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, NHL (1.1)	01/2011
Indications and Usage, WG and MPA (1.4)	04/2011
Dosage and Administration, NHL (2.2)	01/2011
Dosage and Administration, WG and MPA (2.6)	04 2011
Dosage and Administration, Recommended Concomitant Medications (2.7)	04/2011
Warnings and Precautions, HBV Reactivation (5.5)	01/2011
Warnings and Precautions, Concomitant Use with Biologic Agents and DMARDS other than Methotrexate in RA, WG and MPA (5.12)	04/2011
Warnings and Precautions, Retreatment in Patients with WG and MPA (5.14)	04/2011

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)
- Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids (1.4)

Limitations of Use: Rituxan is not recommended for use in patients with severe, active infections (1.5).

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).
- The dose for WG and MPA in combination with glucocorticoids is 375 mg/m^2 once weekly for 4 weeks (2.6).

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 (5.6).
- 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).
- Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA): Common adverse reactions (≥15 %) in the clinical study were infections, nausea, diarrhea, headache, muscle spasms, anemia, peripheral edema (6.3). Other important adverse reactions include infusion reactions (6.3).

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: 04/2011

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) 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)*].

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 first line chemotherapy and, in patients achieving a complete or partial response to Rituxan in combination with chemotherapy, as single-agent maintenance therapy.
- 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 Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

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

1.5 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 (2.7)*]. Administer only as an intravenous (IV) infusion [*see Dosage and Administration (2.7)*].

- **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 chemotherapy, for up to 8 doses. In patients with complete or partial response, initiate Rituxan maintenance eight weeks following completion of Rituxan in combination with chemotherapy. Administer Rituxan as a single-agent every 8 weeks for 12 doses.
- **Non-progressing, Low-Grade, CD20-Positive, B-cell NHL, after first-line CVP chemotherapy**
  Following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses.
- **Diffuse Large B-Cell NHL**
  Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions.

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

- Administer Rituxan as a 375 mg/m^2 intravenous infusion once weekly for 4 weeks.
- Glucocorticoids administered as methylprednisolone 1000 mg intravenously per day for 1 to 3 days followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day and tapered per clinical need) are recommended to treat severe vasculitis symptoms. This regimen should begin within 14 days prior to or with the initiation of Rituxan and may continue during and after the 4 week course of Rituximab treatment.
- Safety and efficacy of treatment with subsequent courses of Rituxan have not been established [*see Warnings and Precautions (5.14)*].

2.7 Recommended Concomitant Medications

Premedicate before each infusion with acetaminophen and an antihistamine.

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

For WG and MPA patients, glucocorticoids are given in combination with Rituxan [*see Dosage and Administration (2.6)*].

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.

PCP prophylaxis is also recommended for patients with WG and MPA during treatment and for at least 6 months following the last Rituxan infusion

2.8 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 intravenously 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).*]

143 **5.2 Tumor Lysis Syndrome (TLS)**

144 Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from
145 tumor lysis, some fatal, can occur within 12–24 hours after the first infusion of Rituxan in patients
146 with NHL. A high number of circulating malignant cells ($\geq$25,000/mm^3) or high tumor burden,
147 confers a greater risk of TLS.

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

152 **5.3 Severe Mucocutaneous Reactions**

153 Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with Rituxan.
154 These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis,
155 vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has varied
156 from 1–13 weeks following Rituxan exposure. Discontinue Rituxan in patients who experience a
157 severe mucocutaneous reaction. The safety of readministration of Rituxan to patients with severe
158 mucocutaneous reactions has not been determined. [*See Boxed Warning, Adverse Reactions (6, 6.1).*]

159 **5.4 Progressive Multifocal Leukoencephalopathy (PML)**

160 JC virus infection resulting in PML and death can occur in Rituxan-treated patients with
161 hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic
162 malignancies diagnosed with PML received Rituxan in combination with chemotherapy or as part of
163 a hematopoietic stem cell transplant. The patients with autoimmune diseases had prior or concurrent
164 immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last
165 infusion of Rituxan.

166 Consider the diagnosis of PML in any patient presenting with new-onset neurologic
167 manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist,
168 brain MRI, and lumbar puncture. Discontinue Rituxan and consider discontinuation or reduction of
169 any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML. [*See*
170 *Boxed Warning, Adverse Reactions (6).*]

171 **5.5 Hepatitis B Virus (HBV) Reactivation**

172 Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death can occur
173 in patients treated with Rituxan. The median time to the diagnosis of hepatitis among patients with
174 hematologic malignancies was approximately 4 months after the initiation of Rituxan and
175 approximately one month after the last dose.

176 Screen patients at high risk of HBV infection before initiation of Rituxan. Closely monitor
177 carriers of hepatitis B for clinical and laboratory signs of active HBV infection for several months
178 following Rituxan therapy. Discontinue Rituxan and any concomitant chemotherapy in patients who
179 develop viral hepatitis, and institute appropriate treatment including antiviral therapy. Insufficient
180 data exist regarding the safety of resuming Rituxan in patients who develop hepatitis subsequent to
181 HBV reactivation. [*See Adverse Reactions (6.5).*]

182 **5.6 Infections**

183 Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during
184 and up to one year following the completion of Rituxan-based therapy. New or reactivated viral
185 infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus,
186 West Nile virus, and hepatitis B and C. Discontinue Rituxan for serious infections and institute
187 appropriate anti-infective therapy. [*See Adverse Reactions (6, 6.1).*]

188 **5.7 Cardiovascular**

189 Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac
190 monitoring during and after all infusions of Rituxan for patients who develop clinically significant
191 arrhythmias, or who have a history of arrhythmia or angina. [*See Adverse Reactions (6).*]

