Rilast® 100 500

[Rituximab]

100mg /10mL, 500mg /50mL

Concentrate for solution for Injection

ریلاسٹ ۱۰۰ ۵۰۰

(ریٹوکسی میب) انجکشن

۱۰۰ ملی گرام/ ۱۰ ملی لیٹر ۵۰۰ ملی گرام/ ۵۰ ملی لیٹر

WARNING: FATAL INFUSION REACTIONS, TUMOR LYSIS SYNDROME (TLS), SEVERE MUCOCUTANEOUS REACTIONS, and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

Infusion Reactions: Rituximab administration can result in serious, 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. Carefully monitor patients during infusions. Discontinue Rituximab infusion and provide medical treatment for Grade 3 or 4 infusion reactions.

Tumor Lysis Syndrome (TLS) Acute renal failure requiring dialysis with instances of fatal outcome can occur in the setting of TLS following treatment of non-Hodgkin's lymphoma (NHL) with Rituximab monotherapy.

Severe Mucocutaneous Reactions

Severe, including fatal, mucocutaneous reactions can occur in patients receiving Rituximab.

Progressive Multifocal Leukoencephalopathy (PML)

JC virus infection resulting in PML and death can occur in patients receiving Rituximab.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Rilast® 100 (concentrate for solution for infusion)
Each 10mL vial contains:
Rituximab (rDNA origin).....100mg
Innovator's Specs.

Rilast® 500 (concentrate for solution for infusion)
Each 50mL vial contains:
Rituximab (rDNA origin).....500mg
Innovator's Specs.

DESCRIPTION

Rilast® (Rituximab) is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. after dilution. Rilast® (Rituximab) is a sterile, clear, colourless, preservative-free liquid concentrate for intravenous administration.

INDICATIONS AND USAGE

Non–Hodgkin's Lymphoma (NHL)

Rituximab is indicated for the treatment of 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 CVP chemotherapy
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent, after first-line CVP chemotherapy
- Previously untreated diffuse large B-cell, CD20-positive NHL in com-

bination with CHOP or other anthracycline-based chemotherapy regimens

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.

Rheumatoid Arthritis (RA)

Rituximab 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.

Limitations of Use

Rituximab is not recommended for use in patients with severe, active infections.

DOSAGE AND ADMINISTRATION

Administration

DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Premedicate before each infusion.

Administer only as an intravenous (IV) infusion.

- 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: 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.
- Interrupt the infusion or slow the infusion rate for infusion. 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/m2 as an IV 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 CVP chemotherapy, for up to 8 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.

Recommended Dose for Chronic Lymphocytic Leukemia (CLL)

The recommended dose is

- 375mg/m2 the day prior to the initiation of FC chemotherapy, then 500 mg/m2 79 on Day 1 of cycles 2-6 (every 28 days).

Recommended Dose for Rheumatoid Arthritis (RA)

- Administer Rituximab as two-1000 mg intravenous infusions separated by 2 weeks
- Glucocorticoids administered as methylprednisolone 100 mg intra-

venous or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion reactions.

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

Recommended Concomitant Medications

Premedicate before each infusion with acetaminophen and an antihistamine.

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

Pneumocystis jiroveci pneumonia (PCP) and anti-herpetic viral prophylaxis is recommended for patients with CLL during treatment and for up to 12 months following treatment as appropriate

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 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.

USE IN SPECIFIC POPULATIONS

Pregnancy

Category C: There are no adequate and well-controlled studies of rituximab in pregnant women. Post marketing 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 and moderate-severe rheumatoid arthritis are serious conditions that require 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 Rituximab should be weighed against the known benefits of breastfeeding. **Pediatric Use:** FDA has not required pediatric studies in polyarticular juvenile idiopathic arthritis (PJIA) patients ages 0 to 16 due to concerns regarding the potential for prolonged immunosuppression as a result of B cell depletion in the developing juvenile immune system. The safety and effectiveness of Rituximab in pediatric patients have not been established.

Geriatric Use

Diffuse Large B-Cell NHL

Among patients with DLBCL evaluated in three randomized, active-controlled trials, 927 patients received Rituximab in combination

with chemotherapy. Of these, 396 (43%) were age 65 or greater and 123 (13%) were age 75 or greater. 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: 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.

Chronic Lymphocytic Leukemia: Among patients with CLL evaluated in two randomized active-controlled trials, 243 of 676 Rituximab-treated patients (36%) were 65 years of age or older; of these, 100 Rituximab-treated patients (15%) were 70 years of age or older.

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 kD 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 recruit's 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. **Pharmacodynamics:** In NHL patients, administration of Rituximab resulted in depletion of circulating and tissue-based B cells. Among 166 patients in Study 1, circulating CD19-positive B cells were depleted within the first three weeks with sustained depletion for up to 6 to 9 months posttreatment 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. 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. **Pharmacokinetics:** 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 375mg/m2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone. Based on a population pharmacokinetic analysis of data 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 pre-treatment had a higher clearance. However, dose adjustment for pre-treatment 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 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). 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 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. The pharmacokinetics of rituximab have not been studied in children and adolescents. No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of rituximab.

