1.14.1.3 **Draft Labeling Text**

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Rituxan safely and effectively. See full prescribing information for Rituxan.

Rituxan (rituximab)
Injection for Intravenous Use
Initial U.S. Approval: 1997

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

See full prescribing information for complete boxed warning.

- **Fatal infusion reactions within 24 hours of Rituxan infusion occur; approximately 80% of fatal reactions occurred with first infusion. Monitor patients and discontinue Rituxan infusion for severe reactions (5.1).**
- **Tumor lysis syndrome (5.2).**
- **Severe mucocutaneous reactions, some with fatal outcomes (5.3).**
- **PML resulting in death (5.4).**

----------RECENT MAJOR CHANGES----------

Warnings and Precautions, PML (5.4)	09/2008

----------INDICATIONS AND USAGE----------

Rituxan is a CD20-directed cytolytic antibody indicated for the treatment of the following:

- Non-Hodgkin's Lymphoma (NHL) (1.1)
- Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies (1.2)

----------DOSAGE AND ADMINISTRATION----------

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.

- The dose for NHL is 375 mg/m^2 (2.1).
- The dose as a component of Zevalin® (Ibritumomab tiuxetan) Therapeutic Regimen is 250 mg/m^2 (2.2).
- The dose for Rheumatoid Arthritis is two-1000 mg IV infusions separated by 2 weeks in combination with methotrexate. Methylprednisolone 100 mg IV or equivalent glucocorticoid is recommended 30 minutes prior to each infusion (2.3).

----------DOSAGE FORMS AND STRENGTHS----------

- 100 mg/10 mL and 500 mg/50 mL solution in a single-use vial (3).

----------CONTRAINDICATIONS----------

None.

----------WARNINGS AND PRECAUTIONS----------

- Tumor lysis syndrome – administer prophylaxis and monitor renal function (5.2).
- PML - monitor neurologic function. Discontinue Rituxan (5.4).
- Hepatitis B reactivation with fulminant hepatitis, sometimes fatal – screen high risk patients and monitor HBV carriers during and several months after therapy. Discontinue Rituxan if reactivation occurs (5.5).
- Cardiac arrhythmias and angina can occur and can be life threatening. Monitor patients with these conditions closely (5.7).
- Bowel obstruction and perforation - evaluate complaints of abdominal pain (5.9).
- Do not administer live virus vaccines prior to or during Rituxan (5.10).
- Monitor CBC at regular intervals for severe cytopenias (5.11, 6.1).

----------ADVERSE REACTIONS----------

- Non-Hodgkin's Lymphoma (NHL) - Common adverse reactions (≥25%) in clinical trials were: infusion reactions, fever, lymphopenia, chills, infection and asthenia (6.1).
- Rheumatoid Arthritis (RA) - Common adverse reactions (≥5%): hypertension, nausea, upper respiratory tract infection, arthralgia, pruritus, and pyrexia (6.2). Other important adverse reactions include infusion reactions, serious infections, and cardiovascular events (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Renal toxicity when used in combination with cisplatin (5.8).

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Limited human data; B-cell lymphocytopenia occurred in infants exposed in utero (8.1).
- Nursing Mothers: Caution should be exercised when administered to a nursing woman (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

Infusion Reactions
Rituxan administration can result in serious, including fatal infusion reactions. Deaths within 24 hours of Rituxan infusion have occurred. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. Carefully monitor patients during infusions. Discontinue Rituxan infusion and provide medical treatment for Grade 3 or 4 infusion reactions [*see Warnings and Precautions (5.1), Adverse Reactions (6.1)*].

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) patients with Rituxan [*see Warnings and Precautions (5.2), Adverse Reactions (6)*].

Severe Mucocutaneous Reactions
Severe, including fatal, mucocutaneous reactions can occur in patients receiving Rituxan [*see Warnings and Precautions (5.3), Adverse Reactions (6)*].

Progressive Multifocal Leukoencephalopathy (PML)
JC virus infection resulting in PML and death can occur in patients receiving Rituxan [*see Warnings and Precautions (5.4), Adverse Reactions (6.4)*].

1 INDICATIONS AND USAGE

1.1 Non–Hodgkin's Lymphoma (NHL)

Rituxan® (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 combination with CHOP or other anthracycline-based chemotherapy regimens

1.2 Rheumatoid Arthritis

Rituxan® (rituximab) in combination with methotrexate is indicated to reduce signs and symptoms and to slow the progression of structural damage in adult patients with moderately-to severely- active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

2 DOSAGE AND ADMINISTRATION

2.1 Administration

DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

Premedicate before each infusion [*see Dosage and Administration (2.5)*]. Administer only as an intravenous infusion [*see Dosage and Administration (2.5)*].

- **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 reactions [*see Boxed Warning, Warnings and Precautions (5.1)*]. Continue the infusion at one-half the previous rate upon improvement of symptoms.

2.2 Recommended Dose for Non-Hodgkin's Lymphoma (NHL)

The recommended dose is 375 mg/m^2 as an intravenous infusion according to the following schedules:

- **Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**
  Administer once weekly for 4 or 8 doses.
- **Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**
  Administer once weekly for 4 doses.
- **Previously Untreated, Follicular, CD20-Positive, B-Cell NHL**
  Administer on Day 1 of each cycle of 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.

2.3 Recommended Dose as a Component of Zevalin®

- Infuse rituximab 250 mg/m^2 within 4 hours prior to the administration of Indium-111-(In-111-) Zevalin and within 4 hours prior to the administration of Yttrium-90- (Y-90-) Zevalin.

- Administer Rituxan and In-111-Zevalin 7-9 days prior to Rituxan and Y-90- Zevalin.
- Refer to the Zevalin package insert for full prescribing information regarding the Zevalin therapeutic regimen.

2.4 Recommended Dose for Rheumatoid Arthritis

- Two-1000 mg intravenous infusions separated by 2 weeks.
- Glucocorticoids administered as methylprednisolone 100 mg intravenous or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion reactions. Safety and efficacy of retreatment have not been established in controlled trials [*see Warnings and Precautions (5.14)*].
- Rituxan is given in combination with methotrexate.