192 **5.8 Renal**
193 Severe, including fatal, renal toxicity can occur after Rituxan administration in patients with NHL.
194 Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with
195 NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin
196 and Rituxan is not an approved treatment regimen. Monitor closely for signs of renal failure and
197 discontinue Rituxan in patients with a rising serum creatinine or oliguria. [*See Warnings and*
198 *Precautions (5.2).*]
199 **5.9 Bowel Obstruction and Perforation**
200 Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in
201 patients receiving Rituxan in combination with chemotherapy. In postmarketing reports, the mean
202 time to documented gastrointestinal perforation was 6 (range 1–77) days in patients with NHL.
203 Perform a thorough diagnostic evaluation and institute appropriate treatment for complaints of
204 abdominal pain. [*See Adverse Reactions (6).*]
205 **5.10 Immunization**
206 The safety of immunization with live viral vaccines following Rituxan therapy has not been
207 studied and vaccination with live virus vaccines is not recommended.
208 For RA patients, physicians should follow current immunization guidelines and administer
209 non-live vaccines at least 4 weeks prior to a course of Rituxan.
210 The effect of Rituxan on immune responses was assessed in a randomized, controlled study in
211 patients with RA treated with Rituxan and methotrexate (MTX) compared to patients treated with
212 MTX alone.
213 A response to pneumococcal vaccination (a T-cell independent antigen) as measured by an
214 increase in antibody titers to at least 6 of 12 serotypes was lower in patients treated with Rituxan
215 plus MTX as compared to patients treated with MTX alone (19% vs. 61%). A lower proportion of
216 patients in the Rituxan plus MTX group developed detectable levels of anti-keyhole limpet
217 hemocyanin antibodies (a novel protein antigen) after vaccination compared to patients on MTX
218 alone (47% vs. 93%).
219 A positive response to tetanus toxoid vaccine (a T-cell dependent antigen with existing immunity)
220 was similar in patients treated with Rituxan plus MTX compared to patients on MTX alone (39% vs.
221 42%). The proportion of patients maintaining a positive Candida skin test (to evaluate delayed type
222 hypersensitivity) was also similar (77% of patients on Rituxan plus MTX vs. 70% of patients on
223 MTX alone).
224 Most patients in the Rituxan-treated group had B-cell counts below the lower limit of normal at
225 the time of immunization. The clinical implications of these findings are not known.
226 **5.11 Laboratory Monitoring**
227 In patients with lymphoid malignancies, during treatment with Rituxan monotherapy, obtain
228 complete blood counts (CBC) and platelet counts prior to each Rituxan course. During treatment
229 with Rituxan and chemotherapy, obtain CBC and platelet counts at weekly to monthly intervals and
230 more frequently in patients who develop cytopenias [*see Adverse Reactions (6.1)*]. In patients with
231 RA, WG or MPA, obtain CBC and platelet counts at two to four month intervals during Rituxan
232 therapy. The duration of cytopenias caused by Rituxan can extend months beyond the treatment
233 period.
234 **5.12 Concomitant Use with Biologic Agents and DMARDS other than Methotrexate in RA,**
235 **WG and MPA**
236 Limited data are available on the safety of the use of biologic agents or DMARDs other than
237 methotrexate in RA patients exhibiting peripheral B-cell depletion following treatment with
238 rituximab. Observe patients closely for signs of infection if biologic agents and/or DMARDs are
239 used concomitantly. Use of concomitant immunosuppressants other than corticosteroids has not
240 been studied in WG or MPA patients exhibiting peripheral B-cell depletion following treatment with
241 Rituxan.

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 (14.5)*]

5.14 Retreatment in Patients with Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

Limited data are available on the safety and efficacy of subsequent courses of Rituxan in patients with WG and MPA. The safety and efficacy of retreatment with Rituxan have not been established [*see Dosage and Administration (2.6), Adverse Reactions (6.3), and 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 2783 patients, with exposures ranging from a single infusion up to 2 years. Rituxan was studied in both single-arm and controlled trials (n=356 and n = 2427=1926). The population included 1180 patients with low grade or 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%)

291 and decreased with each subsequent infusion. [*See Boxed Warning, Warnings and*
292 *Precautions (5.1).*]

293 *Infections*

294 Serious infections (NCI CTCAE Grade 3 or 4), including sepsis, occurred in less than 5% of
295 patients with NHL in the single-arm studies. The overall incidence of infections was 31% (bacterial
296 19%, viral 10%, unknown 6%, and fungal 1%). [*See Warnings and Precautions (5.4), (5.5), (5.6).*]
297 In randomized, controlled studies where Rituxan was administered following chemotherapy for
298 the treatment of follicular or low-grade NHL, the rate of infection was higher among patients who
299 received Rituxan. In diffuse large B-cell lymphoma patients, viral infections occurred more
300 frequently in those who received Rituxan.

301 *Cytopenias and hypogammaglobulinemia*

302 In patients with NHL receiving rituximab monotherapy, NCI-CTC Grade 3 and 4 cytopenias were
303 reported in 48% of patients. These included lymphopenia (40%), neutropenia (6%), leukopenia
304 (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days
305 (range, 1–588 days) and of neutropenia was 13 days (range, 2–116 days). A single occurrence of
306 transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following
307 Rituxan therapy occurred during the single-arm studies.
308 In studies of monotherapy, Rituxan-induced B-cell depletion occurred in 70% to 80% of patients
309 with NHL. Decreased IgM and IgG serum levels occurred in 14% of these patients.

310 *Relapsed or Refractory, Low-Grade NHL*

311 Adverse reactions in Table 1 occurred in 356 patients with relapsed or refractory, low-grade or
312 follicular, CD20-positive, B-cell NHL treated in single-arm studies of Rituxan administered as a
313 single agent [*see Clinical Studies (14.1)*]. Most patients received Rituxan 375 mg/m^2 weekly for
314 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
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

315

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 (%)
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 or Follicular, 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, detailed safety data collection was limited to serious adverse reactions, Grade ≥ 2 infections, and Grade ≥ 3 adverse reactions. In patients receiving Rituxan as single-agent maintenance therapy following Rituxan plus chemotherapy, infections were reported more frequently compared to the observation arm (37% vs. 22%). Grade 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in the Rituxan group were infections (4% vs. 1%) and neutropenia (4% vs. <1%).

In Study 6, 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 7 and 8, [*see Clinical Studies (14.3)*], 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 8, 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 8), neutropenia (Studies 8 and 9), and anemia (Study 9).

352 *CLL*
353 The data below reflect exposure to Rituxan in combination with fludarabine and
354 cyclophosphamide in 676 patients with CLL in Study 10 or Study 11 [*see Clinical Studies (14.4)*].
355 The age range was 30–83 years and 71% were men. Detailed safety data collection in Study 10 was
356 limited to Grade 3 and 4 adverse reactions and serious adverse reactions.
357 Infusion-related adverse reactions were defined by any of the following adverse events occurring
358 during or within 24 hours of the start of infusion: nausea, pyrexia, chills, hypotension, vomiting, and
359 dyspnea.
360 In Study 10, the following Grade 3 and 4 adverse reactions occurred more frequently in
361 R-FC-treated patients compared to FC-treated patients: infusion reactions (9% in R-FC arm),
362 neutropenia (30% vs. 19%), febrile neutropenia (9% vs. 6%), leukopenia (23% vs. 12%), and
363 pancytopenia (3% vs. 1%).
364 In Study 11, the following Grade 3 or 4 adverse reactions occurred more frequently in
365 R-FC-treated patients compared to FC-treated patients: infusion reactions (7% in R-FC arm),
366 neutropenia (49% vs. 44%), febrile neutropenia (15% vs. 12%), thrombocytopenia (11% vs. 9%),
367 hypotension (2% vs. 0%), and hepatitis B (2% vs. <1%). Fifty-nine percent of R-FC-treated patients
368 experienced an infusion reaction of any severity.
369 **6.2 Clinical Trials Experience in Rheumatoid Arthritis**
370 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
371 observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of
372 another drug and may not reflect the rates observed in practice.
373 The data presented below reflect the experience in 2578 RA patients treated with Rituxan in
374 controlled and long-term studies with a total exposure of 5014 patient-years.
375 Among all exposed patients, adverse reactions reported in greater than 10% of patients include
376 infusion-related reactions, upper respiratory tract infection, nasopharyngitis, urinary tract infection,
377 and bronchitis.
378 In placebo-controlled studies, patients received 2 x 500 mg or 2 x 1000 mg intravenous infusions
379 of Rituxan or placebo, in combination with methotrexate, during a 24-week period. From these
380 studies, 938 patients treated with Rituxan (2 x 1000 mg) or placebo have been pooled (see Table 2).
381 Adverse reactions reported in ≥ 5% of patients were hypertension, nausea, upper respiratory tract
382 infection, arthralgia, pyrexia and pruritus (see Table 2). The rates and types of adverse reactions in
383 patients who received Rituxan 2 x 500 mg were similar to those observed in patients who received
384 Rituxan 2 x 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 × 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

403 reactions. Patients in clinical studies also received antihistamines and acetaminophen prior to
404 Rituxan infusions.

