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RITUXAN®
(Rituximab)

WARNINGS

Fatal Infusion Reactions: Deaths within 24 hours of RITUXAN infusion have been reported. These fatal reactions followed an infusion reaction complex which included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. (See WARNINGS and ADVERSE REACTIONS.)

Patients who develop severe infusion reactions should have RITUXAN infusion discontinued and receive medical treatment.

Tumor Lysis Syndrome (TLS): Acute renal failure requiring dialysis with instances of fatal outcome has been reported in the setting of TLS following treatment with RITUXAN. (See WARNINGS.)

Severe Mucocutaneous Reactions: Severe mucocutaneous reactions, some with fatal outcome, have been reported in association with RITUXAN treatment. (See WARNINGS and ADVERSE REACTIONS.)

DESCRIPTION

The RITUXAN® (Rituximab) antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is an IgG_1 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 of approximately 8.0 nM.

The chimeric anti-CD20 antibody is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. The anti-CD20 antibody is purified by affinity and ion exchange chromatography. The purification process includes specific viral inactivation and removal procedures. Rituximab drug product is manufactured from bulk drug substance manufactured by Genentech, Inc. (US License No. 1048).

RITUXAN is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. RITUXAN is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for IV administration in 9 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Water for Injection. The pH is adjusted to 6.5.

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 (1,2). The antigen is also expressed on >90% of B-cell non-Hodgkin's lymphomas (NHL), (3) but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues (4). CD20 regulates an early step(s) in the activation process for cell cycle initiation and differentiation, (4) and possibly functions as a calcium ion channel (5). CD20 is not shed from the cell surface and does not internalize upon antibody binding (6). Free CD20 antigen is not found in the circulation (2).

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) (7) and antibody-dependent cell mediated cytotoxicity (ADCC). The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line (8).

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.

Human Pharmacokinetics/Pharmacodynamics

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 (9). 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 (10,11,12). 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.

RITUXAN 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 RITUXAN (12,13). The mean C_{max} following the fourth infusion was 486 µg/mL (range, 77.5 to 996.6 µg/mL). The peak and trough serum levels of Rituximab were inversely correlated with baseline values for the number of circulating CD20-positive B cells and measures of disease burden. Median steady-state serum levels were higher for responders compared with nonresponders; however, no difference was found in the rate of elimination as measured by serum half-life. Serum levels were higher in

patients with International Working Formulation (IWF) subtypes B, C, and D as compared with those with subtype A (10,13). Rituximab was detectable in the serum of patients 3 to 6 months after completion of treatment.

RITUXAN at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 8 doses to 37 patients (14). The mean C_{max} after 8 infusions was 550 µg/mL (range, 171 to 1177 µg/mL). The mean C_{max} increased with each successive infusion through the eighth infusion (Table 1).

Table 1
Rituximab C_{max} Values

Infusion Number	Mean C_{max} µg/mL	Range µg/mL
1	242.6	16.1–581.9
2	357.5	106.8–948.6
3	381.3	110.5–731.2
4	460.0	138.0–835.8
5	475.3	156.0–929.1
6	515.4	152.7–865.2
7	544.6	187.0–936.8
8	550.0	170.6–1177.0

The pharmacokinetic profile of RITUXAN when administered as 6 infusions of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with RITUXAN alone (15).

Administration of RITUXAN 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 $\geq$100 mg/m^2 (9). 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 (13). 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 nonresponding 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 (13).

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 (13).

CLINICAL STUDIES

Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell, NHL

RITUXAN regimens tested include treatment weekly for 4 doses and treatment weekly for 8 doses. Results for studies with a collective enrollment of 296 patients are summarized below (Table 2):

Table 2
Summary of RITUXAN Efficacy Data by Schedule and Clinical Setting
(See ADVERSE REACTIONS for Risk Factors Associated with Increased Rates of Adverse Events)

	Weekly × 4 N=166	Weekly × 8 N=37	Bulky disease, Weekly × 4 N=39[a]	Retreatment, Weekly × 4 N=60
Overall Response Rate	48%	57%	36%	38%
Complete Response Rate	6%	14%	3%	10%
Median Duration of Response[b, c, d] (Months) [Range]	11.2 [1.9 to 42.1+]	13.4 [2.5 to 36.5+]	6.9 [2.8 to 25.0+]	15.0 [3.0 to 25.1+]

[a] Six of these patients are included in the first column. Thus, data from 296 intent to treat patients are provided in this table.