2.5 Recommended Concomitant Medications

Premedicate before each infusion with acetaminophen and an antihistamine.

2.6 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 Rituxan 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.

3 DOSAGE FORMS AND STRENGTHS

100 mg/10 mL single-use vial
500 mg/50 mL single-use vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

Rituxan can cause severe, including fatal, infusion reactions. Severe reactions typically occurred during the first infusion with time to onset of 30–120 minutes. Rituxan-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, or anaphylactoid events.

Premedicate patients with an antihistamine and acetaminophen prior to dosing. 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, consider resumption of the infusion at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who

experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (≥ 25,000/mm^3). [*See Boxed Warning, Warnings and Precautions (5.7), Adverse Reactions (6.1)*.]

5.2 Tumor Lysis Syndrome (TLS)

Rapid reduction in tumor volume followed by acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia, can occur within 12–24 hours after the first infusion. Fatal TLS cases have occurred after administration of Rituxan. A high number of circulating malignant cells (≥ 25,000/mm^3) or high tumor burden confers a greater risk of TLS after rituximab. Consider prophylaxis for TLS in patients at high risk. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated. [*See Boxed Warning*.]

5.3 Severe Mucocutaneous Reactions

Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with Rituxan. 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 Rituxan exposure. Discontinue Rituxan in patients who experience a severe mucocutaneous reaction. The safety of readministration of Rituxan to patients with severe mucocutaneous reactions has not been determined. [*See Boxed Warning, Adverse Reactions (6.1, 6.4)*.]

5.4 Progressive Multifocal Leukoencephalopathy (PML)

JC virus infection resulting in PML and death can occur in Rituxan-treated patients with hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic malignancies diagnosed with PML received Rituxan 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 Rituxan.

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 Rituxan and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML. [*See Boxed Warning, Adverse Reactions (6.4)*.]

5.5 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 Rituxan. 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.

Screen patients at high risk of HBV infection before initiation of Rituxan. Closely monitor carriers of hepatitis B for clinical and laboratory signs of active HBV infection for several months following Rituxan therapy. Discontinue Rituxan 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 Rituxan in patients who develop hepatitis subsequent to HBV reactivation. [*See Adverse Reactions (6.4).*]

5.6 Other Viral Infections

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 cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred as late as one year following discontinuation of Rituxan and have resulted in death. [*See Adverse Reactions (6.1, 6.4).*]

5.7 Cardiovascular

Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of Rituxan for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina. [*See Adverse Reactions (6.4).*]

5.8 Renal

Severe, including fatal, renal toxicity can occur after Rituxan administration in patients with hematologic malignancies. Renal toxicity has occurred in patients with high numbers of circulating malignant cells ($\geq 25{,}000/mm^3$) or high tumor burden who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and Rituxan is not an approved treatment regimen. Use extreme caution if this non-approved combination is used in clinical trials and monitor closely for signs of renal failure. Consider discontinuation of Rituxan for patients with a rising serum creatinine or oliguria.

5.9 Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving Rituxan 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, especially early in the course of Rituxan therapy. [*See Adverse Reactions (6.4).*]

5.10 Immunization

The safety of immunization with live viral vaccines following Rituxan therapy has not been studied and vaccination with live virus vaccines is not recommended. Physicians should review the vaccination status of patients with RA being considered for Rituxan treatment and follow the Centers for Disease Control and Prevention (CDC) guidelines for adult vaccination with non-live vaccines intended to prevent infectious disease prior to therapy.

For NHL patients, the benefits of primary or booster vaccinations should be weighted against the risks of delay in initiation of Rituxan therapy.

5.11 Laboratory Monitoring

Because Rituxan binds to all CD20-positive B lymphocytes (malignant and nonmalignant), obtain complete blood counts (CBC) and platelet counts at regular intervals during Rituxan therapy and more frequently in patients who develop cytopenias [*see Adverse Reactions (6.1)*]. The duration of cytopenias caused by Rituxan can extend months beyond the treatment period.

5.12 Concomitant Use with Biologic Agents and Disease Modifying Anti-Rheumatic Drugs (DMARDS) other than Methotrexate in RA

Limited data are available on the safety of the use of biologic agents or DMARDs other than methotrexate in patients exhibiting peripheral B-cell depletion following treatment with rituximab. Observe patients closely for signs of infection if biologic agents and/or DMARDs are used concomitantly.

5.13 Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis Factor (TNF) Antagonists

While efficacy of Rituxan was supported in two well-controlled trials in patients with RA with prior inadequate responses to non-biologic DMARDs, a favorable risk benefit relationship has not been established in this population. The use of Rituxan in patients with RA who have not had prior inadequate response to one or more TNF antagonists is not recommended [*see Clinical Studies (14.5)*].

5.14 Retreatment in Patients with RA

Safety and efficacy of retreatment have not been established in controlled trials. A limited number of patients have received two to five courses (two infusions per course) of treatment in an uncontrolled setting. In clinical trials in patients with RA, most of the patients who received additional courses did so 24 weeks after the previous course and none were retreated sooner than 16 weeks.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Infusion reactions [*see Warnings and Precautions (5.1)*]
- Tumor lysis syndrome [*see Warnings and Precautions (5.2)*]
- Mucocutaneous reactions [*see Warnings and Precautions (5.3)*]
- Progressive multifocal leukoencephalopathy [*see Warnings and Precautions (5.4)*]
- Hepatitis B reactivation with fulminant hepatitis [*see Warnings and Precautions (5.5)*]
- Other viral infections [*see Warnings and Precautions (5.6)*]
- Cardiac arrhythmias [*see Warnings and Precautions (5.7)*]
- Renal toxicity [*see Warnings and Precautions (5.8)*]
- Bowel obstruction and perforation [*see Warnings and Precautions (5.9)*]

The most common adverse reactions of Rituxan (incidence ≥ 25%) observed in patients with NHL are infusion reactions, fever, chills, infection, asthenia, and lymphopenia.