405 *Infections*

406 In the pooled, placebo-controlled studies, 39% of patients in the Rituxan group experienced an
407 infection of any type compared to 34% of patients in the placebo group. The most common
408 infections were nasopharyngitis, upper respiratory tract infections, urinary tract infections,
409 bronchitis, and sinusitis.

410 The incidence of serious infections was 2% in the Rituxan-treated patients and 1% in the placebo
411 group.

412 In the experience with Rituxan in 2578 RA patients, the rate of serious infections was 4.31 per
413 100 patient years. The most common serious infections (≥0.5%) were pneumonia or lower
414 respiratory tract infections, cellulitis and urinary tract infections. Fatal serious infections included
415 pneumonia, sepsis and colitis. Rates of serious infection remained stable in patients receiving
416 subsequent courses. In 185 Rituxan-treated RA patients with active disease, subsequent treatment
417 with a biologic DMARD, the majority of which were TNF antagonists, did not appear to increase the
418 rate of serious infection. Thirteen serious infections were observed in 186.1 patient years (6.99 per
419 100 patient years) prior to exposure and 10 were observed in 182.3 patient years (5.49 per
420 100 patient years) after exposure.

421 *Cardiac Adverse Reactions*

422 In the pooled, placebo-controlled studies, the proportion of patients with serious cardiovascular
423 reactions was 1.7% and 1.3% in the Rituxan and placebo treatment groups, respectively. Three
424 cardiovascular deaths occurred during the double-blind period of the RA studies including all
425 rituximab regimens (3/769=0.4%) as compared to none in the placebo treatment group (0/389).

426 In the experience with Rituxan in 2578 RA patients, the rate of serious cardiac reactions was
427 1.93 per 100 patient years. The rate of myocardial infarction (MI) was 0.56 per 100 patient years
428 (28 events in 26 patients), which is consistent with MI rates in the general RA population. These
429 rates did not increase over three courses of Rituxan.

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

433 *Hypophosphatemia and hyperuricemia*

434 In the pooled, placebo-controlled studies, newly-occurring hypophosphatemia (<2.0 mg/dl) was
435 observed in 12% (67/540) of patients on Rituxan versus 10% (39/398) of patients on placebo.
436 Hypophosphatemia was more common in patients who received corticosteroids. Newly-occurring
437 hyperuricemia (>10 mg/dl) was observed in 1.5% (8/540) of patients on Rituxan versus 0.3% (1/398)
438 of patients on placebo.

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

443 *Retreatment in Patients with RA*

444 In the experience with Rituxan in RA patients, 2578 patients have been exposed to Rituxan and
445 have received up to 10 courses of Rituxan in RA clinical trials, with 1890, 1043, and 425 patients
446 having received at least two, three, and four courses, respectively. Most of the patients who received
447 additional courses did so 24 weeks or more after the previous course and none were retreated sooner
448 than 16 weeks. The rates and types of adverse reactions reported for subsequent courses of Rituxan
449 were similar to rates and types seen for a single course of Rituxan.

450 In RA Study 2, where all patients initially received Rituxan, the safety profile of patients who
451 were retreated with Rituxan was similar to those who were retreated with placebo [*see Clinical*
452 *Studies (14.5), and Dosage and Administration (2.5).*]

453 **6.3 Clinical Trial Experience in Wegener's Granulomatosis (WG) and Microscopic**
454 **Polyangiitis (MPA)**

455 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
456 observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of
457 another drug and may not reflect the rates observed in practice.

458 The data presented below reflect the experience in 197 patients with WG and MPA treated with
459 Rituxan or cyclophosphamide in a single controlled study, which was conducted in two phases: a
460 6 month randomized, double-blind, double-dummy, active-controlled remission induction phase and
461 an additional 12 month remission maintenance phase. In the 6-month remission induction phase,
462 197 patients with WG and MPA were randomized to either Rituxan 375 mg/ m^2 once weekly for
463 4 weeks plus glucocorticoids, or oral cyclophosphamide 2 mg/kg daily (adjusted for renal function,
464 white blood cell count, and other factors) plus glucocorticoids to induce remission. Once remission
465 was achieved or at the end of the 6 month remission induction period, the cyclophosphamide group
466 received azathioprine to maintain remission. The Rituxan group did not receive additional therapy
467 to maintain remission. The primary analysis was at the end of the 6 month remission induction
468 period and the safety results for this period are described below.

469 Adverse reactions presented below in Table 3 were adverse events which occurred at a rate of
470 greater than or equal to 10% in the Rituxan group. This table reflects experience in 99 WG and
471 MPA patients treated with Rituxan, with a total of 47.6 patient-years of observation and 98 WG and
472 MPA patients treated with cyclophosphamide, with a total of 47.0 patient-years of observation.
473 Infection was the most common category of adverse events reported (47-62%) and is discussed
474 below.

Table 3
Incidence of All Adverse Reactions
Occurring in ≥ 10% of Rituxan-treated WG and MPA Patients
in the Clinical Study Up to Month 6*

Preferred Term	Rituxan N=99 n (%)	Cyclophosphamide N=98 n (%)
Nausea	18 (18%)	20 (20%)
Diarrhea	17 (17%)	12 (12%)
Headache	17 (17%)	19 (19%)
Muscle spasms	17 (17%)	15 (15%)
Anemia	16 (16%)	20 (20%)
Peripheral edema	16 (16%)	6 (6%)
Insomnia	14 (14%)	12 (12%)
Arthralgia	13 (13%)	9 (9%)
Cough	13 (13%)	11 (11%)
Fatigue	13 (13%)	21 (21%)
Increased ALT	13 (13%)	15 (15%)
Hypertension	12 (12%)	5 (5%)
Epistaxis	11 (11%)	6 (6%)
Dyspnea	10 (10%)	11 (11%)
Leukopenia	10 (10%)	26 (27%)
Rash	10 (10%)	17 (17%)

*The study design allowed for crossover or treatment by best medical judgment, and 13 patients in each treatment group received a second therapy during the 6 month study period.

Infusion Reactions

Infusion-related reactions in the active-controlled, double-blind study were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators. Among the 99 patients treated with Rituxan, 12% experienced at least one infusion related reaction, compared with 11% of the 98 patients in the cyclophosphamide group. Infusion-related reactions included cytokine release syndrome, flushing, throat irritation, and tremor. In the Rituxan group, the proportion of patients experiencing an infusion related reaction was 12%, 5%, 4%, and 1% following the first, second, third, and fourth infusions, respectively. Patients were pre-medicated with antihistamine and acetaminophen before each Rituxan infusion and were on background oral corticosteroids which may have mitigated or masked an infusion reaction; however, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of infusion reactions.