[b] Kaplan-Meier projected with observed range.

[c] "+" indicates an ongoing response.

[d] Duration of response: interval from the onset of response to disease progression.

Weekly for 4 Doses

A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or refractory low-grade or follicular B-cell NHL who received 375 mg/m^2 of RITUXAN given as an IV infusion weekly for 4 doses (13). Patients with tumor masses >10 cm or with >5,000 lymphocytes/μL in the peripheral blood were excluded from the study. Results are summarized in Table 2. The median time to onset of response was 50 days and the median duration of response was 11.2 months (range, 1.9 to 42.1+). Disease-related signs and symptoms (including B-symptoms) were present in 23% (39/166) of patients at study entry and resolved in 64% (25/39) of those patients.

In a multivariate analysis, the ORR was higher in patients with IWF B, C, and D histologic subtypes as compared to IWF subtype A (58% vs. 12%), higher in patients whose largest lesion was <5 cm vs. >7 cm (maximum, 21 cm) in greatest diameter (53% vs. 38%), and higher in patients with chemosensitive relapse as compared with chemoresistant (defined as duration of response <3 months) relapse (53% vs. 36%). ORR in patients previously treated with autologous bone marrow transplant was 78% (18/23). The following adverse prognostic factors were *not* associated with a lower response rate: age ≥60 years, extranodal disease, prior anthracycline therapy, and bone marrow involvement.

Weekly for 8 Doses

In a multicenter, single-arm study, 37 patients with relapsed or refractory, low-grade NHL received 375 mg/m^2 of RITUXAN weekly for 8 doses. Results are summarized in Table 2. (see ADVERSE REACTIONS, Risk Factors Associated with Increased Rates of Adverse Events.)

Bulky Disease, Weekly for 4 Doses

In pooled data from multiple studies of RITUXAN, 39 patients with relapsed or refractory, bulky disease (single lesion >10 cm in diameter), low-grade NHL received 375 mg/m^2 of RITUXAN weekly for 4 doses. Results are summarized in Table 2 (15, 16). (For information on the

higher incidence of Grade 3 and 4 adverse events, see ADVERSE REACTIONS, Risk Factors Associated with Increased Rates of Adverse Events.)

Retreatment Weekly for 4 Doses

In a multi-center, single-arm study, 60 patients received 375 mg/m^2 of RITUXAN weekly for 4 doses (17). All patients had relapsed or refractory, low-grade or follicular B-cell NHL and had achieved an objective clinical response to RITUXAN administered 3.8–35.6 months (median 14.5 months) prior to retreatment with RITUXAN. Of these 60 patients, 55 received their second course of RITUXAN, 3 patients received their third course and 2 patients received their second and third courses of RITUXAN in this study. Results are summarized in Table 2.

Diffuse, Large B-Cell, NHL

The safety and effectiveness of RITUXAN were evaluated in three, randomized, active-controlled, open-label, multicenter studies with a collective enrollment of 1854 patients. Patients with previously untreated diffuse, large B-cell, NHL received RITUXAN in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

Study 1

A total of 632 patients aged ≥60 years with either B-cell NHL Grade F, G, or H by the International Working Formulation classification or DLBCL (including primary mediastinal B-cell lymphoma) in the REAL classification were randomized in a 1:1 ratio to treatment with CHOP or R-CHOP. Patients were given 6 or 8, 21 day cycles of CHOP. Patients in the R-CHOP arm also received 4 or 5 doses of RITUXAN 375 mg/m^2 on Days –7 and –3 (prior to Cycle 1), and 48 to 72 hours pre-Cycle 3, pre-Cycle 5, and pre-Cycle 7 for patients receiving 8 cycles of CHOP induction. The main outcome measure of the study was progression-free survival (PFS), defined as the time from randomization to the first of

progression, relapse or death. Responding patients underwent a second randomization to receive RITUXAN or no further therapy.

Among all enrolled patients, 62% had centrally confirmed DLBCL histology, 73% had Stage III–IV disease, 56% had IPI scores ≥2, 86% had ECOG performance status of <2, 57% had elevated LDH levels, and 30% had two or more extranodal disease sites involved. Efficacy results are presented in Table 3. These results reflect a statistical approach which allows for an evaluation of RITUXAN administered in the induction setting that excludes any potential impact of RITUXAN given after the second randomization.