The most important serious adverse reactions of Rituxan are infusion reactions, tumor lysis syndrome, mucocutaneous toxicities, hepatitis B reactivation with fulminant hepatitis, PML, other viral infections, cardiac arrhythmias, renal toxicity, and bowel obstruction and perforation.

6.1 Clinical Trials Experience Non-Hodgkin's Lymphoma

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 data described below reflect exposure to Rituxan in 1606 patients, with exposures ranging from a single infusion up to 6–8 months. Rituxan was studied in both single-agent and active-controlled trials (n = 356 and n= 1250). These data were obtained in adults with low-grade, follicular, or DLBCL NHL. Most patients received Rituxan as an infusion of 375 mg/m^2 per infusion, given as a single agent weekly for up to 8 doses, in combination with chemotherapy for up to 8 doses, or following chemotherapy for up to 16 doses.

Infusion Reactions

In the majority of patients with NHL, infusion reactions consisting of fever, chills/rigors, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension occurred during the first Rituxan infusion. Infusion reactions typically 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, and intravenous saline). The incidence of infusion reactions was highest during the first infusion (77%) and decreased with each subsequent infusion. [*See Boxed Warning, Warnings and Precautions (5.1).*]

Infections

Serious infections (NCI CTCAE Grade 3 or 4), including sepsis, occurred in less than 5% of patients with NHL in the single-arm studies. The overall incidence of infections was 31% (bacterial 19%, viral 10%, unknown 6%, and fungal 1%). [*See Warnings and Precautions (5.4), (5.5), (5.6).*]

In randomized, controlled studies where Rituxan was administered following chemotherapy for the treatment of follicular or low-grade NHL, the rate of infection was higher among patients who received Rituxan. In diffuse large B-cell lymphoma patients, viral infections occurred more frequently in those who received Rituxan.

Cytopenias and hypogammaglobulinemia

In patients with NHL receiving rituximab monotherapy, NCI-CTC Grade 3 and 4 cytopenias were reported in 48% of patients. These included lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1–588 days) and of neutropenia was 13 days (range, 2–116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following Rituxan therapy occurred during the single-arm studies.

In studies of monotherapy, Rituxan-induced B-cell depletion occurred in 70% to 80% of patients with NHL. Decreased IgM and IgG serum levels occurred in 14% of these patients.

Single-Agent Rituxan

Adverse reactions in Table 1 occurred in 356 patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL treated in single-arm studies of Rituxan administered as a single agent [*see Clinical Studies (14.1)*]. Most patients received Rituxan 375 mg/m^2 weekly for 4 doses.

Table 1
Incidence of Adverse Reactions 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 Reactions	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
Heme and Lymphatic System	67	48
Lymphopenia	48	40
Leukopenia	14	4
Neutropenia	14	6
Thrombocytopenia	12	2
Anemia	8	3
Skin and Appendages	44	2
Night Sweats	15	1
Rash	15	1
Pruritus	14	1
Urticaria	8	1
Respiratory System	38	4
Increased Cough	13	1
Rhinitis	12	1
Bronchospasm	8	1
Dyspnea	7	1
Sinusitis	6	0
Metabolic and Nutritional Disorders	38	3
Angioedema	11	1
Hyperglycemia	9	1
Peripheral Edema	8	0
LDH Increase	7	0

333

Table 1 (cont'd)
Incidence of Adverse Reactions 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 (%)
Digestive System	37	2
Nausea	23	1
Diarrhea	10	1
Vomiting	10	1
Nervous System	32	1
Dizziness	10	1
Anxiety	5	1
Musculoskeletal System	26	3
Myalgia	10	1
Arthralgia	10	1
Cardiovascular System	25	3
Hypotension	10	1
Hypertension	6	1

[a] Adverse reactions observed up to 12 months following Rituxan.
[b] Adverse reactions graded for severity by NCI-CTC criteria.

In these single-arm Rituxan studies, bronchiolitis obliterans occurred during and up to 6 months after Rituxan infusion.

Rituxan in Combination with Chemotherapy

Adverse reactions information below is based on 1250 patients who received Rituxan in combination with chemotherapy or following chemotherapy.

Rituxan in Combination with Chemotherapy for Low-Grade NHL

In Study 4, patients in the R-CVP arm experienced a higher incidence of infusional toxicity and neutropenia compared to patients in the CVP arm. The following adverse reactions occurred more frequently (≥ 5%) in patients receiving R-CVP compared to CVP alone: rash (17% vs. 5%), cough (15% vs. 6%), flushing (14% vs. 3%), rigors (10% vs. 2%), pruritus (10% vs. 1%), neutropenia (8% vs. 3%), and chest tightness (7% vs. 1%). [*See Clinical Studies (14.2).*]

In Study 5, the following adverse reactions were reported more frequently (≥ 5%) in patients receiving Rituxan following CVP compared to patients who received no further therapy: fatigue (39% vs. 14%), anemia (35% vs. 20%), peripheral sensory neuropathy (30% vs. 18%), infections (19% vs. 9%), pulmonary toxicity (18% vs. 10%), hepato-biliary toxicity (17% vs. 7%), rash and/or pruritus (17% vs. 5%), arthralgia (12% vs. 3%), and weight gain (11% vs. 4%). Neutropenia was the only Grade 3 or 4 adverse reaction that occurred more frequently

(≥ 2%) in the Rituxan arm compared with those who received no further therapy (4% vs. 1%). [*See Clinical Studies (14.3)*.]

Rituxan in Combination with Chemotherapy for DLBCL

In Studies 6 and 7, *[see Clinical Studies (14.4)]*, the following adverse reactions, regardless of severity, were reported more frequently (≥ 5%) in patients age ≥ 60 years receiving R-CHOP as compared to CHOP alone: pyrexia (56% vs. 46%), lung disorder (31% vs. 24%), cardiac disorder (29% vs. 21%), and chills (13% vs. 4%). Detailed safety data collection in these studies was primarily limited to Grade 3 and 4 adverse reactions and serious adverse reactions.

In Study 7, a review of cardiac toxicity determined that supraventricular arrhythmias or tachycardia accounted for most of the difference in cardiac disorders (4.5% for R-CHOP vs. 1.0% for CHOP).

