1.14.2.3 **Final 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----------

Indications and Usage, CLL (1.2)	01/2010
Indications and Usage, RA (1.3)	10/2009
Indications and Usage, Limitations of Use (1.4)	01/2010
Dosage and Administration, CLL (2.3)	01/2010
Dosage and Administration, RA (2.5)	10/2009
Dosage and Administration, Recommended Concomitant Medications (2.6)	10/2009
Warnings and Precautions, Infusion Reactions (5.1)	10/2009
Warnings and Precautions, Infections (5.6)	01/2010
Warnings and Precautions, Renal (5.8)	01/2010
Warnings and Precautions, Immunization (5.10)	09/2009
Warnings and Precautions, Laboratory Monitoring (5.11)	01/2010
Warnings and Precautions, Use in RA Patients Who Have Not Had Prior IR to TNF antagonists (5.13)	10/2009

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

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

- Non-Hodgkin's Lymphoma (NHL) (1.1)
- Chronic Lymphocytic Leukemia (CLL) (1.2)
- 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 (1.3)

Limitations of Use: Rituxan is not recommended for use in patients with severe, active infections (1.4)

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

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.

- The dose for NHL is 375 mg/m^2 (2.2).
- The dose for CLL is 375 mg/m^2 in the first cycle and 500 mg/m^2 in cycles 2–6, in combination with FC, administered every 28 days (2.3).
- The dose as a component of Zevalin® (Ibritumomab tiuxetan) Therapeutic Regimen is 250 mg/m^2 (2.4).
- The dose for RA in combination with methotrexate is two-1000 mg IV infusions separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks. Methylprednisolone 100 mg IV or equivalent glucocorticoid is recommended 30 minutes prior to each infusion (2.5).

----------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 aggressive intravenous hydration, anti-hyperuricemic agents, 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).
- Infections - withhold Rituxan and institute appropriate anti-infective therapy
- 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----------

- Lymphoid Malignancies: Common adverse reactions (≥25%) in clinical trials of NHL were: infusion reactions, fever, lymphopenia, chills, infection and asthenia. Common adverse reactions (≥25%) in clinical trials of CLL were: infusion reactions and neutropenia (6.1).
- Rheumatoid Arthritis (RA) - Common adverse reactions (≥10%) in clinical trials: upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis (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).
- Geriatric Use: In CLL patients older than 70 years of age, exploratory analyses suggest no benefit with the addition of Rituxan to FC (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

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

1 INDICATIONS AND USAGE
- 1.1 Non-Hodgkin's Lymphoma (NHL)
- 1.2 Chronic Lymphocytic Leukemia (CLL)
- 1.3 Rheumatoid Arthritis (RA)
- 1.4 Limitations of Use

2 DOSAGE AND ADMINISTRATION
- 2.1 Administration
- 2.2 Recommended Dose for NHL
- 2.3 Recommended Dose for CLL
- 2.4 Recommended Dose as a Component of Zevalin®
- 2.5 Recommended Dose for RA
- 2.6 Recommended Concomitant Medications
- 2.7 Preparation for Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Infusion Reactions
- 5.2 Tumor Lysis Syndrome (TLS)
- 5.3 Severe Mucocutaneous Reactions
- 5.4 Progressive Multifocal Leukoencephalopathy (PML)
- 5.5 Hepatitis B Virus (HBV) Reactivation
- 5.6 Infections
- 5.7 Cardiovascular
- 5.8 Renal
- 5.9 Bowel Obstruction and Perforation
- 5.10 Immunization
- 5.11 Laboratory Monitoring
- 5.12 Concomitant Use with Biologic Agents and Disease Modifying Anti-Rheumatic Drugs (DMARDS) other than Methotrexate in RA
- 5.13 Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis Factor (TNF) Antagonists

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience in Lymphoid Malignancies
- 6.2 Clinical Trials Experience Rheumatoid Arthritis
- 6.3 Immunogenicity
- 6.4 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES
- 14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20 Positive, B-Cell NHL
- 14.2 Previously Untreated, Follicular, CD20-Positive, B-Cell NHL
- 14.3 Non-Progressing, Low-Grade, CD20-Positive, B-Cell NHL Following First-Line CVP Chemotherapy
- 14.4 Diffuse Large B-Cell NHL (DLBCL)
- 14.5 Chronic Lymphocytic Leukemia (CLL)
- 14.6 Rheumatoid Arthritis (RA)

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*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) with Rituxan monotherapy [*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 Chronic Lymphocytic Leukemia (CLL)

Rituxan® (rituximab) is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

1.3 Rheumatoid Arthritis (RA)

Rituxan® (rituximab) in combination with methotrexate is indicated for the treatment of adult patients with moderately- to severely- active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

1.4 Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Administration

DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

Premedicate before each infusion [*see Dosage and Administration (2.6)*].

Administer only as an intravenous (IV) infusion [*see Dosage and Administration (2.6)*].

- **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 IV infusion according to the following schedules:

- **Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**
  Administer once weekly for 4 or 8 doses.
- **Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**
  Administer once weekly for 4 doses.
- **Previously Untreated, Follicular, CD20-Positive, B-Cell NHL**
  Administer on Day 1 of each cycle of CVP chemotherapy, for up to 8 doses.
- **Non-progressing, Low-Grade, CD20-Positive, B-cell NHL, after first-line CVP chemotherapy**
  Following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses.
- **Diffuse Large B-Cell NHL**
  Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions.