Infections

In the active-controlled, double-blind study, 62% (61/99) of patients in the Rituxan group experienced an infection of any type compared to 47% (46/98) patients in the cyclophosphamide group by Month 6. The most common infections in the Rituxan group were upper respiratory tract infections, urinary tract infections, and herpes zoster.

The incidence of serious infections was 11% in the Rituxan-treated patients and 10% in the cyclophosphamide treated patients, with rates of approximately 25 and 28 per 100 patient-years, respectively. The most common serious infection was pneumonia.

Retreatment in Patients with WG and MPA

In the active-controlled, double-blind study, subsequent courses of Rituxan were allowed for patients experiencing a relapse of disease. The limited data preclude any conclusions regarding the safety of subsequent courses of Rituxan with WG and MPA [*see Dosage and Administration (2.6), and Warnings and Precautions (5.14)*].

6.4 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.

A total of 23/99 (23%) Rituxan-treated patients with WG and MPA tested positive for HACA by 18 months. The clinical relevance of HACA formation in Rituxan-treated patients is unclear.

6.5 Postmarketing Experience

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 fatal interstitial lung disease.
- Nervous system: Posterior Reversible Encephalopathy Syndrome (PRES) / Reversible Posterior Leukoencephalopathy Syndrome (RPLS).

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, moderate-severe rheumatoid arthritis, Wegener's Granulomatosis and Microscopic Polyangiitis 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 [*See Non-Clinical Toxicology (13.2)*].

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

Patients with previously untreated follicular NHL evaluated in Study 5 were randomized to Rituxan as single-agent maintenance therapy (n = 505) or observation (n = 513) after achieving a response to Rituxan in combination with chemotherapy. Of these, 123 (24%) patients in the Rituxan arm were age 65 or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other 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.

589 In exploratory analyses defined by age, there was no observed benefit from the addition of
590 Rituxan to fludarabine and cyclophosphamide among patients 70 years of age or older in Study 10 or
591 in Study 11; there was also no observed benefit from the addition of Rituxan to fludarabine and
592 cyclophosphamide among patients 65 years of age or older in Study 11 [*see Clinical Studies (14.4)*].
593 Patients 70 years or older received lower dose intensity of fludarabine and cyclophosphamide
594 compared to younger patients, regardless of the addition of Rituxan. In Study 10, the dose intensity
595 of Rituxan was similar in older and younger patients, however in Study 11 older patients received a
596 lower dose intensity of Rituxan.
597 The incidence of Grade 3 and 4 adverse reactions was higher among patients receiving R-FC who
598 were 70 years or older compared to younger patients for neutropenia [44% vs. 31% (Study 10); 56%
599 vs. 39% (Study 11)], febrile neutropenia [16% vs. 6% (Study 10)], anemia [5% vs. 2% (Study 10);
600 21% vs. 10% (Study 11)], thrombocytopenia [19% vs. 8% (Study 11)], pancytopenia [7% vs. 2%
601 (Study 10); 7% vs. 2% (Study 11)] and infections [30% vs. 14% (Study 11)].

602 *Rheumatoid Arthritis*

603 Among the 2578 patients in global RA studies completed to date, 12% were 65–75 years old and
604 2% were 75 years old and older. The incidences of adverse reactions were similar between older and
605 younger patients. The rates of serious adverse reactions, including serious infections, malignancies,
606 and cardiovascular events were higher in older patients.

607 *Wegener's Granulomatosis and Microscopic Polyangiitis*

608 Of the 99 Rituxan-treated WG and MPA patients, 36 (36%) were 65 years old and over, while
609 8 (8%) were 75 years and over. No overall differences in efficacy were observed between patients
610 that were 65 years old and over and younger patients. The overall incidence and rate of all serious
611 adverse events was higher in patients 65 years old and over. The clinical study did not include
612 sufficient numbers of patients aged 65 and over to determine whether they respond differently from
613 younger subjects.

614 10 OVERDOSAGE

615 There has been no experience with overdosage in human clinical trials. Single doses of up to
616 500 mg/m^2 have been administered in clinical trials.

617 11 DESCRIPTION

618 Rituxan® (rituximab) is a genetically engineered chimeric murine/human monoclonal IgG_1 kappa
619 antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of
620 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.
621 Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a
622 nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final
623 product. Rituxan is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous
624 administration. Rituxan is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or
625 500 mg/50 mL single-use vials. The product is formulated in polysorbate 80 (0.7 mg/mL), sodium
626 citrate dihydrate (7.35 mg/mL), sodium chloride (9 mg/mL) and Water for Injection. The pH is 6.5.

627 12 CLINICAL PHARMACOLOGY

628 12.1 Mechanism of Action

629 Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation
630 antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately
631 35 kD located on pre-B and mature B lymphocytes. The antigen is expressed on >90% of B-cell
632 non-Hodgkin's lymphomas (NHL), but the antigen is not found on hematopoietic stem cells,
633 pro-B-cells, normal plasma cells or other normal tissues. CD20 regulates an early step(s) in the
634 activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion
635 channel. CD20 is not shed from the cell surface and does not internalize upon antibody binding.
636 Free CD20 antigen is not found in the circulation.

637 B cells are believed to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated
638 chronic synovitis. In this setting, B cells may be acting at multiple sites in the
639 autoimmune/inflammatory process, including through production of rheumatoid factor (RF) and
640 other autoantibodies, antigen presentation, T-cell activation, and/or proinflammatory cytokine
641 production.
642 Mechanism of Action: The Fab domain of rituximab binds to the CD20 antigen on B
643 lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis *in vitro*.
644 Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and
645 antibody-dependent cell mediated cytotoxicity (ADCC). The antibody has been shown to induce
646 apoptosis in the DHL-4 human B-cell lymphoma line.
647 Normal Tissue Cross-reactivity: Rituximab binding was observed on lymphoid cells in the
648 thymus, the white pulp of the spleen, and a majority of B lymphocytes in peripheral blood and
649 lymph nodes. Little or no binding was observed in the non-lymphoid tissues examined.

650 **12.2 Pharmacodynamics**

651 *Non-Hodgkins Lymphoma (NHL)*

652 In NHL patients, administration of Rituxan resulted in depletion of circulating and tissue-based
653 B cells. Among 166 patients in Study 1, circulating CD19-positive B cells were depleted within the
654 first three weeks with sustained depletion for up to 6 to 9 months post treatment in 83% of patients.
655 B-cell recovery began at approximately 6 months and median B-cell levels returned to normal by
656 12 months following completion of treatment.
657 There were sustained and statistically significant reductions in both IgM and IgG serum levels
658 observed from 5 through 11 months following rituximab administration; 14% of patients had IgM
659 and/or IgG serum levels below the normal range.