The following Grade 3 or 4 adverse reactions occurred 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 Grade 3 or 4 adverse reactions occurring more frequently among patients receiving R-CHOP were viral infection (Study 7), neutropenia (Studies 7 and 8), and anemia (Study 8).

6.2 Clinical Trials Experience Rheumatoid Arthritis

The types of adverse reactions observed in patients with RA were similar to those seen in patients with non-Hodgkin's lymphoma [*see Warnings and Precautions (5), Adverse Reactions (6.1)*]. Specific safety considerations in this indication are discussed below.

Where specific percentages are noted, these data are based on 938 patients treated in Phase 2 and 3 studies of Rituxan (2 × 1000 mg) or placebo administered in combination with methotrexate.

Table 2
Incidence of All Adverse Reactions* Occurring in ≥ 2%
and at Least 1% Greater than Placebo Among Rheumatoid
Arthritis Patients in Clinical Studies Up to Week 24 (Pooled)

Preferred Term	Placebo + MTX N = 398 n (%)	Rituxan + MTX N = 540 n (%)
Hypertension	21 (5)	43 (8)
Nausea	19 (5)	41 (8)
Upper Respiratory Tract Infection	23 (6)	37 (7)
Arthralgia	14 (4)	31 (6)
Pyrexia	8 (2)	27 (5)
Pruritus	5 (1)	26 (5)
Chills	9 (2)	16 (3)
Dyspepsia	3 (< 1)	16 (3)
Rhinitis	6 (2)	14 (3)
Paresthesia	3 (< 1)	12 (2)
Urticaria	3 (< 1)	12 (2)
Abdominal Pain Upper	4 (1)	11 (2)
Throat Irritation	0 (0)	11 (2)
Anxiety	5 (1)	9 (2)
Migraine	2 (< 1)	9 (2)
Asthenia	1 (< 1)	9 (2)

*Coded using MedDRA.

Infusion Reactions

In Rituxan RA placebo-controlled studies, 32% of Rituxan-treated patients experienced an adverse reaction during or within 24 hours following their first infusion, compared to 23% of placebo-treated patients receiving their first infusion. The incidence of adverse reactions during the 24-hour period following the second infusion, Rituxan or placebo, decreased to 11% and 13%, respectively. Acute infusion reactions (manifested by fever, chills, rigors, pruritus, urticaria/rash, angioedema, sneezing, throat irritation, cough, and/or bronchospasm, with or without associated hypotension or hypertension) were experienced by 27% of Rituxan-treated patients following their first infusion, compared to 19% of placebo-treated patients receiving their first placebo infusion. The incidence of these acute infusion reactions following the second infusion of Rituxan or placebo decreased to 9% and 11%, respectively. Serious acute infusion reactions were experienced by < 1% of patients in either treatment group. Acute infusion reactions required dose modification (stopping, slowing, or interruption of the infusion) in 10% and 2% of patients receiving rituximab or placebo, respectively, after the first course. The proportion of patients experiencing acute infusion reactions decreased with subsequent courses of Rituxan. The administration of intravenous glucocorticoids prior to Rituxan infusions reduced the incidence and severity of such reactions, however, there was no clear benefit from the

administration of oral glucocorticoids for the prevention of acute infusion reactions. Patients in clinical studies also received antihistamines and acetaminophen prior to Rituxan infusions.

Infections

In RA clinical studies, 39% of patients in the Rituxan group experienced an infection of any type compared to 34% of patients in the placebo group. The most common infections were nasopharyngitis, upper respiratory tract infections, urinary tract infections, bronchitis, and sinusitis.

The incidence of serious infections was 2% in the Rituxan-treated patients and 1% in the placebo group. One fatal infection (bronchopneumonia) occurred with rituximab monotherapy during the 24-week, placebo-controlled period in one of the Phase 2 RA studies. In 107 Rituxan-treated RA patients with active disease, subsequent treatment with a TNF inhibitor was associated with a higher rate of serious infections. Six serious infections were observed in 100.8 patient years (0.06 per patient year) prior to exposure and 9 were observed in 97.8 patient years (0.09 per patient year) after exposure.

Cardiac Adverse Reactions

The incidence of serious cardiovascular events in the double-blind part of the RA clinical trials was 1.7% and 1.3% in Rituxan and placebo treatment groups, respectively. Three cardiovascular deaths occurred during the double-blind period of the RA studies including all rituximab regimens (3/769 = 0.4%) as compared to none in the placebo treatment group (0/389).

Since patients with RA are at increased risk for cardiovascular events compared with the general population, patients with RA should be monitored throughout the infusion and Rituxan should be discontinued in the event of a serious or life-threatening cardiac event.

Hypophosphatemia and hyperuricemia

In the 24-week, double-blind RA clinical trial program, newly-occurring hypophosphatemia (<2.0 mg/dl) was observed in 12% (67/540) of patients on Rituxan versus 10% (39/398) of patients on placebo. Hypophosphatemia was more common in patients who received corticosteroids. Newly-occurring hyperuricemia (>10 mg/dl) was observed in 1.5% (8/540) of patients on Rituxan versus 0.3% (1/398) of patients on placebo.

At any time after treatment with up to seven courses of Rituxan, at least one episode of newly-occurring hypophosphatemia was observed in 23% (245/1048) of patients and newly-occurring hyperuricemia was observed in 3% (32/1048) of patients.

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody (including neutralizing antibody)

positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, 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.

Using an ELISA assay, anti-human anti-chimeric antibody (HACA) was detected in 4 of 356 (1.1%) patients with low-grade or follicular NHL receiving single-agent Rituxan. Three of the four patients had an objective clinical response.

A total of 118/1053 patients (11%) with RA tested positive for HACA at any time after treatment with Rituxan. Limited data are available on the safety or efficacy of Rituxan retreatment in patients who develop HACA. Of the 8 patients who experienced serious acute infusion reactions, 2 were subsequently found to be HACA-positive. Approximately 12% (14/118) of patients who were HACA-positive had a subsequent infusion reaction of any severity. The clinical relevance of HACA formation in rituximab-treated patients is unclear.

