

### **i 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, GPA and MPA (1.4)	04/2011
Dosage and Administration, GPA and MPA (2.6)	04/2011
Dosage and Administration, Recommended Concomitant Medications (2.7)	04/2011
Warnings and Precautions, Infections (5.6)	02/2012
Warnings and Precautions, Concomitant Use with Biologic Agents and DMARDS other than Methotrexate in RA, GPA and MPA (5.12)	04/2011
Warnings and Precautions, Retreatment in Patients with GPA 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)
- Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) 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<sup>2</sup> (2.2).
- The dose for CLL is 375 mg/m<sup>2</sup> in the first cycle and 500 mg/m<sup>2</sup> 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<sup>2</sup> (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 GPA and MPA in combination with glucocorticoids is 375 mg/m<sup>2</sup> 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).
- Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) 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](http://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: 03/2012**

**FULL PRESCRIBING INFORMATION: CONTENTS\***

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

**1 INDICATIONS AND USAGE**

- 1.1 Non-Hodgkin's Lymphoma (NHL)
- 1.2 Chronic Lymphocytic Leukemia (CLL)
- 1.3 Rheumatoid Arthritis (RA)
- 1.4 Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)
- 1.5 Limitations of Use

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Administration
- 2.2 Recommended Dose for Non-Hodgkin's Lymphoma (NHL)
- 2.3 Recommended Dose for Chronic Lymphocytic Leukemia (CLL)
- 2.4 Recommended Dose as a Component of Zevalin®
- 2.5 Recommended Dose for Rheumatoid Arthritis (RA)
- 2.6 Recommended Dose for Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)
- 2.7 Recommended Concomitant Medications
- 2.8 Preparation for Administration

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

- 5.1 Infusion Reactions
- 5.2 Tumor Lysis Syndrome (TLS)
- 5.3 Severe Mucocutaneous Reactions
- 5.4 Progressive Multifocal Leukoencephalopathy (PML)
- 5.5 Hepatitis B Virus (HBV) Reactivation
- 5.6 Infections
- 5.7 Cardiovascular
- 5.8 Renal
- 5.9 Bowel Obstruction and Perforation
- 5.10 Immunization
- 5.11 Laboratory Monitoring
- 5.12 Concomitant Use with Biologic Agents and DMARDs other than Methotrexate in RA, GPA and MPA

- 5.13 Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis Factor (TNF) Antagonists
- 5.14 Retreatment in Patients with Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

**6 ADVERSE REACTIONS**

- 6.1 Clinical Trials Experience in Lymphoid Malignancies
- 6.2 Clinical Trials Experience in Rheumatoid Arthritis
- 6.3 Clinical Trials Experience in Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)
- 6.4 Immunogenicity
- 6.5 Postmarketing Experience

**7 DRUG INTERACTIONS**

**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

**10 OVERDOSAGE**

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

**13 NONCLINICAL TOXICOLOGY**

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

**14 CLINICAL STUDIES**

- 14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL
- 14.2 Previously Untreated, Low-Grade or Follicular, CD20-Positive, B-Cell NHL
- 14.3 Diffuse Large B-Cell NHL (DLBCL)
- 14.4 Chronic Lymphocytic Leukemia (CLL)
- 14.5 Rheumatoid Arthritis (RA)
- 14.6 Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

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

## FULL PRESCRIBING INFORMATION

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

#### **Infusion Reactions**

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

#### **Tumor Lysis Syndrome (TLS)**

Acute renal failure requiring dialysis with instances of fatal outcome can occur in the setting of TLS following treatment of non-Hodgkin's lymphoma (NHL) with Rituxan monotherapy [see *Warnings and Precautions (5.2), Adverse Reactions (6)*].

#### **Severe Mucocutaneous Reactions**

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

#### **Progressive Multifocal Leukoencephalopathy (PML)**

JC virus infection resulting in PML and death can occur in patients receiving Rituxan [see *Warnings and Precautions (5.4), Adverse Reactions (6)*].

## **1 INDICATIONS AND USAGE**

### **1.1 Non-Hodgkin's Lymphoma (NHL)**

Rituxan<sup>®</sup> (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<sup>®</sup> (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<sup>®</sup> (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 Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)**

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

### **1.5 Limitations of Use**

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

46 **2 DOSAGE AND ADMINISTRATION**

47 **2.1 Administration**

48 DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

49 Premedicate before each infusion [*see Dosage and Administration (2.7)*]. Administer only as an  
50 intravenous (IV) infusion [*see Dosage and Administration (2.7)*].

- 51 • **First Infusion:** Initiate infusion at a rate of 50 mg/hr. In the absence of infusion toxicity,  
52 increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
- 53 • **Subsequent Infusions:** Initiate infusion at a rate of 100 mg/hr. In the absence of infusion  
54 toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of  
55 400 mg/hr.
- 56 • Interrupt the infusion or slow the infusion rate for infusion reactions [*see Boxed Warning,*  
57 *Warnings and Precautions (5.1)*]. Continue the infusion at one-half the previous rate upon  
58 improvement of symptoms.

59 **2.2 Recommended Dose for Non-Hodgkin's Lymphoma (NHL)**

60 The recommended dose is 375 mg/m<sup>2</sup> as an intravenous infusion according to the following  
61 schedules:

- 62 • **Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**  
63 Administer once weekly for 4 or 8 doses.
- 64 • **Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive,**  
65 **B-Cell NHL**  
66 Administer once weekly for 4 doses.
- 67 • **Previously Untreated, Follicular, CD20-Positive, B-Cell NHL**  
68 Administer on Day 1 of each cycle of chemotherapy, for up to 8 doses. In patients with  
69 complete or partial response, initiate Rituxan maintenance eight weeks following completion  
70 of Rituxan in combination with chemotherapy. Administer Rituxan as a single-agent every 8  
71 weeks for 12 doses.
- 72 • **Non-progressing, Low-Grade, CD20-Positive, B-cell NHL, after first-line CVP**  
73 **chemotherapy**  
74 Following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for  
75 4 doses at 6-month intervals to a maximum of 16 doses.
- 76 • **Diffuse Large B-Cell NHL**  
77 Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions.

78 **2.3 Recommended Dose for Chronic Lymphocytic Leukemia (CLL)**

79 The recommended dose is:

- 80 • 375 mg/m<sup>2</sup> the day prior to the initiation of FC chemotherapy, then 500 mg/m<sup>2</sup> on Day 1 of  
81 cycles 2–6 (every 28 days).

82 **2.4 Recommended Dose as a Component of Zevalin®**

- 83 • Infuse rituximab 250 mg/m<sup>2</sup> within 4 hours prior to the administration of  
84 Indium-111-(In-111-) Zevalin and within 4 hours prior to the administration of  
85 Yttrium-90- (Y-90-) Zevalin.
- 86 • Administer Rituxan and In-111-Zevalin 7–9 days prior to Rituxan and Y-90- Zevalin.
- 87 • Refer to the Zevalin package insert for full prescribing information regarding the Zevalin  
88 therapeutic regimen.

89 **2.5 Recommended Dose for Rheumatoid Arthritis (RA)**

- 90 • Administer Rituxan as two-1000 mg intravenous infusions separated by 2 weeks.
- 91 • Glucocorticoids administered as methylprednisolone 100 mg intravenous or its equivalent  
92 30 minutes prior to each infusion are recommended to reduce the incidence and severity of  
93 infusion reactions.
- 94 • Subsequent courses should be administered every 24 weeks or based on clinical evaluation,  
95 but not sooner than every 16 weeks.

- Rituxan is given in combination with methotrexate.

## 2.6 Recommended Dose for Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

- Administer Rituxan as a 375 mg/m<sup>2</sup> 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 GPA 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 GPA 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 ( $\geq 25,000/\text{mm}^3$ ). [*See Boxed Warning, Warnings and Precautions (5.7), Adverse Reactions (6.1)*].

145 **5.2 Tumor Lysis Syndrome (TLS)**

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

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

154 **5.3 Severe Mucocutaneous Reactions**

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

161 **5.4 Progressive Multifocal Leukoencephalopathy (PML)**

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

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

173 **5.5 Hepatitis B Virus (HBV) Reactivation**

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

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

184 **5.6 Infections**

185 Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during  
186 and following the completion of Rituxan-based therapy. Infections have been reported in some  
187 patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia  $>11$  months  
188 after rituximab exposure). New or reactivated viral infections included cytomegalovirus, herpes  
189 simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C.  
190 Discontinue Rituxan for serious infections and institute appropriate anti-infective therapy. [*See*  
191 *Adverse Reactions (6, 6.1).*]

192 **5.7 Cardiovascular**

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

196 **5.8 Renal**

197 Severe, including fatal, renal toxicity can occur after Rituxan administration in patients with NHL.  
198 Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with  
199 NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin  
200 and Rituxan is not an approved treatment regimen. Monitor closely for signs of renal failure and  
201 discontinue Rituxan in patients with a rising serum creatinine or oliguria. [*See Warnings and*  
202 *Precautions (5.2).*]

203 **5.9 Bowel Obstruction and Perforation**

204 Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in  
205 patients receiving Rituxan in combination with chemotherapy. In postmarketing reports, the mean  
206 time to documented gastrointestinal perforation was 6 (range 1–77) days in patients with NHL.  
207 Perform a thorough diagnostic evaluation and institute appropriate treatment for complaints of  
208 abdominal pain. [*See Adverse Reactions (6).*]

209 **5.10 Immunization**

210 The safety of immunization with live viral vaccines following Rituxan therapy has not been  
211 studied and vaccination with live virus vaccines is not recommended.

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

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

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

223 A positive response to tetanus toxoid vaccine (a T-cell dependent antigen with existing immunity)  
224 was similar in patients treated with Rituxan plus MTX compared to patients on MTX alone (39% vs.  
225 42%). The proportion of patients maintaining a positive Candida skin test (to evaluate delayed type  
226 hypersensitivity) was also similar (77% of patients on Rituxan plus MTX vs. 70% of patients on  
227 MTX alone).

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

230 **5.11 Laboratory Monitoring**

231 In patients with lymphoid malignancies, during treatment with Rituxan monotherapy, obtain  
232 complete blood counts (CBC) and platelet counts prior to each Rituxan course. During treatment  
233 with Rituxan and chemotherapy, obtain CBC and platelet counts at weekly to monthly intervals and  
234 more frequently in patients who develop cytopenias [*see Adverse Reactions (6.1)*]. In patients with  
235 RA, GPA or MPA, obtain CBC and platelet counts at two to four month intervals during Rituxan  
236 therapy. The duration of cytopenias caused by Rituxan can extend months beyond the treatment  
237 period.