660 *Rheumatoid Arthritis*

661 In RA patients, treatment with Rituxan induced depletion of peripheral B lymphocytes, with the
662 majority of patients demonstrating near complete depletion (CD19 counts below the lower limit of
663 quantification, 20 cells/μl) within 2 weeks after receiving the first dose of Rituxan. The majority of
664 patients showed peripheral B-cell depletion for at least 6 months. A small proportion of patients
665 (~4%) had prolonged peripheral B-cell depletion lasting more than 3 years after a single course of
666 treatment.
667 Total serum immunoglobulin levels, IgM, IgG, and IgA were reduced at 6 months with the
668 greatest change observed in IgM. At Week 24 of the first course of Rituxan treatment, small
669 proportions of patients experienced decreases in IgM (10%), IgG (2.8%), and IgA (0.8%) levels
670 below the lower limit of normal (LLN). In the experience with Rituxan in RA patients during
671 repeated Rituxan treatment, 23.3%, 5.5%, and 0.5% of patients experienced decreases in IgM, IgG,
672 and IgA concentrations below LLN at any time after receiving Rituxan, respectively. The clinical
673 consequences of decreases in immunoglobulin levels in RA patients treated with Rituxan are
674 unclear.
675 Treatment with rituximab in patients with RA was associated with reduction of certain biologic
676 markers of inflammation such as interleukin-6 (IL-6), C-reactive protein (CRP), serum amyloid
677 protein (SAA), S100 A8/S100 A9 heterodimer complex (S100 A8/9), anti-citrullinated peptide
678 (anti-CCP), and RF.

679 *Wegener's Granulomatosis and Microscopic Polyangiitis*

680 In WG and MPA patients, peripheral blood CD19 B-cells depleted to less than 10 cells/μl
681 following the first two infusions of Rituxan, and remained at that level in most (84%) patients
682 through Month 6. By Month 12, the majority of patients (81%) showed signs of B-cell return with
683 counts >10 cells/μL. By Month 18, most patients (87%) had counts >10 cells/μL.

12.3 Pharmacokinetics

Non-Hodgkins Lymphoma (NHL)

Pharmacokinetics were characterized in 203 NHL patients receiving 375 mg/m^2 Rituxan weekly by intravenous 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).

Rheumatoid Arthritis

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.

Wegener's Granulomatosis and Microscopic Polyangiitis

Based on the population pharmacokinetic analysis of data in 97 WG and MPA patients who received 375 mg/m^2 rituximab once weekly by intravenous infusion for four weeks, the estimated median terminal elimination half-life was 23 days (range, 9 to 49 days). Rituximab mean clearance and volume of distribution were 0. 312 L/day (range, 0.115 to 0.728 L/day) and 4.50 L (range, 2.21 to 7.52 L) respectively. Male patients and patients with higher BSA or positive HACA levels have higher clearance. However, further dose adjustment based on gender or HACA status is not necessary.

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 4. 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 4.

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 4.

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 4.

Table 4
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.

769

770 **14.2 Previously Untreated, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**

771 The safety and effectiveness of Rituxan in previously untreated, low-grade or follicular, CD20+
772 NHL were demonstrated in 3 randomized, controlled trials enrolling 1,662 patients.

773 *Study 4*

774 A total of 322 patients with previously untreated follicular NHL were randomized (1:1) to receive
775 up to eight 3-week cycles of CVP chemotherapy alone (CVP) or in combination with Rituxan
776 375 mg/m^2 on Day 1 of each cycle (R-CVP) in an open-label, multicenter study. The main outcome
777 measure of the study was progression-free survival (PFS) defined as the time from randomization to
778 the first of progression, relapse, or death.

779 Twenty-six percent of the study population was >60 years of age, 99% had Stage III or IV disease,
780 and 50% had an International Prognostic Index (IPI) score ≥2. The results for PFS as determined by
781 a blinded, independent assessment of progression are presented in Table 5. The point estimates may
782 be influenced by the presence of informative censoring. The PFS results based on investigator
783 assessment of progression were similar to those obtained by the independent review assessment.
784

Table 5
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.

785

786 *Study 5*

787 An open-label, multicenter, randomized (1:1) study was conducted in 1,018 patients with
788 previously untreated follicular NHL who achieved a response (CR or PR) to Rituxan in combination
789 with chemotherapy. Patients were randomized to Rituxan as single-agent maintenance therapy,

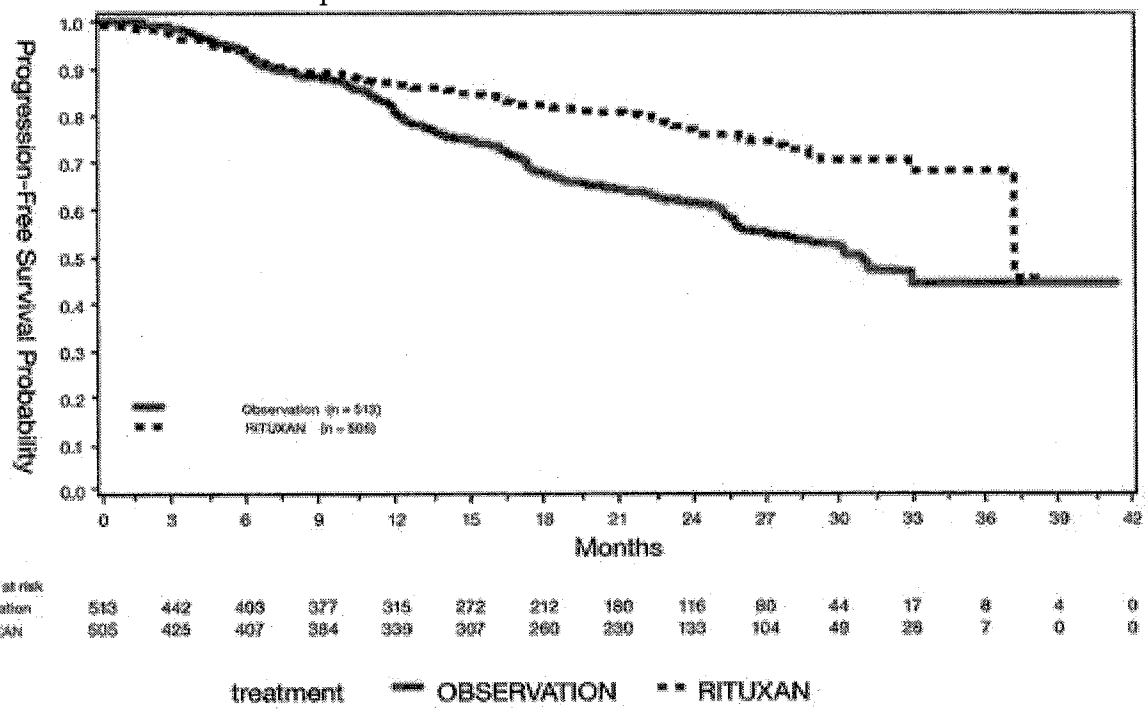
375 mg/m^2 every 8 weeks for up to 12 doses or to observation. Rituxan was initiated at 8 weeks following completion of chemotherapy. The main outcome measure of the study was progression-free survival (PFS), defined as the time from randomization in the maintenance/observation phase to progression, relapse, or death, as determined by independent review.

Of the randomized patients, 40% were ≥60 years of age, 70% had Stage IV disease, 96% had ECOG performance status (PS) 0–1, and 42% had FLIPI scores of 3–5. Prior to randomization to maintenance therapy, patients had received R-CHOP (75%), R-CVP (22%), or R-FCM (3%); 71% had a complete or unconfirmed complete response and 28% had a partial response.