2.3 Recommended Dose for Chronic Lymphocytic Leukemia (CLL)

The recommended dose is:

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

2.4 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.

2.5 Recommended Dose for Rheumatoid Arthritis (RA)

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

2.6 Recommended Concomitant Medications

Premedicate before each infusion with acetaminophen and an antihistamine.

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

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

2.7 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, anaphylactoid events, or death.

Premedicate patients with an antihistamine and acetaminophen prior to dosing. For RA patients, methylprednisolone 100 mg IV or its equivalent is recommended 30 minutes prior to each infusion. Institute medical management (e.g. glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions as needed. Depending on the severity of the infusion reaction and the required interventions, temporarily or permanently discontinue Rituxan. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells ($\geq 25{,}000/mm^3$). [*See Boxed Warning, Warnings and Precautions (5.7), Adverse Reactions (6.1).*]

5.2 Tumor Lysis Syndrome (TLS)

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12–24 hours after

the first infusion of Rituxan in patients with NHL. A high number of circulating malignant cells ($\geq$ 25,000/mm^3) or high tumor burden, confers a greater risk of TLS.

Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated. [*See Boxed Warning, Warnings and Precautions (5.8)].*]

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 Infections

Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and up to one year following the completion of Rituxan-based therapy. New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue Rituxan for serious infections and institute appropriate anti-infective therapy. [*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 NHL. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and Rituxan is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue Rituxan in patients with a rising serum creatinine or oliguria. [*See Warnings and Precautions (5.2).*]

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. [*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.

For RA patients, physicians should follow current immunization guidelines and administer non-live vaccines at least 4 weeks prior to a course of Rituxan.

The effect of Rituxan on immune responses was assessed in a randomized, controlled study in patients with RA treated with Rituxan and methotrexate (MTX) compared to patients treated with MTX alone.

A response to pneumococcal vaccination (a T-cell independent antigen) as measured by an increase in antibody titers to at least 6 of 12 serotypes was lower in patients treated with Rituxan plus MTX as compared to patients treated with MTX alone (19% vs. 61%). A lower proportion of patients in the Rituxan plus MTX group developed detectable levels of anti-keyhole limpet hemocyanin antibodies (a novel protein antigen) after vaccination compared to patients on MTX alone (47% vs. 93%).

A positive response to tetanus toxoid vaccine (a T-cell dependent antigen with existing immunity) was similar in patients treated with Rituxan plus MTX compared to patients on MTX alone (39% vs. 42%). The proportion of patients maintaining a positive Candida skin test (to evaluate delayed type hypersensitivity) was also similar (77% of patients on Rituxan plus MTX vs. 70% of patients on MTX alone).

Most patients in the Rituxan-treated group had B-cell counts below the lower limit of normal at the time of immunization. The clinical implications of these findings are not known.

5.11 Laboratory Monitoring

In patients with lymphoid malignancies, during treatment with Rituxan monotherapy, obtain complete blood counts (CBC) and platelet counts prior to each Rituxan course. During treatment with Rituxan and chemotherapy, obtain CBC and platelet counts at weekly to monthly intervals and more frequently in patients who develop cytopenias [*see Adverse Reactions (6.1)*]. In patients with RA obtain CBC and platelet counts at two to four month intervals during Rituxan therapy. The

duration of cytopenias caused by Rituxan can extend months beyond the treatment period.

5.12 Concomitant Use with Biologic Agents and 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 the efficacy of Rituxan was supported in four controlled trials in patients with RA with prior inadequate responses to non-biologic DMARDs, and in a controlled trial in MTX-naïve patients, a favorable risk-benefit relationship has not been established in these populations. 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 (14.6)*].

6 ADVERSE REACTIONS

The following serious 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)*]
- 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 clinical trials of patients with NHL were infusion reactions, fever, lymphopenia, chills, infection, and asthenia.

The most common adverse reactions of Rituxan (incidence ≥ 25%) observed in clinical trials of patients with CLL were: infusion reactions and neutropenia.

6.1 Clinical Trials Experience in Lymphoid Malignancies

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 2282 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 = 1926). The population included 679 patients with low-grade follicular lymphoma, 927 patients with DLBCL, and 676 patients with CLL. Most NHL 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. CLL patients received Rituxan 375 mg/m^2 as an initial infusion followed

by 500 mg/m^2 for up to 5 doses, in combination with fludarabine and cyclophosphamide. Seventy-one percent of CLL patients received 6 cycles and 90% received at least 3 cycles of Rituxan-based therapy.

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.

Relapsed or Refractory, Low-Grade NHL

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

324

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.

Previously Untreated 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).*]

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).

CLL

The data below reflect exposure to Rituxan in combination with fludarabine and cyclophosphamide in 676 patients with CLL in Study 9 or Study 10 *[see Clinical Studies (14.5)]*. The age range was 30–83 years and 71% were men. Detailed safety data collection in Study 9 was limited to Grade 3 and 4 adverse reactions and serious adverse reactions.

Infusion-related adverse reactions were defined by any of the following adverse events occurring during or within 24 hours of the start of infusion: nausea, pyrexia, chills, hypotension, vomiting, and dyspnea.