238  
239 **5.12 Concomitant Use with Biologic Agents and DMARDs other than Methotrexate in RA,  
240 GPA and MPA**

241 Limited data are available on the safety of the use of biologic agents or DMARDs other than  
242 methotrexate in RA patients exhibiting peripheral B-cell depletion following treatment with  
243 rituximab. Observe patients closely for signs of infection if biologic agents and/or DMARDs are  
244 used concomitantly. Use of concomitant immunosuppressants other than corticosteroids has not  
245 been studied in GPA or MPA patients exhibiting peripheral B-cell depletion following treatment  
246 with Rituxan.

247 **5.13 Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis**  
248 **Factor (TNF) Antagonists**

249 While the efficacy of Rituxan was supported in four controlled trials in patients with RA with  
250 prior inadequate responses to non-biologic DMARDs, and in a controlled trial in MTX-naïve  
251 patients, a favorable risk-benefit relationship has not been established in these populations. The use  
252 of Rituxan in patients with RA who have not had prior inadequate response to one or more TNF  
253 antagonists is not recommended [*see Clinical Studies (14.5)*].

254 **5.14 Retreatment in Patients with Granulomatosis with Polyangiitis (GPA) (Wegener's**  
255 **Granulomatosis) and Microscopic Polyangiitis (MPA)**

256 Limited data are available on the safety and efficacy of subsequent courses of Rituxan in patients  
257 with GPA and MPA. The safety and efficacy of retreatment with Rituxan have not been established  
258 [*see Dosage and Administration (2.6), Adverse Reactions (6.3), and Clinical Studies (14.6)*].

259 **6 ADVERSE REACTIONS**

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

- 262 • Infusion reactions [*see Warnings and Precautions (5.1)*]
- 263 • Tumor lysis syndrome [*see Warnings and Precautions (5.2)*]
- 264 • Mucocutaneous reactions [*see Warnings and Precautions (5.3)*]
- 265 • Progressive multifocal leukoencephalopathy [*see Warnings and Precautions (5.4)*]
- 266 • Hepatitis B reactivation with fulminant hepatitis [*see Warnings and Precautions (5.5)*]
- 267 • Infections [*see Warnings and Precautions (5.6)*]
- 268 • Cardiac arrhythmias [*see Warnings and Precautions (5.7)*]
- 269 • Renal toxicity [*see Warnings and Precautions (5.8)*]
- 270 • Bowel obstruction and perforation [*see Warnings and Precautions (5.9)*]

271  
272 The most common adverse reactions of Rituxan (incidence  $\geq 25\%$ ) observed in clinical trials of  
273 patients with NHL were infusion reactions, fever, lymphopenia, chills, infection, and asthenia.

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

276 **6.1 Clinical Trials Experience in Lymphoid Malignancies**

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

280 The data described below reflect exposure to Rituxan in 2783 patients, with exposures ranging  
281 from a single infusion up to 2 years. Rituxan was studied in both single-arm and controlled trials  
282 ( $n=356$  and  $n = 2427$ ). The population included 1180 patients with low grade or follicular  
283 lymphoma, 927 patients with DLBCL, and 676 patients with CLL. Most NHL patients received  
284 Rituxan as an infusion of  $375 \text{ mg/m}^2$  per infusion, given as a single agent weekly for up to 8 doses,  
285 in combination with chemotherapy for up to 8 doses, or following chemotherapy for up to 16 doses.  
286 CLL patients received Rituxan  $375 \text{ mg/m}^2$  as an initial infusion followed by  $500 \text{ mg/m}^2$  for up to  
287 5 doses, in combination with fludarabine and cyclophosphamide. Seventy-one percent of CLL  
288 patients received 6 cycles and 90% received at least 3 cycles of Rituxan-based therapy.

289 *Infusion Reactions*

290 In the majority of patients with NHL, infusion reactions consisting of fever, chills/rigors, nausea,  
291 pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia,  
292 dizziness, or hypertension occurred during the first Rituxan infusion. Infusion reactions typically  
293 occurred within 30 to 120 minutes of beginning the first infusion and resolved with slowing or  
294 interruption of the Rituxan infusion and with supportive care (diphenhydramine, acetaminophen, and  
295 intravenous saline). The incidence of infusion reactions was highest during the first infusion (77%)

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

### 298 *Infections*

299 Serious infections (NCI CTCAE Grade 3 or 4), including sepsis, occurred in less than 5% of  
300 patients with NHL in the single-arm studies. The overall incidence of infections was 31% (bacterial  
301 19%, viral 10%, unknown 6%, and fungal 1%). [See *Warnings and Precautions (5.4), (5.5), (5.6).*]

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

### 306 *Cytopenias and hypogammaglobulinemia*

307 In patients with NHL receiving rituximab monotherapy, NCI-CTC Grade 3 and 4 cytopenias were  
308 reported in 48% of patients. These included lymphopenia (40%), neutropenia (6%), leukopenia  
309 (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days  
310 (range, 1–588 days) and of neutropenia was 13 days (range, 2–116 days). A single occurrence of  
311 transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following  
312 Rituxan therapy occurred during the single-arm studies.

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

315 In CLL trials, the frequency of prolonged neutropenia and late-onset neutropenia was higher in  
316 patients treated with R-FC compared to patients treated with FC. Prolonged neutropenia is defined  
317 as Grade 3-4 neutropenia that has not resolved between 24 and 42 days after the last dose of study  
318 treatment. Late-onset neutropenia is defined as Grade 3-4 neutropenia starting at least 42 days after  
319 the last treatment dose.

320 In patients with previously untreated CLL, the frequency of prolonged neutropenia was 8.5% for  
321 patients who received R-FC (n=402) and 5.8% for patients who received FC (n=398). In patients  
322 who did not have prolonged neutropenia, the frequency of late-onset neutropenia was 14.8% of 209  
323 patients who received R-FC and 4.3% of 230 patients who received FC.

324 For patients with previously treated CLL, the frequency of prolonged neutropenia was 24.8% for  
325 patients who received R-FC (n=274) and 19.1% for patients who received FC (n=274). In patients  
326 who did not have prolonged neutropenia, the frequency of late-onset neutropenia was 38.7% in 160  
327 patients who received R-FC and 13.6% of 147 patients who received FC.

### 328 *Relapsed or Refractory, Low-Grade NHL*

329 Adverse reactions in Table 1 occurred in 356 patients with relapsed or refractory, low-grade or  
330 follicular, CD20-positive, B-cell NHL treated in single-arm studies of Rituxan administered as a  
331 single agent [see *Clinical Studies (14.1)*]. Most patients received Rituxan 375 mg/m<sup>2</sup> weekly for  
332 4 doses.

**Table 1**  
 Incidence of Adverse Reactions in  $\geq 5\%$  of  
 Patients with Relapsed or Refractory, Low-Grade or Follicular  
 NHL, Receiving Single-agent Rituxan (N=356)<sup>a,b</sup>

	All Grades (%)	Grade 3 and 4 (%)
Any Adverse Reactions	99	57
<u>Body as a Whole</u>	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
<u>Heme and Lymphatic System</u>	67	48
Lymphopenia	48	40
Leukopenia	14	4
Neutropenia	14	6
Thrombocytopenia	12	2
Anemia	8	3
<u>Skin and Appendages</u>	44	2
Night Sweats	15	1
Rash	15	1
Pruritus	14	1
Urticaria	8	1
<u>Respiratory System</u>	38	4
Increased Cough	13	1
Rhinitis	12	1
Bronchospasm	8	1
Dyspnea	7	1
Sinusitis	6	0
<u>Metabolic and Nutritional Disorders</u>	38	3
Angioedema	11	1
Hyperglycemia	9	1
Peripheral Edema	8	0
LDH Increase	7	0
<u>Digestive System</u>	37	2
Nausea	23	1
Diarrhea	10	1
Vomiting	10	1
<u>Nervous System</u>	32	1
Dizziness	10	1
Anxiety	5	1
<u>Musculoskeletal System</u>	26	3
Myalgia	10	1
Arthralgia	10	1

**Table 1 (cont'd)**  
Incidence of Adverse Reactions in  $\geq 5\%$  of  
Patients with Relapsed or Refractory, Low-Grade or Follicular  
NHL, Receiving Single-agent Rituxan (N=356)<sup>a,b</sup>

	All Grades (%)	Grade 3 and 4 (%)
<u>Cardiovascular System</u>	25	3
Hypotension	10	1
Hypertension	6	1

<sup>a</sup> Adverse reactions observed up to 12 months following Rituxan.

<sup>b</sup> Adverse reactions graded for severity by NCI-CTC criteria.

334

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

337 *Previously Untreated, Low-Grade or Follicular, NHL*

338 In Study 4, patients in the R-CVP arm experienced a higher incidence of infusional toxicity and  
339 neutropenia compared to patients in the CVP arm. The following adverse reactions occurred more  
340 frequently ( $\geq 5\%$ ) in patients receiving R-CVP compared to CVP alone: rash (17% vs. 5%), cough  
341 (15% vs. 6%), flushing (14% vs. 3%), rigors (10% vs. 2%), pruritus (10% vs. 1%), neutropenia (8%  
342 vs. 3%), and chest tightness (7% vs. 1%). [See *Clinical Studies (14.2)*.]

343 In Study 5, detailed safety data collection was limited to serious adverse reactions, Grade  $\geq 2$   
344 infections, and Grade  $\geq 3$  adverse reactions. In patients receiving Rituxan as single-agent  
345 maintenance therapy following Rituxan plus chemotherapy, infections were reported more  
346 frequently compared to the observation arm (37% vs. 22%). Grade 3-4 adverse reactions occurring  
347 at a higher incidence ( $\geq 2\%$ ) in the Rituxan group were infections (4% vs. 1%) and neutropenia (4%  
348 vs.  $<1\%$ ).