6.4 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Rituxan in hematologic malignancies. 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: viral infections, including progressive multifocal leukoencephalopathy (PML), increase in fatal infections in HIV-associated lymphoma, and a reported increased incidence of Grade 3 and 4 infections in patients with previously treated lymphoma without known HIV infection.
- Neoplasia: disease progression of Kaposi's sarcoma.
- Skin: severe mucocutaneous reactions.
- Gastrointestinal: bowel obstruction and perforation.
- Pulmonary: fatal bronchiolitis obliterans and pneumonitis (including interstitial pneumonitis).

7 DRUG INTERACTIONS

Formal drug interaction studies have not been performed with Rituxan. In clinical trials of patients with RA, concomitant administration of methotrexate or cyclophosphamide did not alter the pharmacokinetics of rituximab.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Category C: There are no adequate and well-controlled studies of rituximab in pregnant women. Postmarketing 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.

8.3 Nursing Mothers

It is not known whether Rituxan is secreted into human milk. However, Rituxan 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 Rituxan should be weighed against the known benefits of breastfeeding.

8.4 Pediatric Use

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

8.5 Geriatric Use

Diffuse Large B-Cell NHL

Among patients with DLBCL evaluated 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 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 Rituxan 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.

Rheumatoid Arthritis

Among the 517 patients in the Phase 3 RA study, 16% were 65–75 years old and 2% were 75 years old and older. Response rates and adverse reactions were similar in the older (age ≥ 65 years) and younger (age < 65 years) patients.

10 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 dose-escalation clinical trials.

11 DESCRIPTION

Rituxan® (rituximab) is a genetically engineered chimeric murine/human monoclonal IgG_1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

Rituximab 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. Rituxan is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous 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 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 6.5.

12 CLINICAL PHARMACOLOGY

12.1 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 pro-inflammatory cytokine production.

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.

12.2 Pharmacodynamics

Administration of Rituxan resulted in a rapid and sustained 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 post-treatment in 83% of patients. B-cell recovery began at approximately 6 months and median B-cell levels returned to normal by 12 months following completion of treatment.

There were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5 through 11 months following rituximab administration; 14% of patients had IgM and/or IgG serum levels below the normal range.

In RA patients, treatment with Rituxan induced depletion of peripheral B lymphocytes, with all patients demonstrating near complete depletion within 2 weeks after receiving the first dose of Rituxan. The majority of patients showed peripheral B-cell depletion for at least 6 months, followed by subsequent gradual recovery after that timepoint. A small proportion of patients (4%) had prolonged peripheral B-cell depletion lasting more than 3 years after a single course of treatment.

In RA studies, total serum immunoglobulin levels, IgM, IgG, and IgA were reduced at 6 months with the greatest change observed in IgM. However, mean immunoglobulin levels remained within normal levels over the 24-week period. Small proportions of patients experienced decreases in IgM (7%), IgG (2%), and IgA (1%) levels below the lower limit of normal. The clinical consequences of decreases in immunoglobulin levels in RA patients treated with Rituxan 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.

12.3 Pharmacokinetics

Pharmacokinetics were characterized in 203 NHL patients receiving 375 mg/m^2 rituximab weekly by IV infusion for 4 doses. The mean C_{max} increased with each successive infusion and was 486 mcg/mL (range, 78–997 mcg/mL) following the fourth infusion. Peak and trough serum levels of rituximab were inversely correlated with pretreatment circulating CD19-positive B cells and tumor burden. Rituximab was detectable in the serum of patients 3 to 6 months after completion of treatment.

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

Based on a population pharmacokinetic analysis of data from 298 NHL patients who received rituximab once weekly or once every three weeks, the estimated median terminal elimination half-life was 22 days (range, 6.1 to 52 days). Patients with higher CD19-positive cell counts or larger measurable tumor lesions at pretreatment had a higher clearance. However, dose adjustment for pretreatment CD19 count or size of tumor lesion is not necessary. Age and gender had no effect on the pharmacokinetics of rituximab.

Following administration of 2 doses of rituximab in patients with rheumatoid arthritis, the mean C_{max} values were 183 mcg/mL (CV = 24%) for the 2 × 500 mg dose and 370 mcg/mL (CV = 25%) for the 2 × 1000 mg dose, respectively. Following 2 × 1000 mg rituximab dose, mean volume of distribution at steady state was 4.3L (CV = 28%). Mean systemic serum clearance of rituximab was 0.01L/h (CV = 38%), and mean terminal elimination half-life after the second dose was 19 days (CV = 32%).

Female patients with RA (n = 86) had a 37% lower clearance of rituximab than male patients with RA (n = 25). The gender difference in rituximab clearance does not necessitate any dose adjustment because safety and efficacy of rituximab do not appear to be influenced by gender.

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.

13 NONCLINICAL TOXICOLOGY

13.1 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 potential effects on fertility in males or females.

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received rituximab via

the intravenous route during early gestation (organogenesis period; post-coitum days 20 through 50). Rituximab was administered as loading doses on post-coitum (PC) days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on PC Days 29, 36, 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Rituximab crosses the monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have decreased lymphoid tissue B cells.

A subsequent pre- and postnatal reproductive toxicity study in cynomolgus monkeys was completed to assess developmental effects including the recovery of B cells and immune function in infants exposed to rituximab in utero. Animals were treated with a loading dose of 0, 15, or 75 mg/kg every day for 3 days, followed by weekly dosing with 0, 20, or 100 mg/kg dose. Subsets of pregnant females were treated from PC Day 20 through postpartum Day 78, PC Day 76 through PC Day 134, and from PC day 132 through delivery and postpartum Day 28. Regardless of the timing of treatment, decreased B cells and immunosuppression were noted in the offspring of rituximab-treated pregnant animals. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months postpartum.

14 CLINICAL STUDIES

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

The safety and effectiveness of Rituxan in relapsed, refractory CD20+ NHL were demonstrated in 3 single-arm studies enrolling 296 patients.

Study 1

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 intravenous infusion weekly for 4 doses. Patients with tumor masses > 10 cm or with > 5000 lymphocytes/µL in the peripheral blood were excluded from the study.

