, ventricular tachycardia, angina, myocardial ischaemia, bradycardia
Rare: Severe cardiac disorders
Very Rare: Heart failure

Vascular disorders
Common: Hypertension, orthostatic hypotension, hypotension
Very Rare: Vasculitis (predominately cutaneous), leukocytoclastic vasculitis

Respiratory, thoracic and mediastinal disorders
Common: Bronchospasm, respiratory disease, chest pain, dyspnoea, increased cough, rhinitis
Uncommon: Asthma, bronchiolitis obliterans, lung disorder, hypoxia
Rare: Interstitial lung disease
Very Rare: Respiratory failure
Not known: Lung infiltration

Gastrointestinal disorders
Very Common: Nausea
Common: Vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation
Uncommon: Abdominal enlargement
Very Rare: Gastro-intestinal perforation

Skin and subcutaneous tissue disorders
Very Common: Pruritis, rash, alopecia
Common: Urticaria, sweating, night sweats, skin disorder
Very Rare: Severe bullous skin reactions, Stevens - Johnson syndrome toxic epidermal necrolysis (Lyell's Syndrome)

Musculoskeletal and connective tissue disorders
Common: Hypertonia, myalgia, arthralgia, back pain, neck pain, pain

Renal and urinary disorders
Very Rare: Renal failure

General disorders and administration site conditions
Very Common: Fever , chills, asthenia, headache
Common: Tumour pain, flushing, malaise, cold syndrome, fatigue, shivering, multi-organ failure
Uncommon: Infusion site pain

Investigations
Very Common: Decreased IgG levels

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

USE IN SPECIAL POPULATIONS

Pregnancy

Women of childbearing potential / Contraception in females
Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with Rituxim®.

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

Breast-feeding
Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breast-feed while treated with Rituxim® and for 12 months following Rituxim® treatment.

Fertility
Animal studies did not reveal deleterious effects of rituximab on reproductive organs.

Pediatrics
Rituxim® is not indicated in pediatric patients less than 2 years of age with GPA or MPA. The safety and effectiveness of Rituxim® have not been established in pediatric patients with NHL, CLL, PV, or RA.

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

OVER DOSAGE
Limited experience with doses higher than the approved dose of intravenous rituximab formulation is available from clinical trials in humans. The highest intravenous dose of rituximab tested in humans to date is 5,000 mg (2,250 mg/m²), tested in a dose escalation study in patients with chronic lymphocytic leukaemia. No additional safety signals were identified.
Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.
In the post-marketing setting five cases of rituximab overdose have been reported. Three cases had no reported adverse event. The two adverse events that were reported were flu-like symptoms, with a dose of 1.8 g of rituximab and fatal respiratory failure, with a dose of 2 g of rituximab.

PRESENTATION
One vial of Rituxim® 500/50ml.
Two vials of Rituxim® 100/10ml.

INSTRUCTIONS
Do not freeze. Store at 2–8°C.
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.

For suspected adverse drug reaction, email us at reports@pharmevo.biz
For more information on our products call PharmAssist helpline 0800-82222 Monday to Friday 9:00 am to 6:00 pm or email us at : pharmassist@pharmevo.biz

ہدایات:
دوا کو جمنے سے بچائیں ۔
دوا کو ۲ °C سے ۸ °C پر رکھیں ۔
ڈاکٹر کی ہدایات کے مطابق استعمال کریں ۔
تمام دوائیں بچوں کی پہنچ سے دُور رکھیں ۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کی جائے ۔
روشنی، گرمی اور نمی سے محفوظ رکھیں ۔

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