349 In Study 6, the following adverse reactions were reported more frequently ( $\geq 5\%$ ) in patients  
350 receiving Rituxan following CVP compared to patients who received no further therapy: fatigue  
351 (39% vs. 14%), anemia (35% vs. 20%), peripheral sensory neuropathy (30% vs. 18%), infections  
352 (19% vs. 9%), pulmonary toxicity (18% vs. 10%), hepato-biliary toxicity (17% vs. 7%), rash and/or  
353 pruritus (17% vs. 5%), arthralgia (12% vs. 3%), and weight gain (11% vs. 4%). Neutropenia was the  
354 only Grade 3 or 4 adverse reaction that occurred more frequently ( $\geq 2\%$ ) in the Rituxan arm  
355 compared with those who received no further therapy (4% vs. 1%). [See *Clinical Studies (14.3)*.]

356 *DLBCL*

357 In Studies 7 and 8, [see *Clinical Studies (14.3)*], the following adverse reactions, regardless of  
358 severity, were reported more frequently ( $\geq 5\%$ ) in patients age  $\geq 60$  years receiving R-CHOP as  
359 compared to CHOP alone: pyrexia (56% vs. 46%), lung disorder (31% vs. 24%), cardiac disorder  
360 (29% vs. 21%), and chills (13% vs. 4%). Detailed safety data collection in these studies was  
361 primarily limited to Grade 3 and 4 adverse reactions and serious adverse reactions.

362 In Study 8, a review of cardiac toxicity determined that supraventricular arrhythmias or  
363 tachycardia accounted for most of the difference in cardiac disorders (4.5% for R-CHOP vs. 1.0%  
364 for CHOP).

365 The following Grade 3 or 4 adverse reactions occurred more frequently among patients in the  
366 R-CHOP arm compared with those in the CHOP arm: thrombocytopenia (9% vs. 7%) and lung  
367 disorder (6% vs. 3%). Other Grade 3 or 4 adverse reactions occurring more frequently among  
368 patients receiving R-CHOP were viral infection (Study 8), neutropenia (Studies 8 and 9), and anemia  
369 (Study 9).

370 *CLL*

371 The data below reflect exposure to Rituxan in combination with fludarabine and  
372 cyclophosphamide in 676 patients with CLL in Study 10 or Study 11 [*see Clinical Studies (14.4)*].  
373 The age range was 30–83 years and 71% were men. Detailed safety data collection in Study 10 was  
374 limited to Grade 3 and 4 adverse reactions and serious adverse reactions.

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

378 In Study 10, the following Grade 3 and 4 adverse reactions occurred more frequently in  
379 R-FC-treated patients compared to FC-treated patients: infusion reactions (9% in R-FC arm),  
380 neutropenia (30% vs. 19%), febrile neutropenia (9% vs. 6%), leukopenia (23% vs. 12%), and  
381 pancytopenia (3% vs. 1%).

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

## 387 **6.2 Clinical Trials Experience in Rheumatoid Arthritis**

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

391 The data presented below reflect the experience in 2578 RA patients treated with Rituxan in  
392 controlled and long-term studies with a total exposure of 5014 patient-years.

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

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

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

Preferred Term	Placebo+MTX	Rituxan+MTX
	N=398 n (%)	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.

403

404 *Infusion Reactions*

405 In the Rituxan RA pooled placebo-controlled studies, 32% of Rituxan-treated patients experienced  
406 an adverse reaction during or within 24 hours following their first infusion, compared to 23% of  
407 placebo-treated patients receiving their first infusion. The incidence of adverse reactions during the  
408 24-hour period following the second infusion, Rituxan or placebo, decreased to 11% and 13%,  
409 respectively. Acute infusion reactions (manifested by fever, chills, rigors, pruritus, urticaria/rash,  
410 angioedema, sneezing, throat irritation, cough, and/or bronchospasm, with or without associated  
411 hypotension or hypertension) were experienced by 27% of Rituxan-treated patients following their  
412 first infusion, compared to 19% of placebo-treated patients receiving their first placebo infusion.  
413 The incidence of these acute infusion reactions following the second infusion of Rituxan or placebo  
414 decreased to 9% and 11%, respectively. Serious acute infusion reactions were experienced by <1%  
415 of patients in either treatment group. Acute infusion reactions required dose modification (stopping,  
416 slowing, or interruption of the infusion) in 10% and 2% of patients receiving rituximab or placebo,  
417 respectively, after the first course. The proportion of patients experiencing acute infusion reactions  
418 decreased with subsequent courses of Rituxan. The administration of intravenous glucocorticoids  
419 prior to Rituxan infusions reduced the incidence and severity of such reactions, however, there was  
420 no clear benefit from the administration of oral glucocorticoids for the prevention of acute infusion

421 reactions. Patients in clinical studies also received antihistamines and acetaminophen prior to  
422 Rituxan infusions.

#### 423 *Infections*

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

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

430 In the experience with Rituxan in 2578 RA patients, the rate of serious infections was 4.31 per  
431 100 patient years. The most common serious infections ( $\geq 0.5\%$ ) were pneumonia or lower  
432 respiratory tract infections, cellulitis and urinary tract infections. Fatal serious infections included  
433 pneumonia, sepsis and colitis. Rates of serious infection remained stable in patients receiving  
434 subsequent courses. In 185 Rituxan-treated RA patients with active disease, subsequent treatment  
435 with a biologic DMARD, the majority of which were TNF antagonists, did not appear to increase the  
436 rate of serious infection. Thirteen serious infections were observed in 186.1 patient years (6.99 per  
437 100 patient years) prior to exposure and 10 were observed in 182.3 patient years (5.49 per  
438 100 patient years) after exposure.

#### 439 *Cardiac Adverse Reactions*

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

444 In the experience with Rituxan in 2578 RA patients, the rate of serious cardiac reactions was  
445 1.93 per 100 patient years. The rate of myocardial infarction (MI) was 0.56 per 100 patient years  
446 (28 events in 26 patients), which is consistent with MI rates in the general RA population. These  
447 rates did not increase over three courses of Rituxan.

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

#### 451 *Hypophosphatemia and hyperuricemia*

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

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

#### 461 *Retreatment in Patients with RA*

462 In the experience with Rituxan in RA patients, 2578 patients have been exposed  
463 to Rituxan and have received up to 10 courses of Rituxan in RA clinical trials,  
464 with 1890, 1043, and 425 patients having received at least two, three, and four  
465 courses, respectively. Most of the patients who received additional courses did  
466 so 24 weeks or more after the previous course and none were retreated sooner than  
467 16 weeks. The rates and types of adverse reactions reported for subsequent  
468 courses of Rituxan were similar to rates and types seen for a single course of Rituxan.

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

### 472 **6.3 Clinical Trials Experience in Granulomatosis with Polyangiitis (GPA) (Wegener's** 473 **Granulomatosis) and Microscopic Polyangiitis (MPA)**

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

477 The data presented below reflect the experience in 197 patients with GPA and MPA treated with  
478 Rituxan or cyclophosphamide in a single controlled study, which was conducted in two phases: a  
479 6 month randomized, double-blind, double-dummy, active-controlled remission induction phase and  
480 an additional 12 month remission maintenance phase. In the 6-month remission induction phase,  
481 197 patients with GPA and MPA were randomized to either Rituxan 375 mg/ m<sup>2</sup> once weekly for  
482 4 weeks plus glucocorticoids, or oral cyclophosphamide 2 mg/kg daily (adjusted for renal function,  
483 white blood cell count, and other factors) plus glucocorticoids to induce remission. Once remission  
484 was achieved or at the end of the 6 month remission induction period, the cyclophosphamide group  
485 received azathioprine to maintain remission. The Rituxan group did not receive additional therapy  
486 to maintain remission. The primary analysis was at the end of the 6 month remission induction  
487 period and the safety results for this period are described below.

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

**Table 3**  
 Incidence of All Adverse Reactions  
 Occurring in  $\geq 10\%$  of Rituxan-treated GPA 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.

494

495 *Infusion Reactions*

496 Infusion-related reactions in the active-controlled, double-blind study were defined as any adverse  
 497 event occurring within 24 hours of an infusion and considered to be infusion-related by  
 498 investigators. Among the 99 patients treated with Rituxan, 12% experienced at least one infusion  
 499 related reaction, compared with 11% of the 98 patients in the cyclophosphamide group.  
 500 Infusion-related reactions included cytokine release syndrome, flushing, throat irritation, and tremor.  
 501 In the Rituxan group, the proportion of patients experiencing an infusion related reaction was 12%,  
 502 5%, 4%, and 1% following the first, second, third, and fourth infusions, respectively. Patients were  
 503 pre-medicated with antihistamine and acetaminophen before each Rituxan infusion and were on  
 504 background oral corticosteroids which may have mitigated or masked an infusion reaction; however,  
 505 there is insufficient evidence to determine whether premedication diminishes the frequency or  
 506 severity of infusion reactions.

507 *Infections*

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

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

#### 515 *Retreatment in Patients with GPA and MPA*

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

#### 520 **6.4 Immunogenicity**

521 As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence  
522 of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several  
523 factors including assay sensitivity and specificity, assay methodology, sample handling, timing of  
524 sample collection, concomitant medications, and underlying disease. For these reasons, comparison  
525 of the incidence of antibodies to Rituxan with the incidence of antibodies to other products may be  
526 misleading.

527 Using an ELISA assay, anti-human anti-chimeric antibody (HACA) was detected in 4 of  
528 356 (1.1%) patients with low-grade or follicular NHL receiving single-agent Rituxan. Three of the  
529 four patients had an objective clinical response.

530 A total of 273/2578 (11%) patients with RA tested positive for HACA at any time after receiving  
531 Rituxan. HACA positivity was not associated with increased infusion reactions or other adverse  
532 reactions. Upon further treatment, the proportions of patients with infusion reactions were similar  
533 between HACA positive and negative patients, and most reactions were mild to moderate. Four  
534 HACA positive patients had serious infusion reactions, and the temporal relationship between  
535 HACA positivity and infusion reaction was variable.

536 A total of 23/99 (23%) Rituxan-treated patients with GPA and MPA tested positive for HACA by  
537 18 months. The clinical relevance of HACA formation in Rituxan-treated patients is unclear.

#### 538 **6.5 Postmarketing Experience**

539 Because these reactions are reported voluntarily from a population of uncertain size, it is not  
540 always possible to reliably estimate their frequency or establish a causal relationship to drug  
541 exposure. Decisions to include these reactions in labeling are typically based on one or more of the  
542 following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal  
543 connection to Rituxan.