In Study 9, the following Grade 3 and 4 adverse reactions occurred more frequently in R-FC-treated patients compared to FC-treated patients: infusion reactions (9% in R-FC arm), neutropenia (30% vs. 19%), febrile neutropenia (9% vs. 6%), leukopenia (23% vs. 12%), and pancytopenia (3% vs. 1%).

In Study 10, the following Grade 3 or 4 adverse reactions occurred more frequently in R-FC-treated patients compared to FC-treated patients: infusion reactions (7% in R-FC arm), neutropenia (49% vs. 44%), febrile neutropenia (15% vs. 12%), thrombocytopenia (11% vs. 9%), hypotension (2% vs. 0%), and hepatitis B (2% vs. $< 1\%$). Fifty-nine percent of R-FC-treated patients experienced an infusion reaction of any severity.

6.2 Clinical Trials Experience in Rheumatoid Arthritis

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 presented below reflect the experience in 2578 RA patients treated with Rituxan in controlled and long-term studies with a total exposure of 5014 patient-years.

Among all exposed patients, adverse reactions reported in greater than 10% of patients include infusion related reactions, upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis.

In placebo-controlled studies, patients received 2×500 mg or 2×1000 mg intravenous infusions of Rituxan or placebo, in combination with methotrexate, during a 24-week period. From these studies, 938 patients treated with Rituxan (2×1000 mg) or placebo have been pooled (see Table 2). Adverse reactions reported in $\geq 5\%$ of patients were hypertension, nausea, upper respiratory tract infection, arthralgia, pyrexia and pruritus (see Table 2). The rates and types of adverse reactions in patients who received Rituxan 2×500 mg were similar to those observed in patients who received Rituxan 2×1000 mg.

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)

*These data are based on 938 patients treated in Phase 2 and 3 studies of Rituxan (2 x 1000 mg) or placebo administered in combination with methotrexate.

**Coded using MedDRA.

Infusion Reactions

In the Rituxan RA pooled 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 the pooled, placebo-controlled 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.

In the experience with Rituxan in 2578 RA patients, the rate of serious infections was 4.31 per 100 patient years. The most common serious infections (≥0.5%) were pneumonia or lower respiratory tract infections, cellulitis and urinary tract infections. Fatal serious infections included pneumonia, sepsis and colitis. Rates of serious infection remained stable in patients receiving subsequent courses. In 185 Rituxan-treated RA patients with active disease, subsequent treatment with a biologic DMARD, the majority of which were TNF antagonists, did not appear to increase the rate of serious infection. Thirteen serious infections were observed in 186.1 patient years (6.99 per 100 patient years) prior to exposure and 10 were observed in 182.3 patient years (5.49 per 100 patient years).

Cardiac Adverse Reactions

In the pooled, placebo-controlled studies, the proportion of patients with serious cardiovascular reactions was 1.7% and 1.3% in the 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).

In the experience with Rituxan in 2578 RA patients, the rate of serious cardiac reactions was 1.93 per 100 patient years. The rate of myocardial infarction (MI) was 0.56 per 100 patient years (28 events in 26 patients), which is consistent with MI rates in the general RA population. These rates did not increase over three courses of Rituxan.

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 pooled, placebo-controlled studies, 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.

In the experience with Rituxan in RA patients, newly-occurring hypophosphatemia was observed in 21% (528/2570) of patients and newly-occurring hyperuricemia was observed in 2% (56/2570) of patients. The majority of the observed hypophosphatemia occurred at the time of the infusions and was transient.

Retreatment in Patients with RA

In the experience with Rituxan in RA patients, 2578 patients have been exposed to Rituxan and have received up to 10 courses of Rituxan in RA clinical trials, with 1890, 1043, and 425 patients having received at least two, three, and four courses, respectively. Most of the patients who received additional courses did so 24 weeks or more after the previous course and none were retreated sooner than 16 weeks. The

rates and types of adverse reactions reported for subsequent courses of Rituxan were similar to rates and types seen for a single course of Rituxan.

In RA Study 2, where all patients initially received Rituxan, the safety profile of patients who were retreated with Rituxan was similar to those who were retreated with placebo [*see Clinical Studies (14.6), and Dosage and Administration (2.5).*]

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 273/2578 (11%) patients with RA tested positive for HACA at any time after receiving Rituxan. HACA positivity was not associated with increased infusion reactions or other adverse reactions. Upon further treatment, the proportions of patients with infusion reactions were similar between HACA positive and negative patients, and most reactions were mild to moderate. Four HACA positive patients had serious infusion reactions, and the temporal relationship between HACA positivity and infusion reaction was variable. The clinical relevance of HACA formation in Rituxan-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 patients with CLL, Rituxan did not alter systemic exposure to fludarabine or cyclophosphamide. 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

FDA has not required pediatric studies in polyarticular juvenile idiopathic arthritis (PJIA) patients ages 0 to 16 due to concerns regarding the potential for prolonged immunosuppression as a result of B cell depletion in the developing juvenile immune system.

The safety and effectiveness of 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.