Results are summarized in Table 3. The median time to onset of response was 50 days. Disease-related signs and symptoms (including B-symptoms) resolved in 64% (25/39) of those patients with such symptoms at study entry.

Study 2

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 3.

Study 3

In a multicenter, single-arm study, 60 patients received 375 mg/m^2 of Rituxan weekly for 4 doses. 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, 5 received more than one additional course of Rituxan. Results are summarized in Table 3.

Bulky Disease

In pooled data from studies 1 and 3, 39 patients with bulky (single lesion > 10 cm in diameter) and relapsed or refractory, low-grade NHL received Rituxan 375 mg/m^2 weekly for 4 doses. Results are summarized in Table 3.

Table 3
Summary of Rituxan Efficacy Data by Schedule and Clinical Setting

	Study 1 Weekly × 4 N = 166	Study 2 Weekly × 8 N = 37	Study 1 and Study 3 Bulky disease, Weekly × 4 N = 39[a]	Study 3 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.

14.2 Previously Untreated, Follicular, CD20-Positive, B-Cell NHL

Study 4

A total of 322 patients with previously untreated follicular NHL were randomized (1:1) to receive up to eight 3-week cycles of CVP chemotherapy alone (CVP) or in combination with Rituxan 375 mg/m^2 on Day 1 of each cycle (R-CVP) in an open-label, multicenter study. 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.

Twenty-six percent of the study population was > 60 years of age, 99% had Stage III or IV disease, and 50% had an International Prognostic Index (IPI) score ≥ 2. The results for PFS as determined by a blinded, independent assessment of progression are presented in Table 4. The point estimates may be influenced by the presence of informative censoring. The PFS results based on investigator assessment of progression were similar to those obtained by the independent review assessment.

Table 4
Efficacy Results in Study 4

	Study Arm	
	R-CVP N=162	CVP N=160
Median PFS (years)[a]	2.4	1.4
Hazard ratio (95% CI)[b]	0.44 (0.29, 0.65)	

[a] $p < 0.0001$, two-sided stratified log-rank test.
[b] Estimates of Cox regression stratified by center.

745

746 **14.3 Non-Progressing Low-Grade, CD20-Positive, B-Cell NHL**
747 **Following First-Line CVP Chemotherapy**

748 *Study 5*

749 A total of 322 patients with previously untreated low-grade, B-cell NHL
750 who did not progress after 6 or 8 cycles of CVP chemotherapy were
751 enrolled in an open-label, multicenter, randomized trial. Patients were
752 randomized (1:1) to receive Rituxan, 375 mg/m^2 intravenous infusion,
753 once weekly for 4 doses every 6 months for up to 16 doses or no further
754 therapeutic intervention. The main outcome measure of the study was
755 progression-free survival defined as the time from randomization to
756 progression, relapse, or death. Thirty-seven percent of the study
757 population was > 60 years of age, 99% had Stage III or IV disease, and
758 63% had an IPI score ≥ 2.

759 There was a reduction in the risk of progression, relapse, or death
760 (hazard ratio estimate in the range of 0.36 to 0.49) for patients randomized
761 to Rituxan as compared to those who received no additional treatment.

762 **14.4 Diffuse Large B-Cell NHL (DLBCL)**

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

769 *Study 6*

770 A total of 632 patients age ≥ 60 years with DLBCL (including primary
771 mediastinal B-cell lymphoma) were randomized in a 1:1 ratio to treatment
772 with CHOP or R-CHOP. Patients received 6 or 8 cycles of CHOP, each
773 cycle lasting 21 days. All patients in the R-CHOP arm received 4 doses of
774 Rituxan 375 mg/m^2 on Days -7 and -3 (prior to Cycle 1) and 48–72 hours
775 prior to Cycles 3 and 5. Patients who received 8 cycles of CHOP also
776 received Rituxan prior to cycle 7. The main outcome measure of the study
777 was progression-free survival, defined as the time from randomization to
778 the first of progression, relapse, or death. Responding patients underwent
779 a second randomization to receive Rituxan or no further therapy.

780 Among all enrolled patients, 62% had centrally confirmed DLBCL
781 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 5. 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 6 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 7

A total of 399 patients with DLBCL, age ≥ 60 years, were randomized in a 1:1 ratio to receive CHOP or R-CHOP. All patients received up to eight 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, 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 5.

Study 8

A total of 823 patients with DLBCL, aged 18–60 years, were randomized in a 1:1 ratio to receive an anthracycline-containing chemotherapy regimen alone or in combination with Rituxan. The main outcome measure of the study was time to treatment failure, 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 5.

Table 5
Efficacy Results in Studies 6, 7, and 8

	Study 6 (n = 632)		Study 7 (n = 399)		Study 8 (n = 823)	
	R-CHOP	CHOP	R-CHOP	CHOP	R-Chemo	Chemo
Main outcome	Progression-free survival (years)		Event-free survival (years)		Time to treatment failure (years)	
Median of main outcome measure	3.1	1.6	2.9	1.1	NE[b]	NE[b]
Hazard ratio[d]	0.69[a]		0.60[a]		0.45[a]	
Overall survival at 2 years[c]	74%	63%	69%	58%	95%	86%
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 7, overall survival estimates at 5 years were 58% vs. 46% for R-CHOP and CHOP, respectively.

14.5 Rheumatoid Arthritis (RA)

The efficacy and safety of Rituxan were evaluated in 517 patients with active disease who were receiving methotrexate and had a prior inadequate response to at least one TNF inhibitor. Patients were ≥ 18 years, diagnosed with RA according to American College of Rheumatology (ACR) criteria, and had at least 8 swollen and 8 tender joints. Patients received 2 doses of either Rituxan 1000 mg or placebo as an intravenous infusion on days 1 and 15, in combination with continued methotrexate 10–25 mg weekly.

Efficacy was assessed at 24 weeks. Glucocorticoids were given intravenously prior to each Rituxan infusion and orally on a tapering schedule from baseline through Day 16.

The proportions of Rituxan (1000 mg) treated patients achieving ACR 20, 50, and 70 responses in this study is shown in Table 6.