- 544 • Hematologic: prolonged pancytopenia, marrow hypoplasia, Grade 3-4 prolonged or late-onset  
545 neutropenia, hyperviscosity syndrome in Waldenstrom's macroglobulinemia, prolonged  
546 hypogammaglobulinemia [*see Warnings and Precautions (5.6)*].
- 547 • Cardiac: fatal cardiac failure.
- 548 • Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like  
549 syndrome, serum sickness, polyarticular arthritis, and vasculitis with rash.
- 550 • Infection: viral infections, including progressive multifocal leukoencephalopathy (PML),  
551 increase in fatal infections in HIV-associated lymphoma, and a reported increased incidence  
552 of Grade 3 and 4 infections [*see Warnings and Precautions (5.6)*].
- 553 • Neoplasia: disease progression of Kaposi's sarcoma.
- 554 • Skin: severe mucocutaneous reactions.
- 555 • Gastrointestinal: bowel obstruction and perforation.
- 556 • Pulmonary: fatal bronchiolitis obliterans and fatal interstitial lung disease.
- 557 • Nervous system: Posterior Reversible Encephalopathy Syndrome (PRES) / Reversible  
558 Posterior Leukoencephalopathy Syndrome (RPLS).

559 **7 DRUG INTERACTIONS**

560 Formal drug interaction studies have not been performed with Rituxan. In patients with CLL,  
561 Rituxan did not alter systemic exposure to fludarabine or cyclophosphamide. In clinical trials of  
562 patients with RA, concomitant administration of methotrexate or cyclophosphamide did not alter the  
563 pharmacokinetics of rituximab.

564 **8 USE IN SPECIFIC POPULATIONS**

565 **8.1 Pregnancy**

566 Category C: There are no adequate and well-controlled studies of rituximab in pregnant women.  
567 Postmarketing data indicate that B-cell lymphocytopenia generally lasting less than six months can  
568 occur in infants exposed to rituximab in-utero. Rituximab was detected postnatally in the serum of  
569 infants exposed in-utero.

570 Non-Hodgkin's lymphoma, moderate-severe rheumatoid arthritis, Granulomatosis with  
571 Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis are serious conditions  
572 that require treatment. Rituximab should be used during pregnancy only if the potential benefit to  
573 the mother justifies the potential risk to the fetus.

574 Reproduction studies in cynomolgus monkeys at maternal exposures similar to human therapeutic  
575 exposures showed no evidence of teratogenic effects. However, B-cell lymphoid tissue was reduced  
576 in the offspring of treated dams. The B-cell counts returned to normal levels, and immunologic  
577 function was restored within 6 months of birth [*see Non-Clinical Toxicology (13.2)*].

578 **8.3 Nursing Mothers**

579 It is not known whether Rituxan is secreted into human milk. However, Rituxan is secreted in the  
580 milk of lactating cynomolgus monkeys, and IgG is excreted in human milk. Published data suggest  
581 that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts.  
582 The unknown risks to the infant from oral ingestion of Rituxan should be weighed against the known  
583 benefits of breastfeeding.

584 **8.4 Pediatric Use**

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

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

589 **8.5 Geriatric Use**

590 *Diffuse Large B-Cell NHL*

591 Among patients with DLBCL evaluated in three randomized, active-controlled trials, 927 patients  
592 received Rituxan in combination with chemotherapy. Of these, 396 (43%) were age 65 or greater  
593 and 123 (13%) were age 75 or greater. No overall differences in effectiveness were observed  
594 between these patients and younger patients. Cardiac adverse reactions, mostly supraventricular  
595 arrhythmias, occurred more frequently among elderly patients. Serious pulmonary adverse reactions  
596 were also more common among the elderly, including pneumonia and pneumonitis.

597 *Low-Grade or Follicular Non-Hodgkin's Lymphoma*

598 Patients with previously untreated follicular NHL evaluated in Study 5 were randomized to  
599 Rituxan as single-agent maintenance therapy (n = 505) or observation (n = 513) after achieving a  
600 response to Rituxan in combination with chemotherapy. Of these, 123 (24%) patients in the Rituxan  
601 arm were age 65 or older. No overall differences in safety or effectiveness were observed between  
602 these patients and younger patients. Other clinical studies of Rituxan in low-grade or follicular,  
603 CD20-positive, B-cell NHL did not include sufficient numbers of patients aged 65 and over to  
604 determine whether they respond differently from younger subjects.

## 605 *Chronic Lymphocytic Leukemia*

606 Among patients with CLL evaluated in two randomized active-controlled trials, 243 of  
607 676 Rituxan-treated patients (36%) were 65 years of age or older; of these, 100 Rituxan-treated  
608 patients (15%) were 70 years of age or older.

609 In exploratory analyses defined by age, there was no observed benefit from the addition of  
610 Rituxan to fludarabine and cyclophosphamide among patients 70 years of age or older in Study 10 or  
611 in Study 11; there was also no observed benefit from the addition of Rituxan to fludarabine and  
612 cyclophosphamide among patients 65 years of age or older in Study 11 [*see Clinical Studies (14.4)*].  
613 Patients 70 years or older received lower dose intensity of fludarabine and cyclophosphamide  
614 compared to younger patients, regardless of the addition of Rituxan. In Study 10, the dose intensity  
615 of Rituxan was similar in older and younger patients, however in Study 11 older patients received a  
616 lower dose intensity of Rituxan.

617 The incidence of Grade 3 and 4 adverse reactions was higher among patients receiving R-FC who  
618 were 70 years or older compared to younger patients for neutropenia [44% vs. 31% (Study 10); 56%  
619 vs. 39% (Study 11)], febrile neutropenia [16% vs. 6% (Study 10)], anemia [5% vs. 2% (Study 10);  
620 21% vs. 10% (Study 11)], thrombocytopenia [19% vs. 8% (Study 11)], pancytopenia [7% vs. 2%  
621 (Study 10); 7% vs. 2% (Study 11)] and infections [30% vs. 14% (Study 11)].

## 622 *Rheumatoid Arthritis*

623 Among the 2578 patients in global RA studies completed to date, 12% were 65–75 years old and  
624 2% were 75 years old and older. The incidences of adverse reactions were similar between older and  
625 younger patients. The rates of serious adverse reactions, including serious infections, malignancies,  
626 and cardiovascular events were higher in older patients.

## 627 *Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis*

628 Of the 99 Rituxan-treated GPA and MPA patients, 36 (36%) were 65 years old and over, while  
629 8 (8%) were 75 years and over. No overall differences in efficacy were observed between patients  
630 that were 65 years old and over and younger patients. The overall incidence and rate of all serious  
631 adverse events was higher in patients 65 years old and over. The clinical study did not include  
632 sufficient numbers of patients aged 65 and over to determine whether they respond differently from  
633 younger subjects.

## 634 **10 OVERDOSAGE**

635 There has been no experience with overdosage in human clinical trials. Single doses of up to  
636 500 mg/m<sup>2</sup> have been administered in clinical trials.

## 637 **11 DESCRIPTION**

638 Rituxan<sup>®</sup> (rituximab) is a genetically engineered chimeric murine/human monoclonal IgG<sub>1</sub> kappa  
639 antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of  
640 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

641 Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a  
642 nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final  
643 product. Rituxan is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous  
644 administration. Rituxan is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or  
645 500 mg/50 mL single-use vials. The product is formulated in polysorbate 80 (0.7 mg/mL), sodium  
646 citrate dihydrate (7.35 mg/mL), sodium chloride (9 mg/mL) and Water for Injection. The pH is 6.5.

## 647 **12 CLINICAL PHARMACOLOGY**

### 648 **12.1 Mechanism of Action**

649 Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation  
650 antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately  
651 35 kD located on pre-B and mature B lymphocytes. The antigen is expressed on >90% of B-cell  
652 non-Hodgkin's lymphomas (NHL), but the antigen is not found on hematopoietic stem cells,

653 pro-B-cells, normal plasma cells or other normal tissues. CD20 regulates an early step(s) in the  
654 activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion  
655 channel. CD20 is not shed from the cell surface and does not internalize upon antibody binding.  
656 Free CD20 antigen is not found in the circulation.

657 B cells are believed to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated  
658 chronic synovitis. In this setting, B cells may be acting at multiple sites in the  
659 autoimmune/inflammatory process, including through production of rheumatoid factor (RF) and  
660 other autoantibodies, antigen presentation, T-cell activation, and/or proinflammatory cytokine  
661 production.

662 Mechanism of Action: The Fab domain of rituximab binds to the CD20 antigen on B  
663 lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis *in vitro*.  
664 Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and  
665 antibody-dependent cell mediated cytotoxicity (ADCC). The antibody has been shown to induce  
666 apoptosis in the DHL-4 human B-cell lymphoma line.

667 Normal Tissue Cross-reactivity: Rituximab binding was observed on lymphoid cells in the  
668 thymus, the white pulp of the spleen, and a majority of B lymphocytes in peripheral blood and  
669 lymph nodes. Little or no binding was observed in the non-lymphoid tissues examined.

## 670 **12.2 Pharmacodynamics**

### 671 *Non-Hodgkins Lymphoma (NHL)*

672 In NHL patients, administration of Rituxan resulted in depletion of circulating and tissue-based  
673 B cells. Among 166 patients in Study 1, circulating CD19-positive B cells were depleted within the  
674 first three weeks with sustained depletion for up to 6 to 9 months post treatment in 83% of patients.  
675 B-cell recovery began at approximately 6 months and median B-cell levels returned to normal by  
676 12 months following completion of treatment.

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

### 680 *Rheumatoid Arthritis*

681 In RA patients, treatment with Rituxan induced depletion of peripheral B lymphocytes, with the  
682 majority of patients demonstrating near complete depletion (CD19 counts below the lower limit of  
683 quantification, 20 cells/ $\mu$ l) within 2 weeks after receiving the first dose of Rituxan. The majority of  
684 patients showed peripheral B-cell depletion for at least 6 months. A small proportion of patients  
685 (~4%) had prolonged peripheral B-cell depletion lasting more than 3 years after a single course of  
686 treatment.