PFS was longer in patients randomized to Rituxan as single agent maintenance therapy (HR: 0.54, 95% CI: 0.42, 0.70). The PFS results based on investigator assessment of progression were similar to those obtained by the independent review assessment.

Figure 1

Kaplan-Meier Plot of IRC Assessed PFS



Study 6

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.

14.3 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

822 cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based
823 chemotherapy regimens.

824 *Study 7*

825 A total of 632 patients age ≥ 60 years with DLBCL (including primary mediastinal B-cell
826 lymphoma) were randomized in a 1:1 ratio to treatment with CHOP or R-CHOP. Patients received
827 6 or 8 cycles of CHOP, each cycle lasting 21 days. All patients in the R-CHOP arm received 4 doses
828 of Rituxan 375 mg/m^2 on Days –7 and –3 (prior to Cycle 1) and 48–72 hours prior to Cycles 3 and
829 5. Patients who received 8 cycles of CHOP also received Rituxan prior to Cycle 7. The main
830 outcome measure of the study was progression-free survival, defined as the time from randomization
831 to the first of progression, relapse, or death. Responding patients underwent a second randomization
832 to receive Rituxan or no further therapy.

833 Among all enrolled patients, 62% had centrally confirmed DLBCL histology, 73% had
834 Stage III–IV disease, 56% had IPI scores ≥ 2, 86% had ECOG performance status of < 2, 57% had
835 elevated LDH levels, and 30% had two or more extranodal disease sites involved. Efficacy results
836 are presented in Table 6. These results reflect a statistical approach which allows for an evaluation
837 of Rituxan administered in the induction setting that excludes any potential impact of Rituxan given
838 after the second randomization.

839 Analysis of results after the second randomization in Study 7 demonstrates that for patients
840 randomized to R-CHOP, additional Rituxan exposure beyond induction was not associated with
841 further improvements in progression-free survival or overall survival.

842 *Study 8*

843 A total of 399 patients with DLBCL, age ≥ 60 years, were randomized in a 1:1 ratio to receive
844 CHOP or R-CHOP. All patients received up to eight 3-week cycles of CHOP induction; patients in
845 the R-CHOP arm received Rituxan 375 mg/m^2 on Day 1 of each cycle. The main outcome measure
846 of the study was event-free survival, defined as the time from randomization to relapse, progression,
847 change in therapy, or death from any cause. Among all enrolled patients, 80% had Stage III or IV
848 disease, 60% of patients had an age-adjusted IPI ≥ 2, 80% had ECOG performance status scores
849 < 2, 66% had elevated LDH levels, and 52% had extranodal involvement in at least two sites.
850 Efficacy results are presented in Table 6.

851 *Study 9*

852 A total of 823 patients with DLBCL, aged 18–60 years, were randomized in a 1:1 ratio to receive
853 an anthracycline-containing chemotherapy regimen alone or in combination with Rituxan. The main
854 outcome measure of the study was time to treatment failure, defined as time from randomization to
855 the earliest of progressive disease, failure to achieve a complete response, relapse, or death. Among
856 all enrolled patients, 28% had Stage III–IV disease, 100% had IPI scores of ≤ 1, 99% had ECOG
857 performance status of < 2, 29% had elevated LDH levels, 49% had bulky disease, and 34% had
858 extranodal involvement. Efficacy results are presented in Table 6.
859

Table 6
Efficacy Results in Studies 7, 8, and 9

	Study 7 (n=632)		Study 8 (n=399)		Study 9 (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 8, overall survival estimates at 5 years were 58% vs. 46% for R-CHOP and CHOP, respectively.

14.4 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 10 (n = 817)] or previously treated CLL [Study 11 (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 10, 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 11, 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 10) or an independent review committee (Study 11). The investigator assessed results in Study 11 were supportive of those obtained by the independent review committee. Efficacy results are presented in Table 7.

Table 7
Efficacy Results in Studies 10 and 11

	Study 10* (Previously untreated)		Study 11* (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 (95% CI)	86% (82, 89)	73% (68, 77)	54% (48, 60)	45% (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 8.

Table 8
Efficacy Results in Studies 10 and 11 in Subgroups Defined by Age[a]

	Study 10		Study 11	
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.

14.5 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 intravenous 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 9.

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

904 patients achieving ACR 20, 50, and 70 responses at Week 24, before the re-treatment course, and at
905 Week 48, after retreatment, are shown in Table 9.
906

Table 9
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).

907
908 Improvement was also noted for all components of ACR response following treatment with
909 Rituxan, as shown in Table 10.

Table 10
Components of ACR Response at Week 24 in Study 1
(Modified Intent-to-Treat Population)

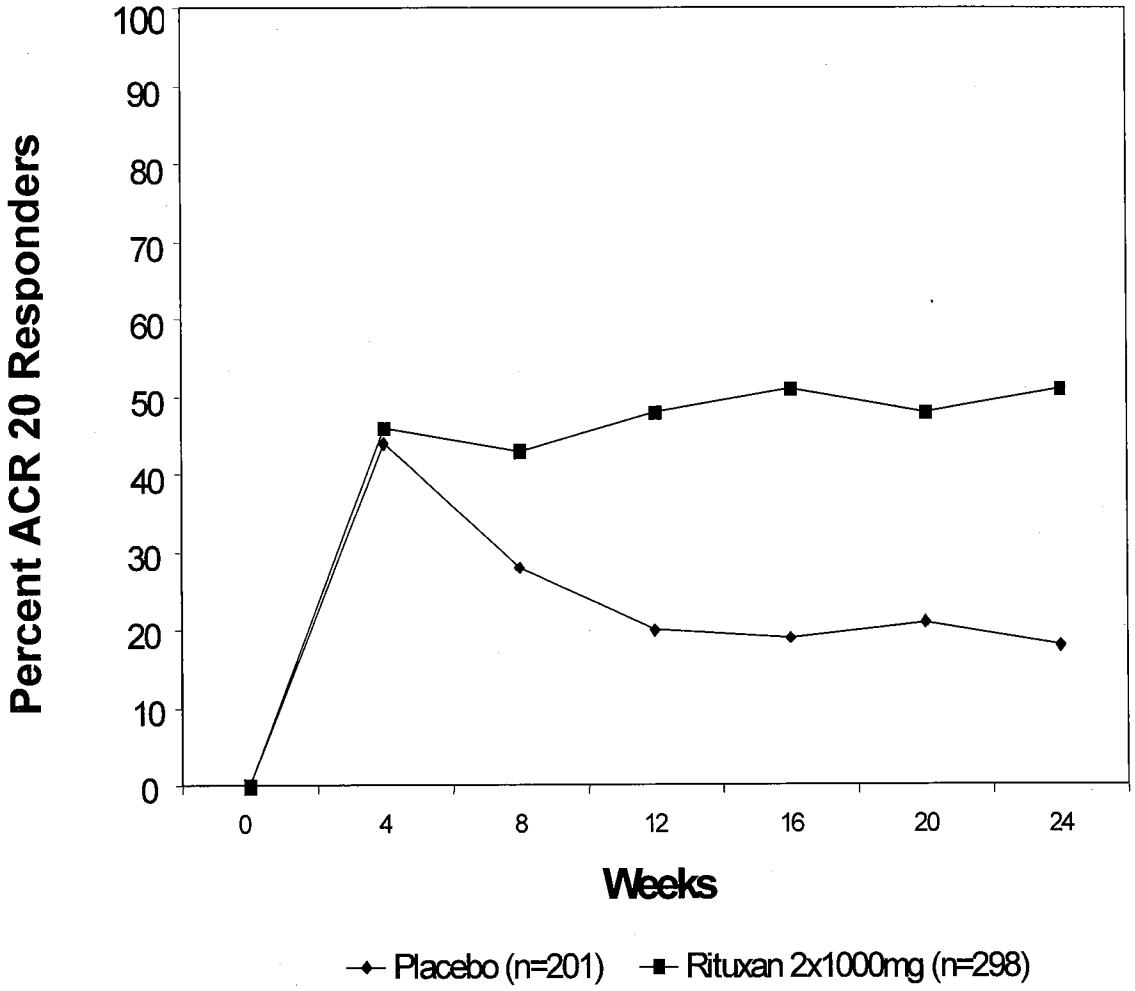
Inadequate Response to TNF Antagonists				
Parameter (median)	Placebo+MTX (n=201)		Rituxan+MTX (n=298)	
	Baseline	Wk 24	Baseline	Wk 24
Tender Joint Count	31.0	27.0	33.0	13.0
Swollen Joint Count	20.0	19.0	21.0	9.5
Physician Global Assessment[a]	71.0	69.0	71.0	36.0
Patient Global Assessment[a]	73.0	68.0	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 2. 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.