Chronic Lymphocytic Leukemia

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

In exploratory analyses defined by age, there was no observed benefit from the addition of Rituxan to fludarabine and cyclophosphamide among patients 70 years of age or older in Study 9 or in Study 10; there was also no observed benefit from the addition of Rituxan to fludarabine and cyclophosphamide among patients 65 years of age or older in Study 10 [*see Clinical Studies (14.5)*]. Patients 70 years or older received lower dose intensity of fludarabine and cyclophosphamide compared to younger patients, regardless of the addition of Rituxan. In Study 9, the dose intensity of Rituxan was similar in older and younger patients, however in Study 10 older patients received a lower dose intensity of Rituxan.

The incidence of Grade 3 and 4 adverse reactions was higher among patients receiving R-FC who were 70 years or older compared to younger patients for neutropenia [44% vs. 31% (Study 9); 56% vs. 39% (Study 10)], febrile neutropenia [16% vs. 6% (Study 9)], anemia [5% vs. 2% (Study 9); 21% vs. 10% (Study 10)], thrombocytopenia [19% vs. 8% (Study 10)], pancytopenia [7% vs. 2% (Study 9); 7% vs. 2% (Study 10)] and infections [30% vs. 14% (Study 10)].

Rheumatoid Arthritis

Among the 2578 patients in global RA studies completed to date, 12% were 65–75 years old and 2% were 75 years old and older. The incidences of adverse reactions were similar between older and younger patients. The rates of serious adverse reactions, including serious infections, malignancies, and cardiovascular events were higher in older 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 administered in 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 proinflammatory 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

In NHL patients, administration of Rituxan resulted in depletion of circulating and tissue-based B cells. Among 166 patients in Study 1, circulating CD19-positive B cells were depleted within the first three weeks with sustained depletion for up to 6 to 9 months posttreatment in 83% of patients. B-cell recovery began at approximately 6 months and median B-cell levels returned to normal by 12 months following completion of treatment.

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

In RA patients, treatment with Rituxan induced depletion of peripheral B lymphocytes, with the majority of patients demonstrating near complete depletion (CD19 counts below the lower limit of quantification, 20 cells/μl) within 2 weeks after receiving the first dose of Rituxan. The majority of patients showed peripheral B-cell depletion for at least 6 months. A small proportion of patients (~4%) had prolonged peripheral B-cell depletion lasting more than 3 years after a single course of treatment.

Total serum immunoglobulin levels, IgM, IgG, and IgA were reduced at 6 months with the greatest change observed in IgM. At Week 24 of the first course of Rituxan treatment, small proportions of patients experienced decreases in IgM (10%), IgG (2.8%), and IgA (0.8%) levels below the lower limit of normal (LLN). In the experience with Rituxan in RA patients during repeated Rituxan treatment, 23.3%, 5.5%, and 0.5% of patients experienced decreases in IgM, IgG, and IgA concentrations below LLN at any time after receiving Rituxan, respectively. 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 Rituxan weekly by IV infusion for 4 doses. 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.

Pharmacokinetics were characterized in 21 patients with CLL receiving rituximab according to the recommended dose and schedule. The estimated median terminal half-life of rituximab was 32 days (range, 14 to 62 days).

Following administration of 2 doses of Rituxan in patients with RA, the mean (± S.D.; % CV) concentrations after the first infusion (Cmax first) and second infusion (Cmax second) were 157 (± 46; 29%) and 183 (± 55; 30%) mcg/mL, and 318 (± 86; 27%) and 381 (± 98; 26%) mcg/mL for the 2 × 500 mg and 2 × 1000 mg doses, respectively.

Based on a population pharmacokinetic analysis of data from 2005 RA patients who received Rituxan, the estimated clearance of rituximab was 0.335 L/day; volume of distribution was 3.1 L and mean terminal elimination half-life was 18.0 days (range, 5.17 to 77.5 days). Age, weight and gender had no effect on the pharmacokinetics of rituximab in RA patients.

The pharmacokinetics of rituximab have not been studied in children and adolescents. No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of rituximab.

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.

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

Study 5

A total of 322 patients with previously untreated low-grade, B-cell NHL who did not progress after 6 or 8 cycles of CVP chemotherapy were enrolled in an open-label, multicenter, randomized trial. Patients were randomized (1:1) to receive Rituxan, 375 mg/m^2 intravenous infusion, once weekly for 4 doses every 6 months for up to 16 doses or no further therapeutic intervention. The main outcome measure of the study was progression-free survival defined as the time from randomization to

progression, relapse, or death. Thirty-seven percent of the study population was > 60 years of age, 99% had Stage III or IV disease, and 63% had an IPI score ≥ 2.

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

14.4 Diffuse Large B-Cell NHL (DLBCL)

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 6

A total of 632 patients age ≥ 60 years with DLBCL (including primary mediastinal B-cell lymphoma) were randomized in a 1:1 ratio to treatment with CHOP or R-CHOP. Patients received 6 or 8 cycles of CHOP, each cycle lasting 21 days. All patients in the R-CHOP arm received 4 doses of Rituxan 375 mg/m^2 on Days –7 and –3 (prior to Cycle 1) and 48–72 hours prior to Cycles 3 and 5. Patients who received 8 cycles of CHOP also received Rituxan prior to Cycle 7. The main outcome measure of the study was progression-free survival, 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 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 Chronic Lymphocytic Leukemia (CLL)

The safety and effectiveness of Rituxan were evaluated in two randomized (1:1) multicenter open-label studies comparing FC alone or in combination with Rituxan for up to 6 cycles in patients with previously untreated CLL [Study 9 (n = 817)] or previously treated CLL [Study 10 (n = 552)]. Patients received fludarabine 25 mg/m^2/day and cyclophosphamide 250 mg/m^2/day on days 1, 2 and 3 of each cycle, with or without Rituxan. In both studies, seventy-one percent of CLL patients received 6 cycles and 90% received at least 3 cycles of Rituxan-based therapy.