687 Total serum immunoglobulin levels, IgM, IgG, and IgA were reduced at 6 months with the  
688 greatest change observed in IgM. At Week 24 of the first course of Rituxan treatment, small  
689 proportions of patients experienced decreases in IgM (10%), IgG (2.8%), and IgA (0.8%) levels  
690 below the lower limit of normal (LLN). In the experience with Rituxan in RA patients during  
691 repeated Rituxan treatment, 23.3%, 5.5%, and 0.5% of patients experienced decreases in IgM, IgG,  
692 and IgA concentrations below LLN at any time after receiving Rituxan, respectively. The clinical  
693 consequences of decreases in immunoglobulin levels in RA patients treated with Rituxan are  
694 unclear.

695 Treatment with rituximab in patients with RA was associated with reduction of certain biologic  
696 markers of inflammation such as interleukin-6 (IL-6), C-reactive protein (CRP), serum amyloid  
697 protein (SAA), S100 A8/S100 A9 heterodimer complex (S100 A8/9), anti-citrullinated peptide  
698 (anti-CCP), and RF.

### 699 *Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis*

700 In GPA and MPA patients, peripheral blood CD19 B-cells depleted to less than 10 cells/ $\mu$ l  
701 following the first two infusions of Rituxan, and remained at that level in most (84%) patients

702 through Month 6. By Month 12, the majority of patients (81%) showed signs of B-cell return with  
703 counts >10 cells/ $\mu$ L. By Month 18, most patients (87%) had counts >10 cells/ $\mu$ L.

### 704 **12.3 Pharmacokinetics**

#### 705 *Non-Hodgkins Lymphoma (NHL)*

706 Pharmacokinetics were characterized in 203 NHL patients receiving 375 mg/m<sup>2</sup> Rituxan weekly  
707 by intravenous infusion for 4 doses. Rituximab was detectable in the serum of patients 3 to  
708 6 months after completion of treatment.

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

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

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

#### 720 *Rheumatoid Arthritis*

721 Following administration of 2 doses of Rituxan in patients with RA, the mean ( $\pm$  S.D.; % CV)  
722 concentrations after the first infusion (C<sub>max</sub> first) and second infusion (C<sub>max</sub> second) were  
723 157 ( $\pm$  46; 29%) and 183 ( $\pm$  55; 30%) mcg/mL, and 318 ( $\pm$  86; 27%) and 381 ( $\pm$  98; 26%)  
724 mcg/mL for the 2  $\times$  500 mg and 2  $\times$  1000 mg doses, respectively.

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

#### 729 *Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis*

730 Based on the population pharmacokinetic analysis of data in 97 GPA and MPA patients who  
731 received 375 mg/m<sup>2</sup> rituximab once weekly by intravenous infusion for four weeks, the estimated  
732 median terminal elimination half-life was 23 days (range, 9 to 49 days). Rituximab mean clearance  
733 and volume of distribution were 0.312 L/day (range, 0.115 to 0.728 L/day) and 4.50 L (range, 2.21  
734 to 7.52 L) respectively. Male patients and patients with higher BSA or positive HACA levels have  
735 higher clearance. However, further dose adjustment based on gender or HACA status is not  
736 necessary.

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

## 740 **13 NONCLINICAL TOXICOLOGY**

### 741 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

742 No long-term animal studies have been performed to establish the carcinogenic or mutagenic  
743 potential of Rituxan or to determine potential effects on fertility in males or females.

### 744 **13.2 Animal Toxicology and/or Pharmacology**

#### 745 *Reproductive Toxicology Studies*

746 An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys.  
747 Pregnant animals received rituximab via the intravenous route during early gestation (organogenesis  
748 period; post-coitum days 20 through 50). Rituximab was administered as loading doses on post-  
749 coitum (PC) days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on PC Days 29, 36,  
750 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the exposure

751 (based on AUC) of those achieved following a dose of 2 grams in humans. Rituximab crosses the  
752 monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have decreased  
753 lymphoid tissue B cells.

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

## 763 **14 CLINICAL STUDIES**

### 764 **14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**

765 The safety and effectiveness of Rituxan in relapsed, refractory CD20+ NHL were demonstrated in  
766 3 single-arm studies enrolling 296 patients.

#### 767 *Study 1*

768 A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or  
769 refractory, low-grade or follicular, B-cell NHL who received 375 mg/m<sup>2</sup> of Rituxan given as an  
770 intravenous infusion weekly for 4 doses. Patients with tumor masses > 10 cm or with  
771 > 5000 lymphocytes/μL in the peripheral blood were excluded from the study.

772 Results are summarized in Table 4. The median time to onset of response was 50 days.  
773 Disease-related signs and symptoms (including B-symptoms) resolved in 64% (25/39) of those  
774 patients with such symptoms at study entry.

#### 775 *Study 2*

776 In a multicenter, single-arm study, 37 patients with relapsed or refractory, low-grade NHL  
777 received 375 mg/m<sup>2</sup> of Rituxan weekly for 8 doses. Results are summarized in Table 4.

#### 778 *Study 3*

779 In a multicenter, single-arm study, 60 patients received 375 mg/m<sup>2</sup> of Rituxan weekly for 4 doses.  
780 All patients had relapsed or refractory, low-grade or follicular, B-cell NHL and had achieved an  
781 objective clinical response to Rituxan administered 3.8–35.6 months (median 14.5 months) prior to  
782 retreatment with Rituxan. Of these 60 patients, 5 received more than one additional course of  
783 Rituxan. Results are summarized in Table 4.

#### 784 *Bulky Disease*

785 In pooled data from studies 1 and 3, 39 patients with bulky (single lesion > 10 cm in diameter)  
786 and relapsed or refractory, low-grade NHL received Rituxan 375 mg/m<sup>2</sup> weekly for 4 doses. Results  
787 are summarized in Table 4.  
788

**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 <sup>a</sup>	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 <sup>b, c,</sup> <sup>d</sup>	11.2	13.4	6.9	15.0
(Months) [Range]	[1.9 to 42.1+]	[2.5 to 36.5+]	[2.8 to 25.0+]	[3.0 to 25.1+]

<sup>a</sup> Six of these patients are included in the first column. Thus, data from 296 intent-to-treat patients are provided in this table.

<sup>b</sup> Kaplan-Meier projected with observed range.

<sup>c</sup> “+” indicates an ongoing response.

<sup>d</sup> Duration of response: interval from the onset of response to disease progression.

789

790 **14.2 Previously Untreated, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**

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

793 *Study 4*

794 A total of 322 patients with previously untreated follicular NHL were randomized (1:1) to receive  
795 up to eight 3-week cycles of CVP chemotherapy alone (CVP) or in combination with Rituxan  
796 375 mg/m<sup>2</sup> on Day 1 of each cycle (R-CVP) in an open-label, multicenter study. The main outcome  
797 measure of the study was progression-free survival (PFS) defined as the time from randomization to  
798 the first of progression, relapse, or death.

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

804

**Table 5**  
Efficacy Results in Study 4

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

<sup>a</sup> p < 0.0001, two-sided stratified log-rank test.

<sup>b</sup> Estimates of Cox regression stratified by center.

805

806 *Study 5*

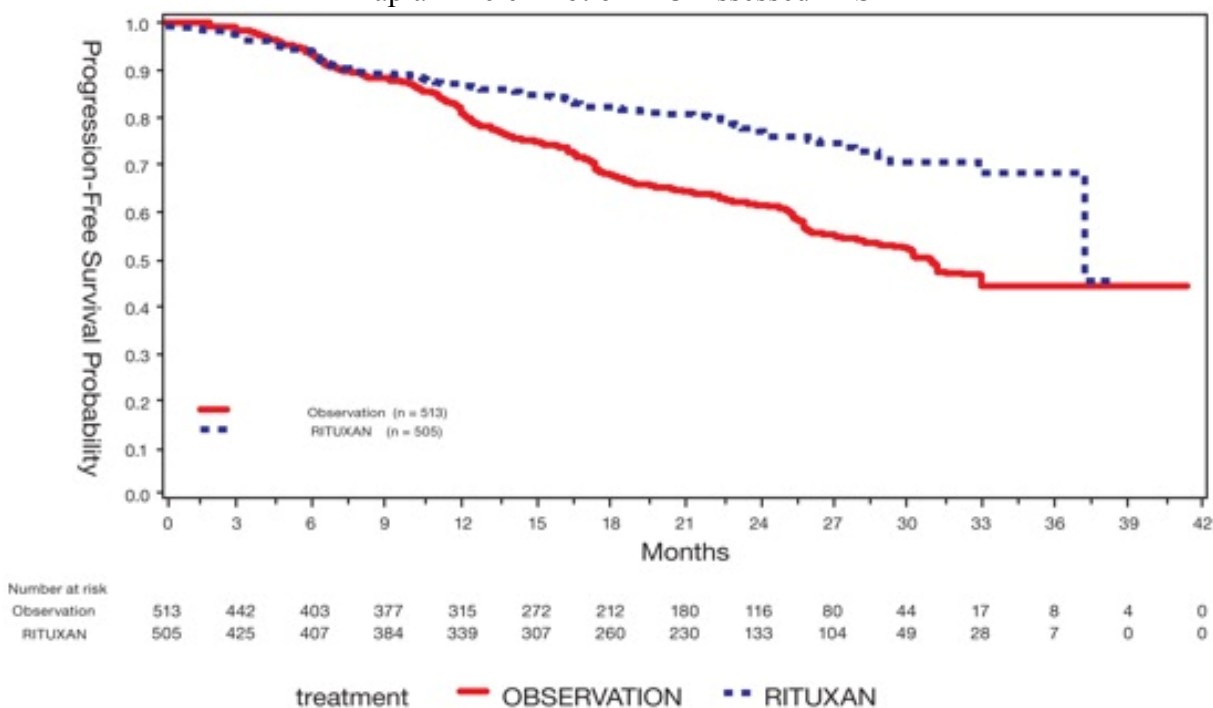
807 An open-label, multicenter, randomized (1:1) study was conducted in 1,018 patients with  
808 previously untreated follicular NHL who achieved a response (CR or PR) to Rituxan in combination  
809 with chemotherapy. Patients were randomized to Rituxan as single-agent maintenance therapy,

810 375 mg/m<sup>2</sup> every 8 weeks for up to 12 doses or to observation. Rituxan was initiated at 8 weeks  
 811 following completion of chemotherapy. The main outcome measure of the study was  
 812 progression-free survival (PFS), defined as the time from randomization in the  
 813 maintenance/observation phase to progression, relapse, or death, as determined by independent  
 814 review.