916 **Figure 2**
917 Percent of Patients Achieving ACR 20 Response by Visit*
918 Study 1 (Inadequate Response to TNF Antagonists)



919
920
921 *The same patients may not have responded at each time point.

922 *Radiographic Response*
923 In RA Study 1, structural joint damage was assessed radiographically and expressed as changes in
924 Genant-modified Total Sharp Score (TSS) and its components, the erosion score (ES) and the joint
925 space narrowing (JSN) score. Rituxan +MTX slowed the progression of structural damage
926 compared to placebo +MTX after 1 year as shown in Table 11.

Table 11

Mean Radiographic Change From Baseline to 104 Weeks

Inadequate Response to TNF Antagonists				
Parameter	Rituxan 2 × 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 × 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.

955 Physical function was assessed at Weeks 24 and 48 using the Health Assessment Questionnaire
956 Disability Index (HAQ-DI). From baseline to Week 24, a greater proportion of Rituxan-treated
957 patients had an improvement in HAQ-DI of at least 0.22 (a minimal clinically important difference)
958 and a greater mean HAQ-DI improvement compared to placebo, as shown in Table 12. HAQ-DI
959 results for the Rituxan 500 mg treatment group were similar to the Rituxan 1000 mg treatment
960 group; however radiographic responses were not assessed (see Dosing Precaution in the
961 Radiographic Responses section above). These improvements were maintained at 48 weeks.
962

Table 12

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

	Placebo +MTX n=172	Rituxan 2×1000 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.

963

964 **14.6 Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)**

965 A total of 197 patients with active, severe WG and MPA (two forms of ANCA Associated
966 Vasculidities) were treated in a randomized, double-blind, active-controlled multicenter,
967 non-inferiority study, conducted in two phases – a 6 month remission induction phase and a
968 12 month remission maintenance phase. Patients were 15 years of age or older, diagnosed with WG
969 (75% of patients) or MPA (24% of patients) according to the Chapel Hill Consensus conference
970 criteria (1% of the patients had unknown vasculitis type). All patients had active disease, with a
971 Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) ≥ 3, and their
972 disease was severe, with at least one major item on the BVAS/WG. Ninety-six (49%) of patients
973 had new disease and 101 (51%) of patients had relapsing disease.

974 Patients in both arms received 1000 mg of pulse intravenous methylprednisolone per day for 1 to
975 3 days within 14 days prior to initial infusion. Patients were randomized in a 1:1 ratio to receive
976 either Rituxan 375 mg/m^2 once weekly for 4 weeks or oral cyclophosphamide 2 mg/kg daily for 3 to
977 6 months in the remission induction phase. Patients were pre-medicated with antihistamine and
978 acetaminophen prior to Rituxan infusion. Following intravenous corticosteroid administration, all
979 patients received oral prednisone (1 mg/kg/day, not exceeding 80 mg/day) with pre-specified
980 tapering. Once remission was achieved or at the end of the 6 month remission induction period, the
981 cyclophosphamide group received azathioprine to maintain remission. The Rituxan group did not
982 receive additional therapy to maintain remission. The main outcome measure for both WG and
983 MPA patients was achievement of complete remission at 6 months defined as a BVAS/WGof 0, and
984 off glucocorticoid therapy. The pre-specified non-inferiority margin was a treatment difference of
985 20%. As shown in Table 13, the study demonstrated non-inferiority of Rituxan to
986 cyclophosphamide for complete remission at 6 months.

Table 13
Percentage of Patients Who Achieved
Complete Remission at 6 Months (Intent-to-Treat Population)

	Rituxan (n=99)	Cyclophosphamide (n=98)	Treatment Difference (Rituxan – Cyclophosphamide)
Rate	64%	53%	11%
95.1%[b] CI	(54%, 73%)	(43%, 63%)	(–3%, 24%)[a]

[a] non-inferiority was demonstrated because the lower bound was higher than the prespecified non-inferiority margin (–3%>–20%).

[b] The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy analysis.

Complete Remission (CR) at 12 and 18 months
In the Rituxan group, 44% of patients achieved CR at 6 and 12 months, and 38% of patients achieved CR at 6, 12, and 18 months. In patients treated with cyclophosphamide (followed by azathioprine for maintenance of CR), 38% of patients achieved CR at 6 and 12 months, and 31% of patients achieved CR at 6, 12, and 18 months.

Retreatment with Rituxan
Based upon investigator judgment, 15 patients received a second course of Rituxan therapy for treatment of relapse of disease activity which occurred between 8 and 17 months after the first course of Rituxan. The limited data preclude any conclusions regarding the efficacy of subsequent courses of Rituxan in patients with WG and MPA [*See Warnings and Precautions (5.14)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

Rituxan vials [100 mg/10 mL single-use vials (NDC 50242-051-21) and 500 mg/50 mL single-use vials (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.