In Study 9, 30% of patients were 65 years or older, 31% were Binet stage C, 45% had B symptoms, more than 99% had ECOG performance status (PS) 0–1, 74% were male, and 100% were White. In Study 10, 44% of patients were 65 years or older, 28% had B symptoms, 82% received a prior alkylating drug, 18% received prior fludarabine, 100% had ECOG PS 0–1, 67% were male and 98% were White.

The main outcome measure in both studies was progression-free survival (PFS), defined as the time from randomization to progression, relapse, or death, as determined by investigators (Study 9) or an independent review committee (Study 10). The investigator assessed results in Study 10 were supportive of those obtained by the independent review committee. Efficacy results are presented in Table 6.

Table 6
Efficacy Results in Studies 9 and 10

	Study 9* (Previously untreated)		Study 10* (Previously treated)	
	R-FC N=408	FC N=409	R-FC N=276	FC N=276
Median PFS (months)	39.8	31.5	26.7	21.7
Hazard ratio (95% CI)	0.56 (0.43, 0.71)		0.76 (0.6, 0.96)	
P value (Log-Rank test)	<0.01		0.02	
Response rate	86%	73%	54%	45%
(95% CI)	(82, 89)	(68, 77)	(48, 60)	(37, 51)

* As defined in 1996 National Cancer Institute Working Group guidelines

Across both studies, 243 of 676 Rituxan-treated patients (36%) were 65 years of age or older and 100 Rituxan-treated patients (15%) were 70 years of age or older. The results of exploratory subset analyses in elderly patients are presented in Table 7.

Table 7
Efficacy Results in Studies 9 and 10 in Subgroups Defined by Age[a]

	Study 9		Study 10	
Age subgroup	Number of Patients	Hazard Ratio for PFS (95% CI)	Number of Patients	Hazard Ratio for PFS (95% CI)
Age < 65 yrs	572	0.52 (0.39, 0.70)	313	0.61 (0.45, 0.84)
Age ≥ 65 yrs	245	0.62 (0.39, 0.99)	233	0.99 (0.70, 1.40)
Age < 70 yrs	736	0.51 (0.39, 0.67)	438	0.67 (0.51, 0.87)
Age ≥ 70 yrs	81	1.17 (0.51, 2.66)	108	1.22 (0.73, 2.04)

[a] From exploratory analyses.

14.6 Rheumatoid Arthritis (RA)

Reducing the Signs and Symptoms: Initial and Re-Treatment Courses

The efficacy and safety of Rituxan were evaluated in two randomized, double-blind, placebo-controlled studies of adult patients with moderately to severely active RA who had a prior inadequate response to at least one TNF inhibitor. Patients were 18 years of age or older, diagnosed with active RA according to American College of Rheumatology (ACR) criteria, and had at least 8 swollen and 8 tender joints.

In RA Study 1, patients were randomized to receive either Rituxan 2 × 1000 mg + MTX or placebo + MTX for 24 weeks. Further courses of Rituxan 2 × 1000 mg + MTX were administered in an open label extension study at a frequency determined by clinical evaluation, but no sooner than 16 weeks after the preceding course of Rituxan. In addition to the IV premedication, glucocorticoids were administered orally on a tapering schedule from baseline through Day 14. The proportions of patients achieving ACR 20, 50, and 70 responses at Week 24 of the placebo-controlled period are shown in Table 8.

In RA Study 2, all patients received the first course of Rituxan 2 × 1000 mg + MTX. Patients who experienced ongoing disease activity were randomized to receive a second course of either Rituxan 2 × 1000 mg MTX or placebo + MTX, the majority between Weeks 24–28. The proportions of patients achieving ACR 20, 50, and 70 responses at Week 24, before the re-treatment course, and at Week 48, after retreatment, are shown in Table 8.

Table 8

ACR Responses in Study 1 and Study 2 (Percent of Patients)
(Modified Intent-to-Treat Population)

Inadequate Response to TNF Antagonists							
Study 1 24 Week Placebo-Controlled (Week 24)				Study 2 Placebo-Controlled Retreatment (Week 24 and Week 48)			
Response	Placebo + MTX n = 201	Rituxan + MTX n = 298	Treatment Difference (Rituxan – Placebo)[c] (95% CI)	Response	Placebo + MTX Retreatment n = 157	Rituxan + MTX Retreatment n = 318	Treatment Difference (Rituxan – Placebo)[a,b,c] (95% CI)
ACR20				ACR20			
Week 24	18%	51%	33% (26%, 41%)	Week 24	48%	45%	NA
				Week 48	45%	54%	11% (2%, 20%)
ACR50				ACR50			
Week 24	5%	27%	21% (15%, 27%)	Week 24	27%	21%	NA
				Week 48	26%	29%	4% (-4%, 13%)
ACR70				ACR70			
Week 24	1%	12%	11% (7%, 15%)	Week 24	11%	8%	NA
				Week 48	13%	14%	1% (-5%, 8%)

[a] In Study 2, all patients received a first course of Rituxan 2 x 1000 mg. Patients who experienced ongoing disease activity were randomized to receive a second course of either Rituxan 2 x 1000 mg + MTX or placebo + MTX at or after Week 24.