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

819 PFS was longer in patients randomized to Rituxan as single agent maintenance therapy (HR: 0.54,  
 820 95% CI: 0.42, 0.70). The PFS results based on investigator assessment of progression were similar  
 821 to those obtained by the independent review assessment.  
 822

823 **Figure 1**  
 824 Kaplan-Meier Plot of IRC Assessed PFS



825  
 826

827 *Study 6*

828 A total of 322 patients with previously untreated low-grade, B-cell NHL who did not progress  
 829 after 6 or 8 cycles of CVP chemotherapy were enrolled in an open-label, multicenter, randomized  
 830 trial. Patients were randomized (1:1) to receive Rituxan, 375 mg/m<sup>2</sup> intravenous infusion, once  
 831 weekly for 4 doses every 6 months for up to 16 doses or no further therapeutic intervention. The  
 832 main outcome measure of the study was progression-free survival defined as the time from  
 833 randomization to progression, relapse, or death. Thirty-seven percent of the study population was  
 834 >60 years of age, 99% had Stage III or IV disease, and 63% had an IPI score ≥2.

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

838 **14.3 Diffuse Large B-Cell NHL (DLBCL)**

839 The safety and effectiveness of Rituxan were evaluated in three randomized, active-controlled,  
 840 open-label, multicenter studies with a collective enrollment of 1854 patients. Patients with  
 841 previously untreated diffuse large B-cell NHL received Rituxan in combination with

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

844 *Study 7*

845 A total of 632 patients age  $\geq 60$  years with DLBCL (including primary mediastinal B-cell  
846 lymphoma) were randomized in a 1:1 ratio to treatment with CHOP or R-CHOP. Patients received  
847 6 or 8 cycles of CHOP, each cycle lasting 21 days. All patients in the R-CHOP arm received 4 doses  
848 of Rituxan  $375 \text{ mg/m}^2$  on Days  $-7$  and  $-3$  (prior to Cycle 1) and 48–72 hours prior to Cycles 3 and  
849 5. Patients who received 8 cycles of CHOP also received Rituxan prior to Cycle 7. The main  
850 outcome measure of the study was progression-free survival, defined as the time from randomization  
851 to the first of progression, relapse, or death. Responding patients underwent a second randomization  
852 to receive Rituxan or no further therapy.

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

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

862 *Study 8*

863 A total of 399 patients with DLBCL, age  $\geq 60$  years, were randomized in a 1:1 ratio to receive  
864 CHOP or R-CHOP. All patients received up to eight 3-week cycles of CHOP induction; patients in  
865 the R-CHOP arm received Rituxan  $375 \text{ mg/m}^2$  on Day 1 of each cycle. The main outcome measure  
866 of the study was event-free survival, defined as the time from randomization to relapse, progression,  
867 change in therapy, or death from any cause. Among all enrolled patients, 80% had Stage III or IV  
868 disease, 60% of patients had an age-adjusted IPI  $\geq 2$ , 80% had ECOG performance status scores  
869  $< 2$ , 66% had elevated LDH levels, and 52% had extranodal involvement in at least two sites.  
870 Efficacy results are presented in Table 6.

871 *Study 9*

872 A total of 823 patients with DLBCL, aged 18–60 years, were randomized in a 1:1 ratio to receive  
873 an anthracycline-containing chemotherapy regimen alone or in combination with Rituxan. The main  
874 outcome measure of the study was time to treatment failure, defined as time from randomization to  
875 the earliest of progressive disease, failure to achieve a complete response, relapse, or death. Among  
876 all enrolled patients, 28% had Stage III–IV disease, 100% had IPI scores of  $\leq 1$ , 99% had ECOG  
877 performance status of  $< 2$ , 29% had elevated LDH levels, 49% had bulky disease, and 34% had  
878 extranodal involvement. Efficacy results are presented in Table 6.  
879

**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 <sup>b</sup>	NE <sup>b</sup>
Hazard ratio <sup>d</sup>	0.69 <sup>a</sup>		0.60 <sup>a</sup>		0.45 <sup>a</sup>	
Overall survival at 2 years <sup>c</sup>	74%	63%	69%	58%	95%	86%
Hazard ratio <sup>d</sup>	0.72 <sup>a</sup>		0.68 <sup>a</sup>		0.40 <sup>a</sup>	

<sup>a</sup> Significant at p<0.05, 2-sided.

<sup>b</sup> NE=Not reliably estimable.

<sup>c</sup> Kaplan-Meier estimates.

<sup>d</sup> R-CHOP vs. CHOP.

880

881 In Study 8, overall survival estimates at 5 years were 58% vs. 46% for R-CHOP and CHOP,  
882 respectively.

883 **14.4 Chronic Lymphocytic Leukemia (CLL)**

884 The safety and effectiveness of Rituxan were evaluated in two randomized (1:1) multicenter  
885 open-label studies comparing FC alone or in combination with Rituxan for up to 6 cycles in patients  
886 with previously untreated CLL [Study 10 (n = 817)] or previously treated CLL [Study 11 (n = 552)].  
887 Patients received fludarabine 25 mg/m<sup>2</sup>/day and cyclophosphamide 250 mg/m<sup>2</sup>/day on days 1, 2 and  
888 3 of each cycle, with or without Rituxan. In both studies, seventy-one percent of CLL patients  
889 received 6 cycles and 90% received at least 3 cycles of Rituxan-based therapy.

890 In Study 10, 30% of patients were 65 years or older, 31% were Binet stage C, 45% had  
891 B symptoms, more than 99% had ECOG performance status (PS) 0–1, 74% were male, and 100%  
892 were White. In Study 11, 44% of patients were 65 years or older, 28% had B symptoms, 82%  
893 received a prior alkylating drug, 18% received prior fludarabine, 100% had ECOG PS 0–1, 67%  
894 were male and 98% were White.

895 The main outcome measure in both studies was progression-free survival (PFS), defined as the  
896 time from randomization to progression, relapse, or death, as determined by investigators (Study 10)  
897 or an independent review committee (Study 11). The investigator assessed results in Study 11 were  
898 supportive of those obtained by the independent review committee. Efficacy results are presented in  
899 Table 7.

900

**Table 7**  
Efficacy Results in Studies 10 and 11

	Study 10*		Study 11*	
	(Previously untreated)		(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.

901  
902 Across both studies, 243 of 676 Rituxan-treated patients (36%) were 65 years of age or older and  
903 100 Rituxan-treated patients (15%) were 70 years of age or older. The results of exploratory subset  
904 analyses in elderly patients are presented in Table 8.  
905

**Table 8**  
Efficacy Results in Studies 10 and 11 in Subgroups Defined by Age<sup>a</sup>

Age subgroup	Study 10		Study 11	
	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)

<sup>a</sup> From exploratory analyses.

906  
907 **14.5 Rheumatoid Arthritis (RA)**

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

909 The efficacy and safety of Rituxan were evaluated in two randomized, double-blind,  
910 placebo-controlled studies of adult patients with moderately to severely active RA who had a prior  
911 inadequate response to at least one TNF inhibitor. Patients were 18 years of age or older, diagnosed  
912 with active RA according to American College of Rheumatology (ACR) criteria, and had at least  
913 8 swollen and 8 tender joints.

914 In RA Study 1, patients were randomized to receive either Rituxan 2×1000 mg+MTX or  
915 placebo+MTX for 24 weeks. Further courses of Rituxan 2×1000 mg+MTX were administered in  
916 an open label extension study at a frequency determined by clinical evaluation, but no sooner than  
917 16 weeks after the preceding course of Rituxan. In addition to the intravenous premedication,  
918 glucocorticoids were administered orally on a tapering schedule from baseline through Day 14. The  
919 proportions of patients achieving ACR 20, 50, and 70 responses at Week 24 of the  
920 placebo-controlled period are shown in Table 9.

921 In RA Study 2, all patients received the first course of Rituxan 2 × 1000 mg + MTX. Patients who  
922 experienced ongoing disease activity were randomized to receive a second course of either Rituxan  
923 2 × 1000 mg + MTX or placebo + MTX, the majority between Weeks 24–28. The proportions of

924 patients achieving ACR 20, 50, and 70 responses at Week 24, before the re-treatment course, and at  
925 Week 48, after retreatment, are shown in Table 9.  
926

**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) <sup>c</sup> (95% CI)	Response	Placebo + MTX Retreatment n = 157	Rituxan + MTX Retreatment n = 318	Treatment Difference (Rituxan – Placebo) <sup>a,b,c</sup> (95% CI)
<b>ACR20</b>				<b>ACR20</b>			
Week 24	18%	51%	33% (26%, 41%)	Week 24	48%	45%	NA
				Week 48	45%	54%	11% (2%, 20%)
<b>ACR50</b>				<b>ACR50</b>			
Week 24	5%	27%	21% (15%, 27%)	Week 24	27%	21%	NA
				Week 48	26%	29%	4% (-4%, 13%)
<b>ACR70</b>				<b>ACR70</b>			
Week 24	1%	12%	11% (7%, 15%)	Week 24	11%	8%	NA
				Week 48	13%	14%	1% (-5%, 8%)

<sup>a</sup> 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.

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

<sup>c</sup> 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).