Analysis of results after the second randomization in Study 1 demonstrates that for patients randomized to R-CHOP, additional RITUXAN exposure beyond induction was not associated with further improvements in progression free survival or overall survival.

Study 2

A total of 399 patients with DLBCL, aged ≥60 years, were randomized in a 1:1 ratio to receive CHOP or R-CHOP induction. All patients received up to 8, 3-week cycles of CHOP induction; patients in the R-CHOP arm received RITUXAN 375 mg/m^2 on Day 1 of each cycle. The main outcome measure of the study was event free survival (EFS), defined as the time from randomization to relapse, progression, change in therapy or death from any cause. Among all enrolled patients, 80% had stage III or IV disease, 60% of patients had an age-adjusted IPI ≥2, 80% had ECOG performance status scores <2, 66% had elevated LDH levels, and 52% had extranodal involvement in at least two sites. Efficacy results are presented in Table 3.

Study 3

A total of 823 patients with DLBCL, aged 18–60 years, were randomized in a 1:1 ratio to receive an anthracycline-containing chemotherapy alone or in combination with RITUXAN. The main outcome measure of the

study was time to treatment failure (TTF), defined as time from randomization to the earliest of progressive disease, failure to achieve a complete response, relapse or death. Among all enrolled patients, 28% had Stage III–IV disease, 100% had IPI scores of ≤1, 99% had ECOG performance status of <2, 29% had elevated LDH levels, 49% had bulky disease and 34% had extranodal involvement. Efficacy results are presented in Table 3.

Table 3
Efficacy Results in Studies 1, 2, and 3

	Study 1 (n=632)		Study 2 (n=399)		Study 3 (n=823)	
	CHOP	R-CHOP	CHOP	R-CHOP	Chemo	R-Chemo
Main outcome	Progression-free survival (years)		Event-free survival (years)		Time to treatment failure (years)	
Median of main outcome measure	1.6	3.1	1.1	2.9	NE[b]	NE[b]
Hazard ratio[d]	0.69[a]		0.60[a]		0.45[a]	
Overall survival at 2 years[c]	63%	74%	58%	69%	86%	95%
Hazard ratio[d]	0.72[a]		0.68[a]		0.40[a]	

[a] Significant at p<0.05, 2-sided.
[b] NE=Not reliably estimable.
[c] Kaplan-Meier estimates.
[d] R-CHOP vs. CHOP.

In Study 2, overall survival estimates at 5 years were 58% vs. 46% for R-CHOP and CHOP, respectively.

INDICATIONS AND USAGE

RITUXAN® (Rituximab) is indicated for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell, non-Hodgkin's lymphoma.

RITUXAN® (Rituximab) is indicated for the first-line treatment of diffuse large B-cell, CD20-positive, non-Hodgkin's lymphoma in combination with CHOP or other anthracycline-based chemotherapy regimens.

CONTRAINDICATIONS

RITUXAN is contraindicated in patients with known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or to any component of this product. (See WARNINGS.)

WARNINGS (See BOXED WARNINGS.)

Severe Infusion Reactions (see BOXED WARNINGS, ADVERSE REACTIONS, and Hypersensitivity Reactions)

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

Tumor Lysis Syndrome [TLS] (See BOXED WARNINGS and ADVERSE REACTIONS)

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 RITUXAN infusion. Rare instances of fatal outcome have been reported in the setting of TLS following treatment with RITUXAN. The risks of TLS appear to be greater in patients with high numbers of circulating malignant cells ($\geq$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, RITUXAN has been tolerated when re-administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with RITUXAN. The majority of patients received RITUXAN in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of RITUXAN and approximately one month after the last dose.

Persons at high risk of HBV infection should be screened before initiation of RITUXAN. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and for up to several months following RITUXAN therapy. In patients who develop viral hepatitis, RITUXAN and any concomitant chemotherapy should be discontinued and appropriate treatment including antiviral therapy initiated. There are insufficient data regarding the safety of resuming RITUXAN therapy in patients who develop hepatitis subsequent to HBV reactivation.

The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or postmarketing reports. The majority of patients received RITUXAN in combination with chemotherapy or as part of a hematopoietic stem cell transplant. These viral infections included JC virus [progressive multifocal leukoencephalopathy (PML)], cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of RITUXAN and have resulted in death.