RITUXAN® [rituximab]
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

10126776
Initial US Approval: November 1997
PI Revision Date 04 2011
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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 systems 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

1056 Your doctor may do blood tests to check you for TLS. Your doctor may give you medicine to
1057 help prevent TLS.

1058 4. **Severe skin and mouth reactions.** Tell your doctor or get medical help right away if you get
1059 any of these symptoms at anytime during your treatment with Rituxan:

1060 - painful sores or ulcers on your skin, lips or in your mouth
1061 - blisters
1062 - peeling skin
1063 - rash
1064 - pustules

1065 See "**What are possible side effects of Rituxan?**" for more information about side effects.

1066 **What is Rituxan?**

1067 Rituxan is a prescription medicine used to treat:

1068 - **Non-Hodgkin's Lymphoma (NHL):** alone or with other chemotherapy medicines.
1069 - **Chronic Lymphocytic Leukemia (CLL):** with the chemotherapy medicines fludarabine and
1070 cyclophosphamide.
1071 - **Rheumatoid Arthritis (RA):** with another prescription medicine called methotrexate, to reduce
1072 the signs and symptoms of moderate to severe active RA in adults, after treatment with at least
1073 one other medicine called a Tumor Necrosis Factor (TNF) antagonist has been used and did not
1074 work well enough.
1075 - **Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA):** with
1076 glucocorticoids, to treat WG and MPA.

1077 People with serious infections should not receive Rituxan.
1078 It is not known if Rituxan is safe or effective in children.
1079
1080 **What should I tell my doctor before receiving Rituxan?**
1081 Before receiving Rituxan, tell your doctor if you:
1082 - have had a severe infusion reaction to Rituxan in the past
1083 - have a history of heart problems, irregular heart beat or chest pain
1084 - have lung or kidney problems
1085 - have an infection or weakened immune system.
1086 - have or have had any severe infections including:
1087 - Hepatitis B virus (HBV)
1088 - Hepatitis C virus (HCV)
1089 - Cytomegalovirus (CMV)
1090 - Herpes simplex virus (HSV)
1091 - Parvovirus B19
1092 - Varicella zoster virus (chickenpox or shingles)
1093 - West Nile Virus

1094 • have had a recent vaccination or are scheduled to receive vaccinations. You should not receive
1095 certain vaccines before or after you receive Rituxan. Tell your doctor if anyone in your
1096 household is scheduled to receive a vaccination. Some types of vaccines can spread to people
1097 with a weakened immune system, and cause serious problems.

1098 • have taken Rituxan for WG or MPA in the past.

1099 • have any other medical conditions

1100 • are pregnant or planning to become pregnant. Rituxan may affect the white blood cell counts of
1101 your unborn baby. It is not known if Rituxan may harm your unborn baby in other ways.

1102 Women who are able to become pregnant should use effective birth-control (contraception)
1103 while using Rituxan and for 12 months after you finish treatment. Talk to your doctor about
1104 effective birth control.

1105 • are breast-feeding or plan to breast-feed. It is not known if Rituxan passes into your breast milk.
1106 You and your doctor should decide the best way to feed your baby if you receive Rituxan.

1107 Tell your doctor about all the medicines you take, including prescription and nonprescription
1108 medicines, vitamins, and herbal supplements. Especially tell your doctor if you take or have taken:

1109 • a Tumor Necrosis Factor (TNF) inhibitor medicine
1110 • a Disease Modifying Anti-Rheumatic Drug (DMARD)

1111 If you are not sure if your medicine is one listed above, ask your doctor or pharmacist.

1112 Know the medicines you take. Keep a list of them to show to your doctor and pharmacist when you
1113 get a new medicine. Do not take any new medicine without talking with your doctor.

1114 **How will I receive Rituxan?**

1115 • Rituxan is given by infusion through a needle placed in a vein (intravenous infusion), in
1116 your arm. Talk to your doctor about how you will receive Rituxan.

1117 • Your doctor may prescribe medicines before each infusion of Rituxan to reduce side effects
1118 of infusions such as fever and chills.

1119 • Your doctor should do regular blood tests to check for side effects to Rituxan.

1120 Before each Rituxan treatment, your doctor or nurse will ask you questions about your general
1121 health. Tell your doctor or nurse about any new symptoms.

1122 **What are the possible side effects of Rituxan?**

1123 Rituxan can cause serious and life-threatening side effects, including:

1124 See **"What is the most important information I should know about Rituxan?"**

1125 • **Hepatitis B virus (HBV) reactivation.** If you have had hepatitis B or are a carrier of hepatitis B
1126 virus, receiving Rituxan could cause the virus to become an active infection again. This may
1127 cause serious liver problems including liver failure, and death. You should not receive Rituxan
1128 if you have active hepatitis B liver disease.

1129 • **Serious infections.** Serious infections that happen with Rituxan can lead to death. Call your
1130 doctor right away if you have any symptoms of infection:

1131 ○ fever

1132 ○ cold symptoms, such as runny nose or sore throat that do not go away

1133 ○ flu symptoms, such as cough, tiredness, and body aches

1134 ○ earache or headache

1135 ○ pain during urination

1136 ○ white patches in the mouth or throat

1137 ○ cuts, scrapes or incisions that are red, warm, swollen or painful

1138 • **Heart problems.** Rituxan may cause chest pain and irregular heart beats which may need
1139 treatment, or your doctor may decide to stop your treatment with Rituxan.

1140 • **Kidney problems,** especially if you are receiving Rituxan for NHL. Your doctor should do
1141 blood tests to check how well your kidneys are working.

1142 • **Stomach and Serious bowel problems that can sometimes lead to death.** Bowel problems,
1143 including blockage or tears in the bowel can happen if you receive Rituxan with chemotherapy
1144 medicines to treat non-Hodgkin's lymphoma. Tell your doctor right away if you have any
1145 stomach area pain during treatment with Rituxan.

1146 • **Low blood cell counts.** Your doctor may do blood tests during treatment with Rituxan to check
1147 your blood cell counts.

1148 ○ **White blood cells.** White blood cells fight against bacterial infections. Low white
1149 blood cells can cause you to get infections, which may be serious. See "Increased
1150 risk of infections" above for a list of symptoms of infection.

1151 ○ **Red blood cells.** Red blood cells carry oxygen to your body tissues and organs.

1152 ○ **Platelets.** Platelets are blood cells that help your blood to clot.

1153 **Common side effects during Rituxan treatment include:**

1154 • infusion reactions (see What is the most important information I should know about Rituxan?)

1155 • chills

1156 • infections

1157 • body aches

1158 • tiredness

1159 • low white blood cells

1160 Other side effects with Rituxan include:

1161 • aching joints during or within hours of receiving an infusion

1162 • more frequent upper respiratory tract infection

1163 Tell your doctor about any side effect that bothers you or that does not go away.
1164 These are not all of the possible side effects with Rituxan. For more information, ask your doctor or
1165 pharmacist.

1166 Call your doctor for medical advice about side effects. You may report side effects to FDA at
1167 1-800-FDA-1088.

1168 **General information about Rituxan**

1169 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This
1170 Medication Guide provides a summary of the most important information about Rituxan. If you
1171 would like more information, talk with your doctor. You can ask your doctor for information about
1172 Rituxan that is written for healthcare professionals.

1173 For more information, go to www.Rituxan.com or call 1-877-474-8892.

1174 **What are the ingredients in Rituxan?**

1175 Active ingredient: rituximab

1176 Inactive ingredients: sodium chloride, sodium citrate dihydrate, polysorbate 80, and water for
1177 injection.

1178 Jointly Marketed by: Biogen Idec Inc. and Genentech USA, Inc.
1179

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1180

1181 This Medication Guide has been approved by the U.S. Food and Drug Administration.