927 Improvement was also noted for all components of ACR response following treatment with  
928 Rituxan, as shown in Table 10.  
929

**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 <sup>a</sup>	71.0	69.0	71.0	36.0
Patient Global Assessment <sup>a</sup>	73.0	68.0	71.0	41.0
Pain <sup>a</sup>	68.0	68.0	67.0	38.5
Disability Index (HAQ) <sup>b</sup>	2.0	1.9	1.9	1.5
CRP (mg/dL)	2.4	2.5	2.6	0.9

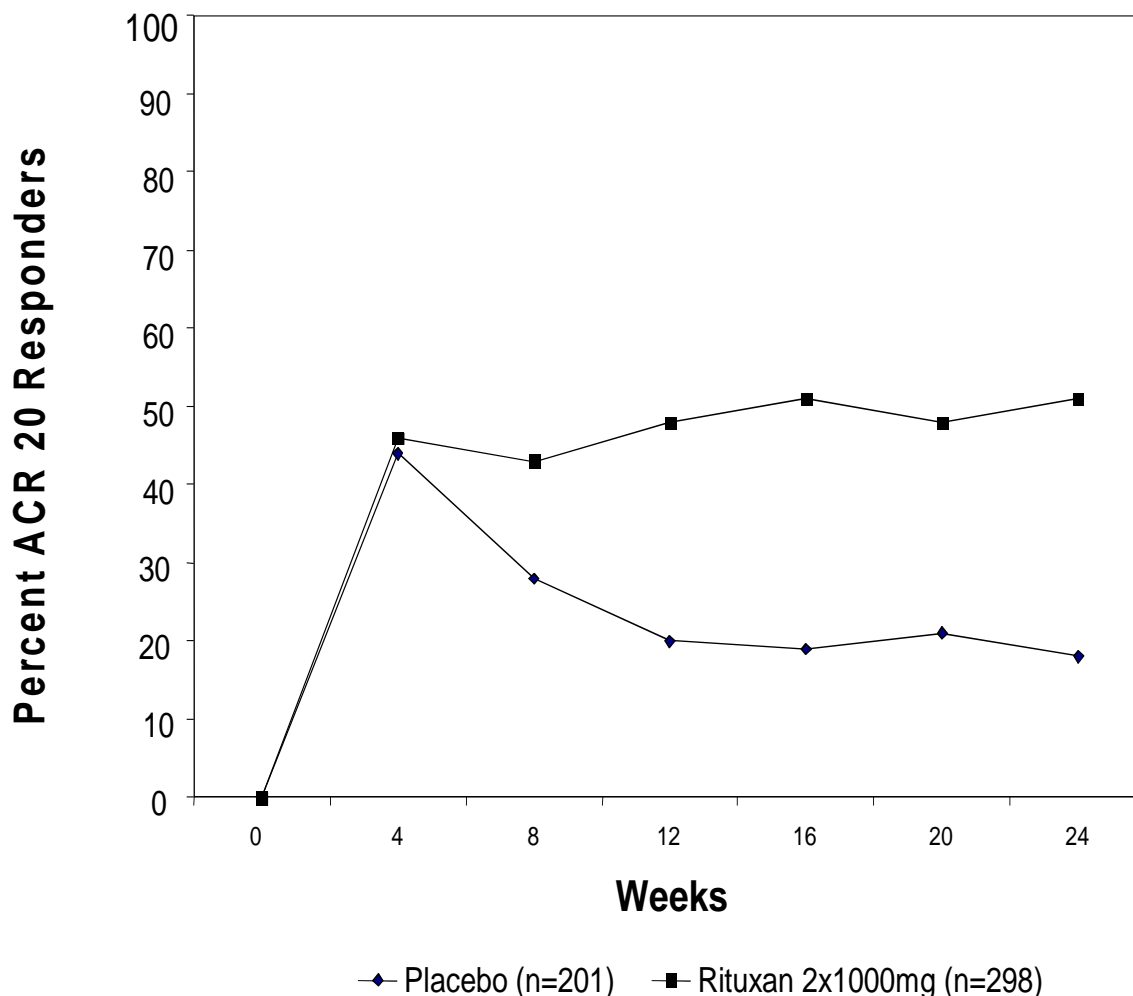
<sup>a</sup> Visual Analogue Scale: 0=best, 100=worst.

<sup>b</sup> Disability Index of the Health Assessment Questionnaire: 0=best, 3=worst.

930  
 931 The time course of ACR 20 response for Study 1 is shown in Figure 2. Although both treatment  
 932 groups received a brief course of intravenous and oral glucocorticoids, resulting in similar benefits at  
 933 Week 4, higher ACR 20 responses were observed for the Rituxan group by Week 8. A similar  
 934 proportion of patients achieved these responses through Week 24 after a single course of treatment  
 935 (2 infusions) with Rituxan. Similar patterns were demonstrated for ACR 50 and 70 responses.

936  
937  
938

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



939  
940  
941

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

942 *Radiographic Response*

943 In RA Study 1, structural joint damage was assessed radiographically and expressed as changes in  
944 Genant-modified Total Sharp Score (TSS) and its components, the erosion score (ES) and the joint  
945 space narrowing (JSN) score. Rituxan +MTX slowed the progression of structural damage  
946 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 <sup>b</sup>	Placebo+MTX <sup>c</sup>	Treatment Difference (Placebo – Rituxan)	95% CI
<u>Change during First Year</u>				
TSS	0.66	1.77	1.11	(0.47, 1.75)
ES	0.44	1.19	0.75	(0.32, 1.19)
JSN Score	0.22	0.58	0.36	(0.10, 0.62)
<u>Change during Second Year<sup>a</sup></u>				
TSS	0.48	1.04	—	—
ES	0.28	0.62	—	—
JSN Score	0.20	0.42	—	—

<sup>a</sup> Based on radiographic scoring following 104 weeks of observation.

<sup>b</sup> Patients received up to 2 years of treatment with Rituxan+MTX.

<sup>c</sup> Patients receiving Placebo+MTX. Patients receiving Placebo+MTX could have received retreatment with Rituxan+MTX from Week 16 onward.

947

948 In RA Study 1 and its open-label extension, 70% of patients initially randomized to Rituxan  
949 + MTX and 72% of patients initially randomized to placebo + MTX were evaluated  
950 radiographically at Year 2. As shown in Table 11 progression of structural damage in Rituxan  
951 + MTX patients was further reduced in the second year of treatment.

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

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

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

970 *Physical Function Response*

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

975 Physical function was assessed at Weeks 24 and 48 using the Health Assessment Questionnaire  
976 Disability Index (HAQ-DI). From baseline to Week 24, a greater proportion of Rituxan-treated  
977 patients had an improvement in HAQ-DI of at least 0.22 (a minimal clinically important difference)  
978 and a greater mean HAQ-DI improvement compared to placebo, as shown in Table 12. HAQ-DI  
979 results for the Rituxan 500 mg treatment group were similar to the Rituxan 1000 mg treatment  
980 group; however radiographic responses were not assessed (see Dosing Precaution in the  
981 Radiographic Responses section above). These improvements were maintained at 48 weeks.  
982

**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) <sup>b</sup> (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) <sup>a</sup>	48%	58%	11% (0%, 21%)

<sup>a</sup> Minimal Clinically Important Difference: MCID for HAQ=0.22.

<sup>b</sup> 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.

983  
984 **14.6 Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic**  
985 **Polyangiitis (MPA)**

986 A total of 197 patients with active, severe GPA and MPA (two forms of ANCA Associated  
987 Vasculidities) were treated in a randomized, double-blind, active-controlled multicenter,  
988 non-inferiority study, conducted in two phases – a 6 month remission induction phase and a  
989 12 month remission maintenance phase. Patients were 15 years of age or older, diagnosed with GPA  
990 (75% of patients) or MPA (24% of patients) according to the Chapel Hill Consensus conference  
991 criteria (1% of the patients had unknown vasculitis type). All patients had active disease, with a  
992 Birmingham Vasculitis Activity Score for Granulomatosis with Polyangiitis (BVAS/GPA) ≥ 3, and  
993 their disease was severe, with at least one major item on the BVAS/GPA. Ninety-six (49%) of  
994 patients had new disease and 101 (51%) of patients had relapsing disease.

995 Patients in both arms received 1000 mg of pulse intravenous methylprednisolone per day for 1 to  
996 3 days within 14 days prior to initial infusion. Patients were randomized in a 1:1 ratio to receive  
997 either Rituxan 375 mg/m<sup>2</sup> once weekly for 4 weeks or oral cyclophosphamide 2 mg/kg daily for 3 to  
998 6 months in the remission induction phase. Patients were pre-medicated with antihistamine and  
999 acetaminophen prior to Rituxan infusion. Following intravenous corticosteroid administration, all  
1000 patients received oral prednisone (1 mg/kg/day, not exceeding 80 mg/day) with pre-specified  
1001 tapering. Once remission was achieved or at the end of the 6 month remission induction period, the  
1002 cyclophosphamide group received azathioprine to maintain remission. The Rituxan group did not  
1003 receive additional therapy to maintain remission. The main outcome measure for both GPA and  
1004 MPA patients was achievement of complete remission at 6 months defined as a BVAS/GPA of 0,  
1005 and off glucocorticoid therapy. The pre-specified non-inferiority margin was a treatment difference  
1006 of 20%. As shown in Table 13, the study demonstrated non-inferiority of Rituxan to  
1007 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% <sup>b</sup> CI	(54%, 73%)	(43%, 63%)	(–3%, 24%) <sup>a</sup>

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

<sup>b</sup> The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy analysis.

1008

1009 *Complete Remission (CR) at 12 and 18 months*

1010 In the Rituxan group, 44% of patients achieved CR at 6 and 12 months, and 38% of patients  
1011 achieved CR at 6, 12, and 18 months. In patients treated with cyclophosphamide (followed by  
1012 azathioprine for maintenance of CR), 38% of patients achieved CR at 6 and 12 months, and 31% of  
1013 patients achieved CR at 6, 12, and 18 months.

1014 *Retreatment with Rituxan*

1015 Based upon investigator judgment, 15 patients received a second course of Rituxan therapy for  
1016 treatment of relapse of disease activity which occurred between 8 and 17 months after the first  
1017 course of Rituxan. The limited data preclude any conclusions regarding the efficacy of subsequent  
1018 courses of Rituxan in patients with GPA and MPA [see *Warnings and Precautions (5.14)*].

1019 **16 HOW SUPPLIED/STORAGE AND HANDLING**

1020 Rituxan vials [100 mg/10 mL single-use vials (NDC 50242-051-21) and 500 mg/50 mL single-use  
1021 vials (NDC 50242-053-06)] are stable at 2°C–8°C (36°F–46°F). Do not use beyond expiration date  
1022 stamped on carton. Rituxan vials should be protected from direct sunlight. Do not freeze or shake.

1023 Rituxan solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for 24 hours. Rituxan  
1024 solutions for infusion have been shown to be stable for an additional 24 hours at room temperature.  
1025 However, since Rituxan solutions do not contain a preservative, diluted solutions should be stored  
1026 refrigerated (2°C–8°C). No incompatibilities between Rituxan and polyvinylchloride or  
1027 polyethylene bags have been observed.