Hypersensitivity Reactions

RITUXAN 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 RITUXAN infusion (see Severe Infusion Reactions). RITUXAN 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. (See DOSAGE AND ADMINISTRATION.) 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 RITUXAN. Patients with pre-existing cardiac conditions including arrhythmias and angina have had recurrences of these

events during RITUXAN therapy and should be monitored throughout the infusion and immediate post-infusion period.

Renal (See BOXED WARNINGS: Tumor Lysis Syndrome [TLS] and ADVERSE REACTIONS)

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

Severe Mucocutaneous Reactions (See BOXED WARNINGS)

Mucocutaneous reactions, some with fatal outcome, have been reported in patients treated with RITUXAN. These reports include paraneoplastic pemphigus (an uncommon disorder which is a manifestation of the patient's underlying malignancy) (18), 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 RITUXAN 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 RITUXAN to patients with any of these mucocutaneous reactions has not been determined.

Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, were observed in patients receiving RITUXAN in combination

with chemotherapy for DLBCL. In post-marketing reports, which include both patients with low-grade or follicular NHL and DLBCL, the mean time to onset of symptoms was 6 days (range 1–77) in patients with documented gastro-intestinal perforation. Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

PRECAUTIONS

Laboratory Monitoring

Because RITUXAN targets all CD20 positive B lymphocytes, malignant and nonmalignant, complete blood counts (CBC) and platelet counts should be obtained at regular intervals during RITUXAN therapy and more frequently in patients who develop cytopenias (see ADVERSE REACTIONS). The duration of cytopenias caused by RITUXAN can extend well beyond the treatment period.

Drug/Laboratory Interactions

There have been no formal drug interaction studies performed with RITUXAN. However, renal toxicity was seen with this drug in combination with cisplatin in clinical trials. (See WARNINGS, Renal.)

Immunization

The safety of immunization with live viral vaccines following RITUXAN 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 RITUXAN, 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 RITUXAN therapy.

Pregnancy Category C

Animal reproduction studies have not been conducted with RITUXAN. It is not known whether RITUXAN 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, RITUXAN should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether RITUXAN is excreted in human milk. Because human IgG is excreted in human milk and the potential for absorption and immunosuppression in the infant is unknown, women should be advised to discontinue nursing until circulating drug levels are no longer detectable. (See CLINICAL PHARMACOLOGY.)

Pediatric Use

The safety and effectiveness of RITUXAN in pediatric patients have not been established.

Geriatric Use

Among patients with DLBCL in three randomized, active-controlled trials, 927 patients received RITUXAN 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 subjects and younger subjects. However, elderly patients were more likely to experience cardiac adverse events, mostly supraventricular arrhythmias. Serious pulmonary adverse events were also more common among the elderly, including pneumonia and pneumonitis.

Among the 331 patients with low-grade or follicular lymphoma enrolled in clinical studies of single agent RITUXAN, 24% were 65 to 75 years old and 5% were 75 years old and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

ADVERSE REACTIONS

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

The overall safety database for RITUXAN is based on clinical trial data from 1283 patients with NHL, who received RITUXAN either as a single agent or in combination with chemotherapy. Additional safety information was obtained from post-marketing safety surveillance. The most common adverse reactions were infusion reactions (see INFUSION REACTIONS below).

The following serious adverse reactions, some with fatal outcomes, have been reported in patients treated with RITUXAN (see BOXED WARNINGS and WARNINGS): severe or fatal infusion reactions, tumor lysis syndrome, severe mucocutaneous reactions, hepatitis B reactivation with fulminant hepatitis, other viral infections, hypersensitivity reactions, cardiac arrhythmias, renal toxicity, bowel obstruction and perforation.

Except as noted, adverse events described below occurred in the setting of relapsed or refractory, low-grade or follicular, CD20-positive, B-cell, NHL and are based on 356 patients treated in nonrandomized, single-arm studies of RITUXAN administered as a single agent. Most patients received RITUXAN 375 mg/m^2 weekly for 4 doses.

Infusion Reactions (See BOXED WARNINGS and WARNINGS)

Mild to moderate infusion reactions consisting of fever and chills/rigors occurred in the majority of patients during the first RITUXAN 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 RITUXAN infusion and with supportive care (diphenhydramine, acetaminophen, IV saline, and vasopressors. 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). Injection site pain was reported in less than 5% of patients.

