Rituximab INN

RITURIS

COMPOSITION:

RITURIS 100 Concentrated Solution for IV Infusion: Each single use vial contains Rituximab INN 100 mg as 10 ml concentrated solution for IV infusion.

RITURIS 500 Concentrated Solution for IV Infusion: Each single use vial contains Rituximab INN 500 mg as 50 ml concentrated solution for IV infusion.

CLINICAL PHARMACOLOGY:

Rituximab is a human monoclonal antibody that binds specifically to the transmembrane antigen CD20. This antigen is located on pre-B and mature B lymphocytes, but not on hemopoietic stem cells, pro-B cells, normal plasma cells, or other normal tissue. Rituximab binds to the CD20 antigen on B lymphocytes and initiates immunologic reactions that mediate B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC), and induction of apoptosis.

INDICATIONS:

RITURIS is indicated for the treatment of patients with:

Non-Hodgkin's Lymphoma:

- Patients with CD20 positive diffuse large B-cell non-Hodgkin's lymphoma (DLCL) in combination with CHOP chemotherapy.
- Previously untreated patients with stage III-IV follicular lymphoma in combination with CVP chemotherapy.
- Patients with relapsed or chemoresistant indolent B-cell non-Hodgkin's lymphomas.

RITURIS maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

Chronic Lymphocytic Leukaemia:

RITURIS 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:

RITURIS in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to one or more tumour necrosis factor (TNF) inhibitor therapies.

DOSAGE & ADMINISTRATION:

RITURIS should be administered under the close supervision of an experienced physician. RITURIS should be administered as an IV infusion through a dedicated line. The prepared infusion solution must not be administered as an IV injection or bolus infusion.

Premedication and Prophylactic Medications:

Premedication consisting of an analgesic/anti-pyretic and an antihistaminic drug should always be given before each administration of RITURIS. Premedication with glucocorticoids should be considered if RITURIS is not given in combination with glucocorticoid-containing chemotherapy for treatment of non-Hodgkin's lymphoma. Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm and hypoxia should have the infusion interrupted immediately. The patient should then be evaluated for evidence of tumour lysis syndrome and the infusion should not be restarted until complete resolution of all symptoms. 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. Mild or moderate infusion-related reactions are supposed to respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.

Intravenous Infusion Rate:

First intravenous infusion- The recommended initial infusion rate is 50 mg/h; subsequently, the rate can be escalated in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h. ***Subsequent intravenous infusions-*** Subsequent infusions of **RITURIS** can be started at a rate of 100 mg/h and increased by 100 mg/h increments every 30 minutes to a maximum of 400 mg/h.

Low-grade or follicular non-Hodgkin's lymphoma:

Initial monotherapy: The recommended dosage of **RITURIS** monotherapy for adult patients is 375 mg/m^2, administered as an IV infusion once weekly for 4 weeks.

Initial combination therapy: The recommended dosage of **RITURIS** in combination with CVP chemotherapy is 375 mg/m^2 for 8 cycles (21 days/cycle), administered on day 1 of each chemotherapy cycle after IV administration of the corticosteroid component of CVP. Rituximab has shown acceptable safety in combination with other chemotherapies.

Re-treatment following relapse: Patients who have responded to **RITURIS** initially will have to be treated again with at a dose of 375 mg/m^2, administered as an IV infusion once weekly for 4 weeks.

Maintenance treatment for Previously untreated follicular lymphoma: The recommended dose of **RITURIS** used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 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.

Maintenance treatment for Relapsed/refractory follicular lymphoma: Patients who have responded to induction treatment may receive maintenance therapy with **RITURIS** given at 375 mg/m^2 once every 3 months until disease progression or for a maximum period of two years.

Diffuse Large B-cell Non-Hodgkin's Lymphoma:

RITURIS should be used in combination with CHOP chemotherapy. The recommended dosage is 375 mg/m^2, administered on day 1 of each chemotherapy cycle after IV administration of the corticosteroid component of CHOP.

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 >25x109/L it is recommended to administer prednisone/prednisolone 100 mg IV shortly before infusion with **RITURIS** to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

The recommended dosage of RITURIS for CLL is 375 mg/m^2 in the first cycle and 500 mg/m^2 in cycles 2-6, in combination with FC, administered every 28 days.

Rheumatoid arthritis:

The recommended dosage of **RITURIS** is 1000 mg by IV infusion followed two weeks later by the second 1000 mg IV infusion. Patients may receive further courses of treatment, based on signs and symptoms of disease.

INSTRUCTION FOR ADMINISTRATION:

Use sterile needle and syringe to withdraw the required amount of **RITURIS** under aseptic conditions and dilute to a calculated rituximab concentration of 1-4 mg/ml in an infusion bag containing sterile, non-pyrogenic, 0.9% aqueous saline solution or 5% aqueous dextrose solution. To mix the solution, gently invert the bag to avoid foaming. Parenteral medications should be inspected visually for particulate matter or discoloration prior to administration.

Prepared infusion solution of **RITURIS** is stable for 12 hours at room temperature. If necessary, the prepared solutions may be stored in the refrigerator at 2-8°C for up to 24 hours if dilution has taken place in controlled and validated aseptic conditions.

CONTRAINDICATIONS:

Contraindicated in patients with known hypersensitivity to rituximab.

ADVERSE EFFECTS:

The most frequent reported or observed serious adverse drug reactions are Infusion-related reactions (including cytokine-release syndrome, tumour-lysis syndrome), Infections, Cardiovascular events. Other serious adverse drug reactions include hepatitis B reactivation and PML.

PRECAUTIONS:

Pregnancy: Rituximab should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Nursing mothers: Rituximab should not be administered to nursing mothers.

Pediatric use: The safety and efficacy of Rituximab in children and adolescents (<18 years) have not been established.

Geriatric Use: No dose adjustment is required in patients aged ≥65 years of age.

Hepatic and Renal Insufficiency: The safety and efficacy of renal and hepatic impairment in Rituximab patients has not been established.

DRUG INTERACTIONS:

In CLL patients, co-administration with Rituximab IV 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 IV in rheumatoid arthritis patients.

OVERDOSE:

Reported adverse events caused flu-like symptoms with a dose of 1.8 g of rituximab and fatal respiratory failure with a dose of 2 g of rituximab.

STORAGE:

Store at 2°C to 8°C, protected from light. Keep out of the reach of children.

PRESENTATION:

RITURIS 100 Concentrated Solution for IV Infusion: Each box contains 1 single use vial of Rituximab 100 mg.

RITURIS 500 Concentrated Solution for IV Infusion: Each box contains 1 single use vial of Rituximab 500 mg.

Manufactured by:
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