Recelbia®

Rituximab INN

Composition

Recelbia® 100 Injection: Each vial contains Rituximab INN 100 mg.
Recelbia® 500 Injection: Each vial contains Rituximab INN 500 mg.

Description

The Rituximab antibody is a genetically engineered chimeric murine/human monoclonal antibody. It is directed against the CD20 antigen which found on the surface of normal and malignant B lymphocytes. The antibody is an IgG kappa immunoglobulin containing murine light- and heavy chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen approximately 8.0 nM. Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration.

Clinical pharmacology

General

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 also expressed on > 90% of Bcell non-Hodgkin is lymphomas (NHL), but 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.

Preclinical Pharmacology and Toxicology

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.

Pharmacokinetics:

In patients 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 naive to Rituximab. The mean Cmax 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 non-responders; 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. The mean Cmax after 8 infusions was 550 µg/mL (range, 171 to 1177 µg/mL). The mean Cmax increased with each successive infusion through the eighth infusion. 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. 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 who had received single doses of Rituximab >100 mg/m^2. Among the 166 patients in the pivotal 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.

Indications and usage

Recelbia® is indicated for the treatment of

Non-Hodgkin's Lymphoma (NHL)

• 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 linechemotherapy and, in patients achieving a complete or partial response to Recelbia® incombination with chemotherapy, as single-agent maintenance therapy.
• Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a singleagent after first-line CVP chemotherapy
• Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens

Chronic Lymphocytic Leukemia (CLL)

In combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

Rheumatoid Arthritis (RA)

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.

Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

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

Dosage and administration

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 Recelbia® maintenance eight weeks following completion of Recelbia® in combination with chemotherapy.
Administer Recelbia® 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.

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 Day1 of cycles 2-6 (every 28 days).

Recommended Dose as a Component of ibritumomab tiuxetan

Infuse rituximab 250 mg/m^2 within 4 hours prior to the administration of Indium-111-(In-111-) ibritumomab tiuxetan and within 4 hours prior to the administration of Yttrium-90- (Y-90-) ibritumomab tiuxetan. Administer Recelbia® and In-111- ibritumomab tiuxetan 7-9 days prior to Recelbia® and Y-90- ibritumomab tiuxetan.

Rheumatoid Arthritis (RA)

The recommended dose of RA in combination with methotrexate is two-1000 mg intravenous infusions separated by 2 weeks every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks. Methylprednisolone 100 mg intravenous or its equivalent glucocorticoid is recommended 30 minutes prior to each infusion

Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

Administer Recelbia® as a 375 mg/m^2 intravenous infusion once weekly for 4 weeks.

Instructions for Administration

Preparation for Administration: Withdraw the necessary amount of Recelbia® 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. Recelbia® solutions for infusion may be stored at
2-8^{o}C (36-46^{o}F) for 24 hours. Recelbia® solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since Recelbia® solutions do not contain a preservative, diluted solutions should be stored refrigerated (2^{o}C-8^{o}C). No incompatibilities between Recelbia® and polyvinylchloride or polyethylene bags have been observed.

Do not administer as an intravenous push or bolus

Infusion and hypersensitivity reactions may occur. Premedication consisting of acetaminophen and diphenhydramine should be considered before each infusion of Rituximab. Premedication may attenuate infusion reactions. Since transient hypotension may occur during Rituximab infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to Rituximab infusion.
First Infusion: The Recelbia® solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Recelbia® should not be mixed or diluted with other drugs. If hypersensitivity or infusion reactions do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If a hypersensitivity (non-IgEmediated) or an infusion reaction develops, the infusion should be temporarily slowed or interrupted. The infusion can continue at one-half the previous rate upon improvement of patient symptoms.
Subsequent Infusions: If the patient tolerated the first infusion well, subsequent Recelbia® infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated. If the patient did not tolerate the first infusion well, follow the guidelines under First Infusion.

Contraindications

Recelbia® is contraindicated in patients with known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or to any component of this product.

Warnings

Severe infusion reactions: Rituximab has common 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 sequelae include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. In the reported cases, the following factors were more frequently associated with fatal outcomes: female gender, pulmonary infiltrates, and chronic lymphocytic leukemia or mantle cell lymphoma.
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) after 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.

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. The risks of TLS appear to be greater in patients with high numbers of circulating malignant cells (>25,000/mm^3) or high tumor burden. Prophylaxis for TLS should be considered for patients at high risk. 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.

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. Rituximab infusion should be interrupted for severe hypersensitivity reactions and can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Treatment of these symptoms with diphenhydramine and acetaminophen is recommended; additional treatment with bronchodilators or IV saline may be indicated. In most cases, patients who have experienced non-life-threatening hypersensitivity reactions have been able to complete the full course of therapy. 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.

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. Patients with pre-existing cardiac conditions including arrhythmias and angina have had recurrences of these events during Rituximab therapy and should be monitored throughout the infusion and immediate post-infusion period.

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. Renal toxicity has occurred in patients with high numbers of circulating malignant cells (> 25,000/mm^3) or high tumor burden who experience tumor lysis syndrome and in patients administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and Rituximab is not an approved treatment regimen. If this combination is used in clinical trials extreme caution should be exercised; patients should be monitored closely for signs of renal failure. Discontinuation of

Rituximab should be considered for those with rising serum creatinine or oliguria.

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. Patients experiencing a severe mucocutaneous reaction should not receive any further infusions and seek prompt medical evaluation. Skin biopsy may help to distinguish among different mucocutaneous reactions and guide subsequent treatment. The safety of readministration of Rituximab to patients with any of these mucocutaneous reactions has not been determined.