Table 6
ACR Responses at Week 24 in
Placebo-Controlled Study (Percent of Patients)
(Modified Intent-to-Treat Population)

Response	Placebo + MTX n = 201	Rituxan + MTX n = 298
ACR 20	18%	51%
		p < 0.0001
ACR 50	5%	27%
		p < 0.0001
ACR 70	1%	12%
		p < 0.0001

Improvement was also noted for all components of ACR response following treatment with Rituxan, as shown in Table 7.

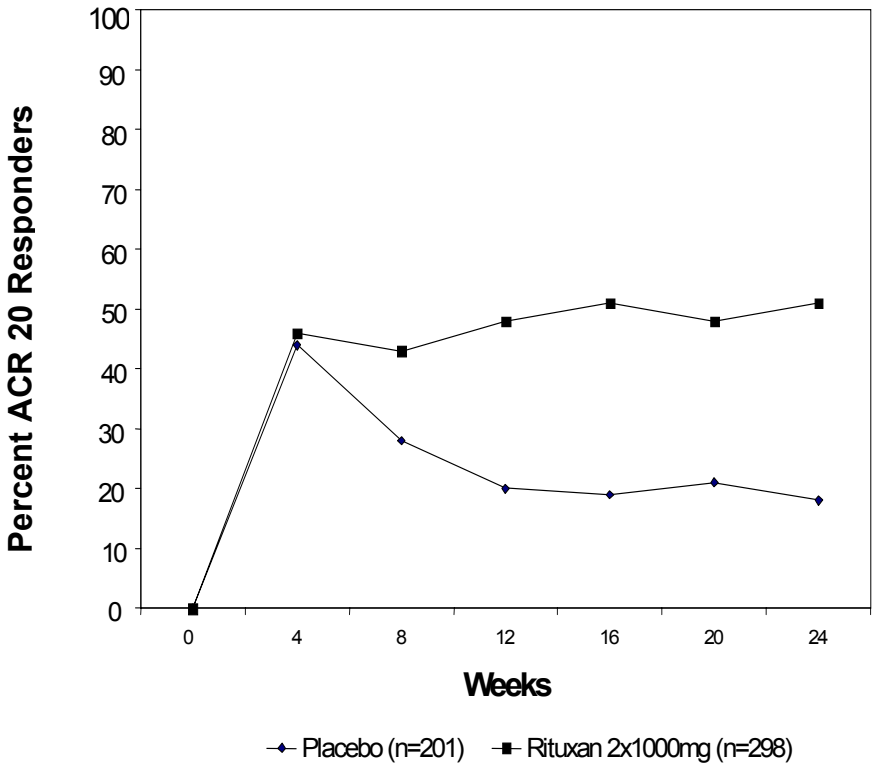
Table 7
Components of ACR Response
(Modified Intent-to-Treat Population)

Parameter (median)	Placebo + MTX (n = 201)		Rituxan + MTX (n = 298)	
	Baseline	Wk 24	Baseline	Wk 24
Tender Joint Count	31.0	27.0	33.0	13.0*
Swollen Joint Count	20.0	19.0	21.0	9.5*
Physician Global Assessment [a]	71.0	69.0	71.0	36.0*
Patient Global Assessment [a]	73.0	68.0	71.0	41.0*
Pain [a]	68.0	68.0	67.0	38.5*
Disability Index (HAQ) [b]	2.0	1.9	1.9	1.5*
CRP (mg/dL)	2.4	2.5	2.6	0.9*

[a] Visual Analogue Scale: 0 = best, 100 = worst.
[b] Disability Index of the Health Assessment Questionnaire: 0 = best, 3 = worst.
* p < 0.001, Rituxan + MTX vs. Placebo + MTX.

The time course of ACR 20 response for this study is shown in Figure 1. Although both treatment groups received a brief course of intravenous and oral glucocorticoids, resulting in similar benefits at week 4, higher ACR 20 responses were observed for the Rituxan group by week 8 and were maintained through week 24 after a single course of treatment (2 infusions) with Rituxan. Similar patterns were demonstrated for ACR 50 and 70 responses.

Figure 1
ACR 20 Responses Over 24 Weeks



While the efficacy of Rituxan was supported by two well-controlled trials in RA patients who had inadequate responses to non-biologic DMARDs, but who had not failed TNF antagonist therapy, a favorable risk benefit relationship has not been established in this population [*see Warnings and Precautions (5.13)*].

Radiographic Response

Structural joint damage was assessed radiographically and expressed as changes in Sharp-Genant Total Score and its components, joint space narrowing score and erosion score. The results are shown in Table 8. Rituxan plus MTX slowed the progression of structural damage compared to placebo plus MTX at 56 weeks.

Table 8
Mean Radiographic Change From Baseline to 56 Weeks

Parameter	Placebo + MTX (n=184) Mean Change	Rituxan + MTX (n=273) Mean Change	Treatment Difference (Placebo - Rituxan)	95% CI for the Treatment Difference
Sharp-Genant Total Score	2.31	1.00	1.31	(0.48, 2.14)
Total Joint Space Narrowing Score	0.99	0.41	0.58	(0.18, 0.98)
Total Erosion Score	1.32	0.59	0.73	(0.22, 1.24)

16 HOW SUPPLIED/STORAGE AND HANDLING

Rituxan vials [100 mg (NDC 50242-051-21) and 500 mg (NDC 50242-053-06)] are stable at 2°C–8°C (36°F–46°F). Do not use beyond expiration date stamped on carton. Rituxan vials should be protected from direct sunlight. Do not freeze or shake.

Rituxan solutions for infusion may be stored at 2°C–8°C (36°F–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°C–8°C). No incompatibilities between Rituxan and polyvinylchloride or polyethylene bags have been observed.

17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.2).

17.1 General Counseling Information

Patients should be provided the Rituxan Medication Guide and provided an opportunity to read prior to each treatment session. Because caution should be exercised in administering Rituxan to patients with active infections, it is important that the patient's overall health be assessed at each visit and any questions resulting from the patient's reading of the Medication Guide be discussed.