[b] Since all patients received a first course of Rituxan, no comparison between Placebo + MTX and Rituxan + MTX is made at Week 24.

[c] For Study 1, weighted difference stratified by region (US, rest of the world) and Rheumatoid Factor (RF) status (positive >20 IU/mL, negative <20 IU/mL) at baseline; For Study 2, weighted difference stratified by RF status at baseline and ≥20% improvement from baseline in both SJC and TJC at Week 24 (Yes/No).

Improvement was also noted for all components of ACR response following treatment with Rituxan, as shown in Table 9.

Table 9
Components of ACR Response at Week 24 in Study 1
(Modified Intent-to-Treat Population)

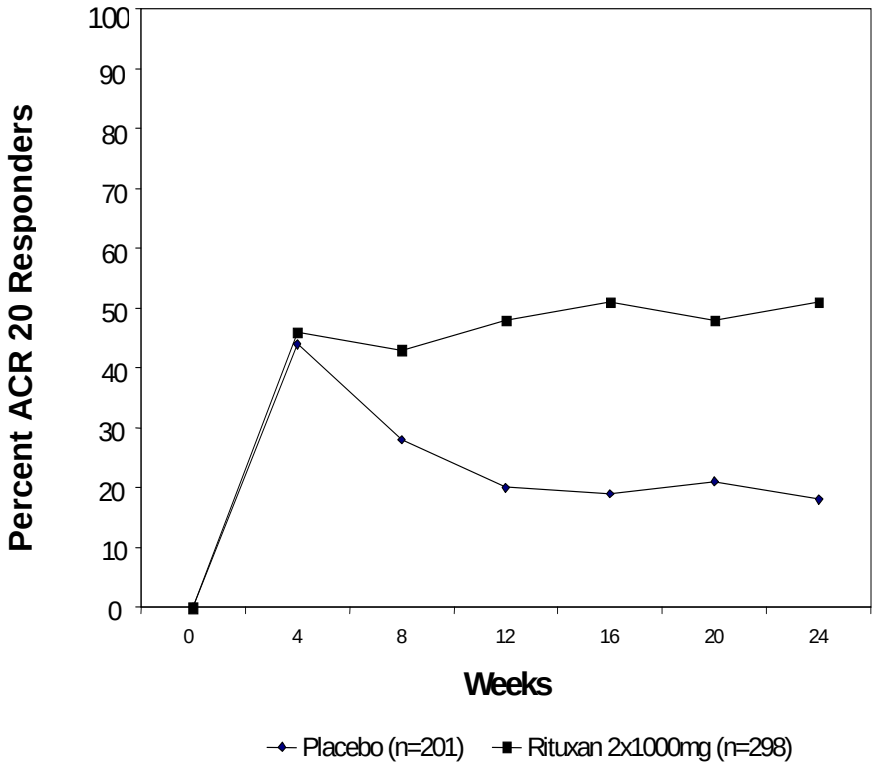
Inadequate Response to TNF Antagonists				
Parameter (median)	Placebo + MTX (n = 201)		Rituxan + MTX (n = 298)	
	Baseline	Wk 24	Baseline	Wk 24
Tender Joint Count	31.0	27.0	33.0	13.0
Swollen Joint Count	20.0	19.0	21.0	9.5
Physician Global Assessment[a]	71.0	69.0	71.0	36.0
Patient Global Assessment[a]	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.

The time course of ACR 20 response for Study 1 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. A similar proportion of patients achieved these responses 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
Percent of Patients Achieving ACR 20 Response by Visit*
Study 1 (Inadequate Response to TNF Antagonists)



*The same patients may not have responded at each time point.

Radiographic Response

In RA Study 1, structural joint damage was assessed radiographically and expressed as changes in Genant-modified Total Sharp Score (TSS) and its components, the erosion score (ES) and the joint space narrowing (JSN) score. Rituxan + MTX slowed the progression of structural damage compared to placebo + MTX after 1 year as shown in Table 10.

Table 10

Mean Radiographic Change From Baseline to 104 Weeks

Inadequate Response to TNF Antagonists				
Parameter	Rituxan 2 x 1000 mg + MTX[b]	Placebo + MTX[c]	Treatment Difference (Placebo – Rituxan)	95% CI
Change during First Year				
TSS	0.66	1.78	1.12	(0.48, 1.76)
ES	0.44	1.19	0.75	(0.32, 1.18)
JSN Score	0.22	0.59	0.37	(0.11, 0.63)
Change during Second Year[a]				
TSS	0.48	1.04	—	—
ES	0.28	0.62	—	—
JSN Score	0.20	0.42	—	—

[a] Based on radiographic scoring following 104 weeks of observation.

[b] Patients received up to 2 years of treatment with Rituxan + MTX.

[c] Patients receiving Placebo + MTX. Patients receiving Placebo + MTX could have received retreatment with Rituxan + MTX from Week 16 onward.