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. 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 developed 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.

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.

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 Recelbia® 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 Recelbia® is excreted in human milk. Because human IgG is excreted in human milk and the potential for absorption and immunosuppressant in the infant is unknown, women should be advised to discontinue nursing until circulating drug levels are no longer detectable.

Pediatric Use: The safety and effectiveness of Recelbia® in pediatric patients have not been established.

Adverse reactions

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.

Risk Factors Associated with Increased Rates of Adverse Events:

Administration of Rituximab weekly for 8 doses resulted in higher rates of (Grade 3 and 4) adverse events overall (70%) compared with administration weekly for 4 doses (57%). The incidence of Grade 3 or 4 adverse events was similar in patients retreated with Rituximab compared with initial treatment (58% and 57%, respectively). The incidence of the following clinically significant adverse events was higher in patients with bulky disease (lesions >_10 cm) (N = 39) versus patients with lesions < 10 cm (N = 195): abdominal pain, anemia, dyspnea, hypotension, and neutropenia.

Infusion Reactions: Mild to moderate infusion reactions consisting of fever and chills/rigors occurred in the majority of patients during the first Rituximab infusion. Other frequent infusion reaction symptoms included nausea, pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and hypertension. These reactions generally occurred within 30 to 120 minutes of beginning the first infusion, and resolved with slowing or interruption of the Rituximab infusion and with supportive care (diphenhydramine, acetaminophen, IV saline, and vasopressors). In an analysis of data from 356 patients with relapsed or refractory, low-grade NHL who received 4 (N = 319) or 8 (N = 37) weekly infusions of Rituximab, the incidence of infusion reactions was highest during the first infusion (77%) and decreased with each subsequent infusion (30% with fourth infusion and 14% with eighth infusion).

Infectious Events: Rituximab induced B-cell depletion in 70% to 80% of patients and was associated with decreased serum immunoglobulins in a minority of patients; the lymphopenia lasted a median of 14 days (range, 1 to 588 days). Infectious events occurred in 31% of patients:

19% of patients had bacterial infections, 10% had viral infections, 1% had fungal infections, and 6% were unknown infections. Incidence is not additive because a single patient may have had more than one type of infection. Serious infectious events (Grade 3 or 4) including sepsis, occurred in 2% of patients.

Hematologic Events: In clinical trials, Grade 3 and 4 cytopenias were reported in 48% of patients treated with Recelbia®; these include: lymphopenia (40%), neutropenia (6%), leucopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following Rituximab therapy were reported. In addition, there have been a limited number of postmarketing reports of prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia (defined as occurring 40 days after the last dose of Rituximab) in patients with hematologic malignancies. In reported cases of late onset neutropenia (NCI-CTC Grade 3 and 4), the median duration of neutropenia was 10 days (range 3 to 148 days). Documented resolution of the neutropenia was described in approximately one-half of the reported cases; of those with documented recovery, approximately half received growth factor support. In the remaining cases, information on resolution was not provided. More than half of the reported cases of delayed onset neutropenia occurred in patients who had undergone a prior autologous bone marrow transplantation. In an adequately designed, controlled, clinical trial, the reported incidence of NCI-CTC Grade 3 and 4 neutropenia was higher in patients receiving Rituximab in combination with fludarabine as compared to those receiving fludarabine alone (76% [39/51] vs. 39% [21/53]).

Cardiac: Grade 3 or 4 cardiac-related events include hypotension. Rare, fatal cardiac failure with symptomatic onset weeks after Rituximab has also been reported. Patients who develop clinically significant cardiopulmonary events should have Rituximab infusion discontinued.

Pulmonary Events: 135 patients (38%) experienced pulmonary events in clinical trials. The most common respiratory system adverse events experienced were increased cough, rhinitis, bronchospasm, dyspnea, and sinusitis. In both clinical studies and post-marketing surveillance, there have been a limited number of reports of bronchiolitis obliterans presenting up to 6 months post- Rituximab infusion and a limited number of reports of pneumonitis (including interstitial pneumonitis) presenting up to 3 months post- Rituximab infusion, some of which resulted in fatal outcomes. The safety of resumption or continued administration of Rituximab in patients with pneumonitis or bronchiolitis obliterans is unknown.

Immune/Autoimmune Events: Immune/ autoimmune events have been reported, including uveitis, optic neuritis in a patient with systemic vasculitis, pleuritis in a patient with a lupuslike syndrome, serum sickness with polyarticular arthritis, and vasculitis with rash.

Less Commonly Observed Events: In clinical trials, < 5% and > 1% of the patients experienced the following events regardless of causality assessment: agitation, anorexia, arthritis, conjunctivitis, depression, dyspepsia, edema, hyperkinesia, hypertonia, hypesthesia, hypoglycemia, injection site pain, insomnia, lacrimation disorder, malaise, nervousness, neuritis, neuropathy, paresthesia, somnolence, vertigo, weight decrease.

Disposal

Rituximab is not considered as carcinogenic but as it is a biologic product the vials, syringe or used product must be disposed by putting in 0.5% sodium hupochloride solution and allow 30 minutes to be neutralized or safe for environment.

Overdosage

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

Storage condition

Store the vial in original carton at 2-8 ^{o}C. Protect from light.

Presentation & Packaging

Recelbia® 100 mg Injection: Each commercial box contains 1 vial of Rituximab INN 100 mg.

Recelbia® 500 mg Injection: Each commercial box contains 1 vial of Rituximab INN 500 mg.

Medicine: Keep out of reach of children

For further information, please contact: 01977 157 108
(9.00 am - 5.00 pm)

Healthcare

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