1028 **17 PATIENT COUNSELING INFORMATION**

1029 Patients should be provided the Rituxan Medication Guide and provided an opportunity to read  
1030 prior to each treatment session. It is important that the patient’s overall health be assessed at each  
1031 visit and the risks of Rituxan therapy and any questions resulting from the patient’s reading of the  
1032 Medication Guide be discussed. See FDA approved patient labeling (Medication Guide).

1033 Rituxan is detectable in serum for up to six months following completion of therapy. Individuals  
1034 of childbearing potential should use effective contraception during treatment and for 12 months after  
1035 Rituxan therapy.

1036

---

**RITUXAN<sup>®</sup> [rituximab]**

Manufactured by:

**Genentech, Inc.**

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080-4990

10134808

Initial US Approval: November 1997

PI Revision Date 03 2012

Rituxan<sup>®</sup> is a registered trademark of Biogen Idec, Inc.

©2012 Biogen Idec Inc. and Genentech, Inc.

1037  
1038  
1039  
1040  
1041  
1042  
1043  
1044  
1045  
1046  
1047  
1048  
1049  
1050  
1051  
1052  
1053  
1054  
1055  
1056  
1057  
1058  
1059  
1060  
1061  
1062  
1063  
1064  
1065  
1066  
1067  
1068  
1069  
1070  
1071  
1072  
1073  
1074  
1075  
1076  
1077  
1078  
1079

**MEDICATION GUIDE**  
**Rituxan<sup>®</sup> (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

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

1080 **4. Severe skin and mouth reactions.** Tell your doctor or get medical help right away if you get  
1081 any of these symptoms at anytime during your treatment with Rituxan:

- 1082 • painful sores or ulcers on your skin, lips or in your mouth
- 1083 • blisters
- 1084 • peeling skin
- 1085 • rash
- 1086 • pustules

1087 See “**What are possible side effects of Rituxan?**” for more information about side effects.

#### 1088 **What is Rituxan?**

1089 Rituxan is a prescription medicine used to treat:

- 1090 • **Non-Hodgkin’s Lymphoma (NHL):** alone or with other chemotherapy medicines.
- 1091 • **Chronic Lymphocytic Leukemia (CLL):** with the chemotherapy medicines fludarabine and  
1092 cyclophosphamide.
- 1093 • **Rheumatoid Arthritis (RA):** with another prescription medicine called methotrexate, to reduce  
1094 the signs and symptoms of moderate to severe active RA in adults, after treatment with at least  
1095 one other medicine called a Tumor Necrosis Factor (TNF) antagonist has been used and did not  
1096 work well enough.
- 1097 • **Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic  
1098 Polyangiitis (MPA):** with glucocorticoids, to treat GPA and MPA.

1099 People with serious infections should not receive Rituxan.

1100 It is not known if Rituxan is safe or effective in children.

1101

#### 1102 **What should I tell my doctor before receiving Rituxan?**

1103 Before receiving Rituxan, tell your doctor if you:

- 1104 • have had a severe infusion reaction to Rituxan in the past
- 1105 • have a history of heart problems, irregular heart beat or chest pain
- 1106 • have lung or kidney problems
- 1107 • have an infection or weakened immune system.
- 1108 • have or have had any severe infections including:
  - 1109 • Hepatitis B virus (HBV)
  - 1110 • Hepatitis C virus (HCV)
  - 1111 • Cytomegalovirus (CMV)
  - 1112 • Herpes simplex virus (HSV)
  - 1113 • Parvovirus B19
  - 1114 • Varicella zoster virus (chickenpox or shingles)
  - 1115 • West Nile Virus
- 1116 • have had a recent vaccination or are scheduled to receive vaccinations. You should not receive  
1117 certain vaccines before or after you receive Rituxan. Tell your doctor if anyone in your  
1118 household is scheduled to receive a vaccination. Some types of vaccines can spread to people  
1119 with a weakened immune system, and cause serious problems.
- 1120 • have taken Rituxan for GPA or MPA in the past.

- 1121 • have any other medical conditions
- 1122 • are pregnant or planning to become pregnant. Rituxan may affect the white blood cell counts of
- 1123 your unborn baby. It is not known if Rituxan may harm your unborn baby in other ways.
- 1124 Women who are able to become pregnant should use effective birth-control (contraception)
- 1125 while using Rituxan and for 12 months after you finish treatment. Talk to your doctor about
- 1126 effective birth control.
- 1127 • are breast-feeding or plan to breast-feed. It is not known if Rituxan passes into your breast milk.
- 1128 You and your doctor should decide the best way to feed your baby if you receive Rituxan.

1129 Tell your doctor about all the medicines you take, including prescription and nonprescription

1130 medicines, vitamins, and herbal supplements. Especially tell your doctor if you take or have taken:

- 1131 • a Tumor Necrosis Factor (TNF) inhibitor medicine
- 1132 • a Disease Modifying Anti-Rheumatic Drug (DMARD)

1133 If you are not sure if your medicine is one listed above, ask your doctor or pharmacist.

1134 Know the medicines you take. Keep a list of them to show to your doctor and pharmacist when you

1135 get a new medicine. Do not take any new medicine without talking with your doctor.

### 1136 **How will I receive Rituxan?**

- 1137 • Rituxan is given by infusion through a needle placed in a vein (intravenous infusion), in
- 1138 your arm. Talk to your doctor about how you will receive Rituxan.
- 1139 • Your doctor may prescribe medicines before each infusion of Rituxan to reduce side effects
- 1140 of infusions such as fever and chills.
- 1141 • Your doctor should do regular blood tests to check for side effects to Rituxan.

1142 Before each Rituxan treatment, your doctor or nurse will ask you questions about your general

1143 health. Tell your doctor or nurse about any new symptoms.

### 1144 **What are the possible side effects of Rituxan?**

1145 Rituxan can cause serious and life-threatening side effects, including:

1146 See **“What is the most important information I should know about Rituxan?”**

- 1147 • **Hepatitis B virus (HBV) reactivation.** If you have had hepatitis B or are a carrier of hepatitis B
- 1148 virus, receiving Rituxan could cause the virus to become an active infection again. Hepatitis B
- 1149 reactivation may cause serious liver problems including liver failure, and death. You should not
- 1150 receive Rituxan if you have active hepatitis B liver disease. Your doctor should monitor you for
- 1151 hepatitis B infection during and for several months after you stop receiving Rituxan.

- 1152
- 1153 • **Serious infections.** Serious infections can happen during and after treatment with Rituxan, and
- 1154 can lead to death. Rituxan can lower the ability of your immune system to fight infections.
- 1155 Types of serious infections that can happen with Rituxan include bacterial, fungal, and viral
- 1156 infections. After receiving Rituxan, some patients have developed low levels of certain
- 1157 antibodies in their blood for a long period of time (longer than 11 months). Some of these
- 1158 patients with low antibody levels developed infections. Call your doctor right away if you have
- 1159 any symptoms of infection:

- 1160 ○ fever
- 1161 ○ cold symptoms, such as runny nose or sore throat that do not go away

- 1162 ○ flu symptoms, such as cough, tiredness, and body aches
- 1163 ○ earache or headache
- 1164 ○ pain during urination
- 1165 ○ white patches in the mouth or throat
- 1166 ○ cuts, scrapes or incisions that are red, warm, swollen or painful
- 1167 ● **Heart problems.** Rituxan may cause chest pain and irregular heart beats which may need
- 1168 treatment, or your doctor may decide to stop your treatment with Rituxan.
- 1169 ● **Kidney problems,** especially if you are receiving Rituxan for NHL. Your doctor should do
- 1170 blood tests to check how well your kidneys are working.
- 1171 ● **Stomach and Serious bowel problems that can sometimes lead to death.** Bowel problems,
- 1172 including blockage or tears in the bowel can happen if you receive Rituxan with chemotherapy
- 1173 medicines to treat non-Hodgkin’s lymphoma. Tell your doctor right away if you have any
- 1174 stomach area pain during treatment with Rituxan.
- 1175 ● **Low blood cell counts.** Your doctor may do blood tests during treatment with Rituxan to check
- 1176 your blood cell counts.
  - 1177 ○ **White blood cells.** White blood cells fight against bacterial infections. Low white
  - 1178 blood cells can cause you to get infections, which may be serious. See “Increased
  - 1179 risk of infections” above for a list of symptoms of infection.
  - 1180 ○ **Red blood cells.** Red blood cells carry oxygen to your body tissues and organs.
  - 1181 ○ **Platelets.** Platelets are blood cells that help your blood to clot.

1182 **Common side effects during Rituxan treatment include:**

- 1183 ● infusion reactions (see What is the most important information I should know about Rituxan?)
- 1184 ● chills
- 1185 ● infections
- 1186 ● body aches
- 1187 ● tiredness
- 1188 ● low white blood cells

1189 Other side effects with Rituxan include:

- 1190 ● aching joints during or within hours of receiving an infusion
- 1191 ● more frequent upper respiratory tract infection

1192 Tell your doctor about any side effect that bothers you or that does not go away.

1193 These are not all of the possible side effects with Rituxan. For more information, ask your doctor or

1194 pharmacist.

1195 Call your doctor for medical advice about side effects. You may report side effects to FDA at

1196 1-800-FDA-1088.

1197 **General information about Rituxan**

1198 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This

1199 Medication Guide provides a summary of the most important information about Rituxan. If you

1200 would like more information, talk with your doctor. You can ask your doctor for information about

1201 Rituxan that is written for healthcare professionals.

1202 For more information, go to [www.Rituxan.com](http://www.Rituxan.com) or call 1-877-474-8892.

1203 **What are the ingredients in Rituxan?**

1204 Active ingredient: rituximab

1205 Inactive ingredients: sodium chloride, sodium citrate dihydrate, polysorbate 80, and water for  
1206 injection.

1207 This Medication Guide has been approved by the U.S. Food and Drug Administration.

1208 Jointly Marketed by: Biogen Idec Inc. and Genentech USA, Inc.

1209

---

**RITUXAN<sup>®</sup> [rituximab]**

Manufactured by:

10134808

**Genentech, Inc.**

Initial US Approval: November 1997

A Member of the Roche Group

Med Guide Revision Date: February 2012

1 DNA Way

Rituxan<sup>®</sup> is a registered trademark of Biogen Idec, Inc.

South San Francisco, CA 94080-4990

©2012 Biogen Idec Inc. and Genentech, Inc.

1210

1211