In RA Study 1 and its open-label extension, 70% of patients initially randomized to Rituxan + MTX and 72% of patients initially randomized to placebo + MTX were evaluated radiographically at Year 2. As shown in Table 10, progression of structural damage in Rituxan + MTX patients was further reduced in the second year of treatment.

Following 2 years of treatment with Rituxan + MTX, 57% of patients had no progression of structural damage. During the first year, 60% of Rituxan + MTX treated patients had no progression, defined as a change in TSS of zero or less compared to baseline, compared to 46% of placebo + MTX treated patients. In their second year of treatment with Rituxan + MTX, more patients had no progression than in the first year (68% vs. 60%), and 87% of the Rituxan + MTX treated patients who had no progression in the first year also had no progression in the second year.

Lesser Efficacy of 500 Vs. 1000 mg Treatment Courses for Radiographic Outcomes

RA Study 3 is a randomized, double-blind, placebo-controlled study which evaluated the effect of placebo + MTX compared to Rituxan 2 x 500 mg + MTX and Rituxan 2 x 1000 mg + MTX treatment courses in MTX-naïve RA patients with moderately to severely active disease. Patients received a first course of two infusions of rituximab or placebo on Days 1 and 15. MTX was initiated at 7.5 mg/week and escalated up to 20 mg/week by week 8 in all three treatment arms. After a minimum of 24 weeks, patients with ongoing disease activity were eligible to receive re-treatment with additional courses of their assigned treatment. After one year of treatment, the proportion of patients achieving ACR 20/50/70 responses were similar in both Rituxan dose groups and were higher than in the placebo group. However, with respect to radiographic scores, only the Rituxan 1000 mg treatment group demonstrated a statistically significant reduction in TSS: a change of 0.36 units compared to 1.08 units for the placebo group, a 67% reduction.

Physical Function Response

RA Study 4 is a randomized, double-blind, placebo-controlled study in adult RA patients with moderately to severely active disease with inadequate response to MTX. Patients were randomized to receive an initial course of Rituxan 500 mg, Rituxan 1000 mg, or placebo in addition to background MTX.

Physical function was assessed at Weeks 24 and 48 using the Health Assessment Questionnaire Disability Index (HAQ-DI). From baseline to Week 24, a greater proportion of Rituxan-treated patients had an improvement in HAQ-DI of at least 0.22 (a minimal clinically important difference) and a greater mean HAQ-DI improvement compared to placebo, as shown in Table 11. HAQ-DI results for the Rituxan 500 mg treatment group were similar to the Rituxan 1000 mg treatment group; however radiographic responses were not assessed (see Dosing Precaution in the Radiographic Responses section above). These improvements were maintained at 48 weeks.

Table 11

Improvement from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 24 in Study 4

	Placebo + MTX n = 172	Rituxan 2 x 1000 mg + MTX n = 170	Treatment Difference (Rituxan – Placebo)[b] (95% CI)
Mean Improvement from Baseline	0.19	0.42	0.23 (0.11, 0.34)
Percent of patients with "Improved" score (Change from Baseline ≥ MCID)[a]	48%	58%	11% (0%, 21%)

[a] Minimal Clinically Important Difference: MCID for HAQ = 0.22.

[b] Adjusted difference stratified by region (US, rest of the world) and rheumatoid factor (RF) status (positive ≥ 20 IU/mL, negative < 20 IU/mL) at baseline.

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

Patients should be provided the Rituxan Medication Guide and provided an opportunity to read prior to each treatment session. It is important that the patient's overall health be assessed at each visit and the risks of Rituxan therapy 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.

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

Read this Medication Guide before you start Rituxan and before each Rituxan infusion. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or your treatment.

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

Rituxan can cause serious side effects that can lead to death, including:

1. **Infusion reactions.** Infusion reactions are the most common side effect of Rituxan treatment. Serious infusion reactions can happen during your infusion or within 24 hours after your infusion of Rituxan. Your doctor should give you medicines before your infusion of Rituxan to decrease your chance of having a severe infusion reaction.

   Tell your doctor or get medical help right away if you get any of these symptoms during or after an infusion of Rituxan:

   - hives (red itchy welts) or rash
   - itching
   - swelling of your lips, tongue, throat or face
   - sudden cough
   - shortness of breath, difficulty breathing, or wheezing
   - weakness
   - dizziness or feel faint
   - palpitations (feel like your heart is racing or fluttering)
   - chest pain

2. **Progressive Multifocal Leukoencephalopathy (PML).** PML is a rare, serious brain infection caused by a virus. People with weakened immune system can get PML. Your chance of getting PML may be higher if you are treated with Rituxan alone or with other medicines that weaken your immune system. PML can result in death or severe disability. There is no known treatment, prevention, or cure for PML.

   Tell your doctor right away if you have any of the following symptoms or if anyone close to you notices these symptoms:

   - confusion or problems thinking
   - loss of balance
   - change in the way you walk or talk
   - decreased strength or weakness on one side of your body
   - blurred vision or loss of vision

3. **Tumor Lysis Syndrome (TLS).** TLS is caused by the fast breakdown of cancer cells. TLS can cause you to have:

   - kidney failure and the need for dialysis treatment

- abnormal heart rhythm

Your doctor may do blood tests to check you for TLS. Your doctor may give you medicine to help prevent TLS.