Infectious Events (See WARNINGS: Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections)

RITUXAN 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

Grade 3 and 4 cytopenias were reported in 48% of patients treated with RITUXAN; these include: lymphopenia (40%), neutropenia (6%), leukopenia (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 RITUXAN therapy were reported.

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-RITUXAN infusion and a limited number of reports of pneumonitis (including interstitial pneumonitis) presenting up to 3 months post-RITUXAN infusion, some of which resulted in fatal outcomes. The safety of resumption or continued administration of RITUXAN in patients with pneumonitis or bronchiolitis obliterans is unknown.

Immunogenicity

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 RITUXAN with the incidence of antibodies to other products may be misleading.

In clinical studies of patients with low-grade or follicular NHL receiving single-agent RITUXAN, human antichimeric antibody (HACA) was detected in 4 of 356 (1.1%) patients and 3 had an objective clinical response. These data reflect the percentage of patients whose test results were considered positive for antibodies to RITUXAN using an enzyme-linked immunosorbant assay (limit of detection = 7 ng/mL).

Single Agent RITUXAN for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell, NHL

Study subjects ranged from 22 to 81 years of age. Sixty percent were male; 93% were Caucasian, 1% were African American, 2% were Hispanic, 2% were Asian, and 2% were from other racial groups.

Table 4 lists the most common, as well as Grade 3 and 4, adverse events observed.

Table 4

Incidence of Adverse Events in ≥5% of Patients with Relapsed or Refractory, Low-Grade or Follicular NHL, Receiving Single-agent RITUXAN (N=356)[a,b]

	All Grades (%)	Grade 3 and 4 (%)
Any Adverse Events	99	57
Body as a Whole	86	10
Fever	53	1
Chills	33	3
Infection	31	4
Asthenia	26	1
Headache	19	1
Abdominal Pain	14	1
Pain	12	1
Back Pain	10	1
Throat Irritation	9	0
Flushing	5	0
Cardiovascular System	25	3
Hypotension	10	1
Hypertension	6	1
Digestive System	37	2
Nausea	23	1
Diarrhea	10	1
Vomiting	10	1
Hemic and Lymphatic System	67	48
Lymphopenia	48	40
Leukopenia	14	4
Neutropenia	14	6
Thrombocytopenia	12	2
Anemia	8	3
Metabolic and Nutritional Disorders	38	3
Angioedema	11	1
Hyperglycemia	9	1
Peripheral Edema	8	0
LDH Increase	7	0

Table 4 (cont'd)
Incidence of Adverse Events in ≥5% of Patients with Relapsed or Refractory, Low-Grade or Follicular NHL, Receiving Single-agent RITUXAN (N=356)[a,b]

	All Grades (%)	Grade 3 and 4 (%)
Musculoskeletal System	26	3
Myalgia	10	1
Arthralgia	10	1
Nervous System	32	1
Dizziness	10	1
Anxiety	5	1
Respiratory System	38	4
Increased Cough	13	1
Rhinitis	12	1
Bronchospasm	8	1
Dyspnea	7	1
Sinusitis	6	0
Skin and Appendages	44	2
Night Sweats	15	1
Rash	15	1
Pruritus	14	1
Urticaria	8	1

[a] Adverse Events observed up to 12 months following RITUXAN.

[b] Adverse Events graded for severity by NCI-CTC criteria (19).

Risk Factors Associated with Increased Rates of Adverse Events

Administration of RITUXAN weekly for 8 doses resulted in higher rates of Grade 3 and 4 adverse events (14) 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 RITUXAN 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.

RITUXAN in Combination with Chemotherapy for DLBCL

Except as noted, adverse events described in the setting of DLBCL are based on three randomized, active-controlled clinical trials in which 927 patients received RITUXAN in combination with chemotherapy and 802 received chemotherapy alone. Detailed safety data collection was primarily limited to Grade 3 and 4 adverse events and serious adverse events.

The population varied from 18 to 92 years of age and 55% were male; racial distribution was collected only for Study 1 (see CLINICAL STUDIES section) where 90% of patients were Caucasian, 5% were African American, 3% were Hispanic and 2% were from other racial groups. Patients received 4–8 doses of RITUXAN at 375 mg/m^2.

The following adverse events, regardless of severity, were reported more frequently (≥5%) in patients age ≥60 years receiving R-CHOP as compared to CHOP alone: cardiac disorder (29% vs. 21%), pyrexia (56% vs. 46%), chills (13% vs. 4%) and lung disorder (31% vs. 24%). In one of these studies (Study 2), more detailed assessment of cardiac toxicity revealed that supraventricular arrhythmias or tachycardia accounted for most of the difference in cardiac disorders, with 4.5% vs. 1.0% incidences for R-CHOP and CHOP, respectively.