CONTRAINDICATIONS

None.

OVERDOSAGE

There has been no experience with overdosage in human clinical

trials. Single doses of up to 500 mg/m2 have been administered in clinical trials.

ADVERSE REACTIONS

Infusion reactions, Tumor lysis syndrome, Mucocutaneous reactions, Progressive multifocal leukoencephalopathy, Hepatitis B reactivation with fulminant hepatitis, Infections, Cardiac arrhythmias, Renal toxicity, Bowel obstruction and perforation. The most common adverse reactions of Rituximab (incidence ≥ 25%) observed in clinical trials of patients with NHL were infusion reactions, fever, lymphopenia, chills, infection, and asthenia. The most common adverse reactions of Rituximab (incidence ≥ 25%) observed in clinical trials of patients with CLL were: infusion reactions and neutropenia.

WARNINGS AND PRECAUTIONS

Infusion Reactions: Rituximab can cause severe, including fatal, infusion reactions. Severe reactions typically occurred during the first infusion with time to onset of 30–120 minutes. Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death. Premedicate patients with an antihistamine and acetaminophen prior to dosing. For RA patients, methylprednisolone 100 mg IV 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/mm3) **Tumor Lysis Syndrome (TLS):** Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12–24 hours after 6 of 35 the first infusion of Rituximab 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. **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 varied from 1–13 weeks following 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. **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. **Hepatitis B Virus (HBV) Reactivation:** Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death can occur in patients with hematologic malignancies treated with Rituximab. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of Rituximab and approximately one month after the last dose. Screen patients at high risk of HBV infection before initiation of Rituximab. Closely monitor carriers of hepatitis B for clinical and laboratory signs of active HBV infection for several months following Rituximab therapy. Discontinue Rituximab and any concomitant chemotherapy in patients who develop viral hepatitis, and institute appropriate treatment including antiviral therapy. Insufficient data exist regarding the safety of resuming Rituximab in patients who develop hepatitis subsequent to HBV reactivation. **Infections:** Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and up to one year following the completion of Rituximab-based therapy. 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 antiinfective 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. Perform a thorough diagnostic evaluation and institute appropriate treatment for complaints of abdominal pain. **Immunization:** The safety of immunization with live viral vaccines following Rituximab therapy has not been studied and vaccination with live virus vaccines is not recommended. For RA patients, physicians should follow current immunization guidelines and administer non-live vaccines at least 4 weeks prior to a course of Rituximab. The effect of Rituximab on immune responses was assessed in a randomized, controlled study in patients with RA treated with Rituximab and methotrexate (MTX) compared to patients treated with MTX alone. A response to pneumococcal vaccination (a T-cell independent antigen) as measured by an increase in antibody titers to at least 6 of 12 serotypes was lower in patients treated with Rituximab plus MTX as compared to patients treated with MTX alone

(19% vs. 61%). A lower proportion of patients in the Rituximab plus MTX group developed detectable levels of anti-keyhole limpet hemocyanin antibodies (a novel protein antigen) after vaccination compared to patients on MTX alone (47% vs. 93%). A positive response to tetanus toxoid vaccine (a T-cell dependent antigen with existing immunity) was similar in patients treated with Rituximab plus MTX compared to patients on MTX alone (39% vs. 42%). The proportion of patients maintaining a positive Candida skin test (to evaluate delayed type hypersensitivity) was also similar (77% of patients on Rituximab plus MTX vs. 70% of patients on MTX alone). Most patients in the Rituximab-treated group had B-cell counts below the lower limit of normal at the time of immunization. The clinical implications of these findings are not known. **Laboratory Monitoring:** In patients with lymphoid malignancies, during treatment with Rituximab monotherapy, obtain complete blood counts (CBC) and platelet counts prior to each Rituximab course. During treatment with Rituximab and chemotherapy, obtain CBC and platelet counts at weekly to monthly intervals and more frequently in patients who develop cytopenia's. In patients with RA obtain CBC and platelet counts at two to four-month intervals during Rituximab therapy.

DOSAGE

As directed by the physician.

INSTRUCTIONS

Store between 2°C-8°C. Do not freeze or shake. Protect from sunlight and heat. Keep all medicines out of the reach of children.

خوراک: معالج کی ہدایت کے مطابق استعمال کریں۔

ہدایات: ۲ سے ۸ ڈگری سینٹی گریڈ پر رکھیں۔ منجمد ہونے سے بچائیں۔
سورج کی روشنی اور گرمی سے محفوظ رکھیں۔ صرف وریدی استعمال کیلئے۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

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