4. **Severe skin and mouth reactions.** Tell your doctor or get medical help right away if you get any of these symptoms at anytime during your treatment with Rituxan:

- painful sores or ulcers on your skin, lips or in your mouth
- blisters
- peeling skin
- rash
- pustules

See "**What are possible side effects of Rituxan?"** for more information about side effects.

What is Rituxan?

Rituxan is a prescription medicine used to treat:

- **Non-Hodgkin's Lymphoma (NHL):** alone or with other chemotherapy medicines.
- **Chronic Lymphocytic Leukemia (CLL):** with the chemotherapy medicines fludarabine and cyclophosphamide.
- **Rheumatoid Arthritis (RA):** with another prescription medicine called methotrexate, to reduce the signs and symptoms of moderate to severe active RA in adults, after treatment with at least one other medicine called a Tumor Necrosis Factor (TNF) antagonist has been used and did not work well enough.

People with serious infections should not receive Rituxan.
It is not known if Rituxan is safe or effective in children.

What should I tell my doctor before receiving Rituxan?
Before receiving Rituxan, tell your doctor if you:

- have had a severe infusion reaction to Rituxan in the past
- have a history of heart problems, irregular heart beat or chest pain
- have lung or kidney problems
- have an infection or weakened immune system.
- have or have had any severe infections including:
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - Cytomegalovirus (CMV)
  - Herpes simplex virus (HSV)
  - Parvovirus B19
  - Varicella zoster virus (chickenpox or shingles)

- West Nile Virus

- have had a recent vaccination or are scheduled to receive vaccinations. You should not receive certain vaccines before or after you receive Rituxan. Tell your doctor if anyone in your household is scheduled to receive a vaccination. Some types of vaccines can spread to people with a weakened immune system, and cause serious problems.
- have any other medical conditions
- are pregnant or planning to become pregnant. Rituxan may affect the white blood cell counts of your unborn baby. It is not known if Rituxan may harm your unborn baby in other ways.

  Women who are able to become pregnant should use effective birth-control (contraception) while using Rituxan and for 12 months after you finish treatment. Talk to your doctor about effective birth control.
- are breast-feeding or plan to breast-feed. It is not known if Rituxan passes into your breast milk. You and your doctor should decide the best way to feed your baby if you receive Rituxan.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Especially tell your doctor if you take or have taken:

- a Tumor Necrosis Factor (TNF) inhibitor medicine
- a Disease Modifying Anti-Rheumatic Drug (DMARD)

If you are not sure if your medicine is one listed above, ask your doctor or pharmacist.

Know the medicines you take. Keep a list of them to show to your doctor and pharmacist when you get a new medicine. Do not take any new medicine without talking with your doctor.

How will I receive Rituxan?

- Rituxan is given by infusion 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. Tell your doctor or nurse about any new symptoms.

What are the possible side effects of Rituxan?

Rituxan can cause serious and life-threatening side effects, including:

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

- **Hepatitis B virus (HBV) reactivation.** If you have had hepatitis B or are a carrier of hepatitis B virus, receiving Rituxan could cause the virus to become an active infection again. This may cause serious liver problems including liver

failure, and death. You should not receive Rituxan if you have active hepatitis B liver disease.

- **Serious infections.** Serious infections that happen with Rituxan can lead to death. Call your doctor right away if you have any symptoms of infection:
  - fever
  - cold symptoms, such as runny nose or sore throat that do not go away
  - flu symptoms, such as cough, tiredness, and body aches
  - earache or headache
  - pain during urination
  - white patches in the mouth or throat
  - cuts, scrapes or incisions that are red, warm, swollen or painful
- **Heart problems.** Rituxan may cause chest pain and irregular heart beats which may need treatment, or your doctor may decide to stop your treatment with Rituxan.
- **Kidney problems,** especially if you are receiving Rituxan for NHL. Your doctor should do blood test to check how well your kidneys are working.
- **Stomach and Serious bowel problems that can sometimes lead to death.** Bowel problems, including blockage or tears in the bowel can happen if you receive Rituxan with chemotherapy medicines to treat non-Hodgkin's lymphoma. Tell your doctor right away if you have any stomach area pain during treatment with Rituxan.
- **Low blood cell counts.** Your doctor may do blood test during treatment with Rituxan to check you blood cell counts.
  - **White blood cells.** White blood cells fight against bacterial infections. Low white blood cells can cause you to get infections, which may be serious. See "Increased risk of infections" above for a list of symptoms of infection.
  - **Red blood cells.** Red blood cells carry oxygen to your body tissues and organs.
  - **Platelets.** Platelets are blood cells that help your blood to clot.

Common side effects during Rituxan treatment include:

- infusion reactions (see What is the most important information I should know about Rituxan?)
- chills
- infections
- body aches
- tiredness
- low white blood cells

Other side effects with Rituxan include:

- aching joints during or within hours of receiving an infusion
- more frequent upper respiratory tract infection

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. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about Rituxan

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide provides a summary of the most important information about Rituxan. If you would like more information talk with your doctor. You can ask your doctor for information about Rituxan that is written for healthcare professionals.

For more information, go to 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.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

Revised 02/2010 (4851501)

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