Rituxan is detectable in serum for up to six months following completion of therapy. Individuals of childbearing potential should use effective contraception during treatment and for 12 months after Rituxan therapy.

17.2 Medication Guide

MEDICATION GUIDE
RITUXAN® (ri-tuk´-san)
(rituximab)

Read the Medication Guide given to you before you start Rituxan and before each Rituxan infusion. The information may have changed. This Medication Guide does not take the place of talking to your doctor about your medical condition or your treatment. Talk with your doctor if you have any questions about your treatment with Rituxan.

What is the most important information I should know about Rituxan?

Rituxan can cause serious side effects including:

- **Progressive Multifocal Leukoencephalopathy (PML)**
  - PML is a rare brain infection. PML usually causes death or severe disability.
  - Call your doctor right away if you notice any new or worsening medical problems, such as a new or sudden change in thinking, walking, strength, vision, or other problems that have lasted over several days.
  - PML usually happens in patients with weakened immune systems.
  - PML can occur during treatment with Rituxan or after treatment has finished.
  - There is no known treatment, prevention, or cure for PML.
- **Infusion reactions**. Tell your doctor or get medical treatment right away if you get hives, swelling, dizziness, blurred vision, drowsiness, headache, cough, wheezing, or have trouble breathing while receiving or after receiving Rituxan.
- **Tumor Lysis Syndrome (TLS)**. TLS is caused by the fast breakdown of certain types of cancer cells. TLS can cause kidney failure and the need for dialysis treatment. Patients receiving Rituxan for non-Hodgkin's lymphoma (NHL) may get TLS. Your doctor will check you for TLS.
- **Severe skin reactions**. Tell your doctor or get medical treatment right away if you get any of these symptoms: painful sores on your skin or in your mouth, ulcers, blisters, or peeling skin while receiving or after receiving Rituxan.

See "**What are possible side effects with Rituxan?"** for other serious side effects.

What is Rituxan?

Rituxan is a prescription medicine used in adults:

- alone or with other anti-cancer medicines to treat certain types of NHL.
- with another medicine called methotrexate to reduce the signs and symptoms of Rheumatoid Arthritis (RA) after at least one other medicine called a tumor necrosis factor (TNF) inhibitor has been used and did not work well.

Rituxan has not been studied in children.

What should I tell my doctor before treatment with Rituxan?

Tell your doctor about all of your medical conditions, including if you:

- had a severe infusion reaction to Rituxan in the past.
- have an infection or have an infection that will not go away or that keeps coming back.
- have or had hepatitis (liver) infection. See "**What are the possible side effects of Rituxan**?" If so, your doctor should check you closely for signs of hepatitis infection during treatment with Rituxan and for several months after treatment ends.
- are scheduled to receive any vaccinations. You should not receive live vaccines after you receive Rituxan.
- have heart or lung problems.
- are pregnant or planning to become pregnant. It is not known if Rituxan can harm your unborn baby.
- are breastfeeding. It is not known if Rituxan passes into human breast milk. You should not breastfeed while being treated with Rituxan and after finishing treatment, until blood tests show that there is no Rituxan in your blood.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, or herbal supplements. If you have RA, especially tell your doctor if you take or have taken another medicine called a TNF inhibitor or a DMARD (disease modifying anti-rheumatic drug).

How do I receive Rituxan?

- Rituxan is given through a needle placed in a vein (IV or intravenous infusion), in your arm. Talk to your doctor about how you will receive Rituxan.
- Your doctor may prescribe medicines before each infusion of Rituxan to reduce side effects of infusions (such as fever and chills).
- Your doctor should do regular blood tests to check for side effects to Rituxan.

Before each Rituxan treatment, your doctor or nurse will ask you questions about your general health to make sure that Rituxan is still right for you. Tell your doctor or nurse about any new symptoms, and symptoms that get worse over a few days or that will not go away.

What are the possible side effects of Rituxan?

The **"What is the most important information I should know about Rituxan?"** section lists certain serious and life-threatening side effects with Rituxan. Rituxan can cause other serious and life-threatening side effects including:

- **Hepatitis B virus reactivation.** Tell your doctor if you had hepatitis B virus or are a carrier of hepatitis B virus. Receiving Rituxan could cause the hepatitis B virus to become an active infection again. This may cause serious liver problems and death. People with active liver disease due to hepatitis B should stop receiving Rituxan.
- **Heart problems.** Tell your doctor about any heart problems you have including chest pain (angina) and irregular heart beats. Rituxan can cause chest pain and irregular heart beats which may require treatment.
- **Infections.** Rituxan can increase your chances for getting infections. Call your doctor right away if you have a cough that will not go away, fever, chills, congestion, or any flu-like symptoms while receiving Rituxan. These symptoms may be signs of a serious infection.
- **Stomach and bowel problems.** Serious stomach and bowel problems have been seen when Rituxan has been used with anti-cancer medicines in some patients with non-Hodgkin's lymphoma. Call your doctor right away if you have any stomach area pain during treatment with Rituxan.

Common side effects during Rituxan infusions include:

- fever
- chills and shakes
- itching
- cough
- throat irritation or tightness
- headache
- nausea
- hives
- sneezing

Other side effects with Rituxan include:

- aching joints
- upper respiratory tract infection
- decreased blood cell counts
- lung problems

Tell your doctor about any side effect that bothers you or that does not go away. These are not all of the possible side effects with Rituxan. Ask your doctor for more information.

General Information about Rituxan

This Medication Guide provides a summary of the most important information about Rituxan. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information or have any questions, talk with your doctor. You can ask your doctor for information about Rituxan that is written for healthcare professionals. You can also visit www.Rituxan.com or call 1-877-474-8892.

What are the ingredients in Rituxan?
Active ingredient: rituximab
Inactive ingredients: sodium chloride, sodium citrate dihydrate, polysorbate 80, and water for injection.

Jointly Marketed by: Biogen Idec Inc. and Genentech USA, Inc.

Manufactured by:

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

Revised 09/2008 (4835504)

This Medication Guide has been approved by the U.S. Food and Drug Administration.