The following Grade 3 or 4 adverse events were reported more frequently among patients in the R-CHOP arm compared with those in the CHOP arm: thrombocytopenia (9% vs. 7%) and lung disorder (6% vs. 3%). Other severe adverse events reported more commonly among patients receiving R-CHOP in one or more studies were viral infection, neutropenia and anemia.

Post-Marketing Reports

The following adverse reactions have been identified during post-approval use of RITUXAN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate

their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to RITUXAN.

Hematologic: prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia, hyperviscosity syndrome in Waldenstrom's macroglobulinemia.

Cardiac: fatal cardiac failure.

Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis and vasculitis with rash.

Infection: increased in fatal infections in HIV-associated lymphoma.

Skin: severe mucocutaneous reactions

Gastrointestinal: bowel obstruction and perforation

OVERDOSAGE

There has been no experience with overdosage in human clinical trials. Single doses of up to 500 mg/m2 have been given in dose-escalating clinical trials (9).

DOSAGE AND ADMINISTRATION

Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell, Non-Hodgkin's Lymphoma

The recommended dose of RITUXAN is 375 mg/m^2 IV infusion once weekly for 4 or 8 doses.

Retreatment Therapy

The recommended dose of RITUXAN is 375 mg/m^2 IV infusion once weekly for 4 doses in responding patients who develop progressive disease

after previous RITUXAN therapy. Currently there are limited data concerning more than 2 courses.

Diffuse Large B-Cell NHL

The recommended dose of RITUXAN is 375 mg/m^2 IV per infusion given on Day 1 of each cycle of chemotherapy for up to 8 infusions.

RITUXAN as a Component of Zevalin™ (Ibritumomab Tiuxetan) Therapeutic Regimen

As a required component of the Zevalin therapeutic regimen, RITUXAN 250 mg/m^2 should be infused within 4 hours prior to the administration of Indium-111- (In-111-) Zevalin and within 4 hours prior to the administration of Yttrium90- (Y-90-) Zevalin. Administration of RITUXAN and In-111-Zevalin should precede RITUXAN and Y-90-Zevalin by 7–9 days. Refer to the Zevalin package insert for full prescribing information regarding the Zevalin therapeutic regimen.

RITUXAN may be administered in an outpatient setting. **DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.**
(See Administration.)

Instructions for Administration

Preparation for Administration

Use appropriate aseptic technique. Withdraw the necessary amount of RITUXAN 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.

RITUXAN solutions for infusion may be stored at 2–8°C (36–46°F) for 24 hours. RITUXAN solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since RITUXAN solutions do not contain a preservative, diluted solutions

should be stored refrigerated (2–8°C). No incompatibilities between RITUXAN and polyvinylchloride or polyethylene bags have been observed.

Administration: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS

Infusion and hypersensitivity reactions may occur (see BOXED WARNINGS, WARNINGS, and ADVERSE REACTIONS). Premedication consisting of acetaminophen and diphenhydramine should be considered before each infusion of RITUXAN. Premedication may attenuate infusion reactions. Since transient hypotension may occur during RITUXAN infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to RITUXAN infusion.

First Infusion

The RITUXAN solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. RITUXAN 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-IgE-mediated) or an infusion reaction develops, the infusion should be temporarily slowed or interrupted (see BOXED WARNINGS and WARNINGS). 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 RITUXAN 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.

Stability and Storage

RITUXAN vials are stable at 2–8°C (36–46°F). Do not use beyond expiration date stamped on carton. RITUXAN vials should be protected from direct sunlight. Do not freeze or shake. Refer to the "Preparation and Administration" section for information on the stability and storage of solutions of RITUXAN diluted for infusion.

HOW SUPPLIED

RITUXAN® (Rituximab) is supplied as 100 mg and 500 mg of sterile, preservative-free, single-use vials.

Single unit 100 mg carton: Contains one 10 mL vial of RITUXAN (10 mg/mL).

NDC 50242-051-21

Single unit 500 mg carton: Contains one 50 mL vial of RITUXAN (10 mg/mL).

NDC 50242-053-06

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South San Francisco, CA 94080-4990