

## 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, WG and MPA (1.4)	04/2011
Dosage and Administration, WG 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, WG and MPA (5.12)	04/2011
Warnings and Precautions, Retreatment in Patients with WG and MPA (5.14)	04/2011

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

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

- Non-Hodgkin's Lymphoma (NHL) (1.1)
- Chronic Lymphocytic Leukemia (CLL) (1.2)
- Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies (1.3)
- Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids (1.4)

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

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

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.

- The dose for NHL is 375 mg/m<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<sup>®</sup> (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 WG 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).
- Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA): Common adverse reactions (≥15 %) in the clinical study were infections, nausea, diarrhea, headache, muscle spasms, anemia, peripheral edema (6.3). Other important adverse reactions include infusion reactions (6.3).

**To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](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: 02/2012

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## 1 FULL PRESCRIBING INFORMATION

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#### 5 **Infusion Reactions**

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

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

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

#### 15 **Severe Mucocutaneous Reactions**

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

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

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

## 21 1 INDICATIONS AND USAGE

### 22 1.1 Non-Hodgkin's Lymphoma (NHL)

23 Rituxan<sup>®</sup> (rituximab) is indicated for the treatment of patients with:

- 24 • Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
- 25 • Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line  
26 chemotherapy and, in patients achieving a complete or partial response to Rituxan in  
27 combination with chemotherapy, as single-agent maintenance therapy.
- 28 • Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single  
29 agent after first-line CVP chemotherapy
- 30 • Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or  
31 other anthracycline-based chemotherapy regimens

### 32 1.2 Chronic Lymphocytic Leukemia (CLL)

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

### 35 1.3 Rheumatoid Arthritis (RA)

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

### 39 1.4 Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

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

### 42 1.5 Limitations of Use

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

## 44 2 DOSAGE AND ADMINISTRATION

### 45 2.1 Administration

46 DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

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

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

## 57 2.2 Recommended Dose for Non-Hodgkin's Lymphoma (NHL)

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

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

## 76 2.3 Recommended Dose for Chronic Lymphocytic Leukemia (CLL)

77 The recommended dose is:

- 78 • 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  
79 cycles 2–6 (every 28 days).

## 80 2.4 Recommended Dose as a Component of Zevalin®

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

## 87 2.5 Recommended Dose for Rheumatoid Arthritis (RA)

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

95 **2.6 Recommended Dose for Wegener’s Granulomatosis (WG) and Microscopic Polyangiitis**  
96 **(MPA)**

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

105 **2.7 Recommended Concomitant Medications**

106 Premedicate before each infusion with acetaminophen and an antihistamine.

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

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

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

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

115 **2.8 Preparation for Administration**

116 Use appropriate aseptic technique. Parenteral drug products should be inspected visually for  
117 particulate matter and discoloration prior to administration. Do not use vial if particulates or  
118 discoloration is present. Withdraw the necessary amount of Rituxan and dilute to a final  
119 concentration of 1 to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride, USP, or  
120 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Do not mix or dilute with  
121 other drugs. Discard any unused portion left in the vial.

122 **3 DOSAGE FORMS AND STRENGTHS**

123 100 mg/10 mL single-use vial

124 500 mg/50 mL single-use vial

125 **4 CONTRAINDICATIONS**

126 None.

127 **5 WARNINGS AND PRECAUTIONS**

128 **5.1 Infusion Reactions**

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

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

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

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

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

152 **5.3 Severe Mucocutaneous Reactions**

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

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

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

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

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

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

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

182 **5.6 Infections**

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

190 **5.7 Cardiovascular**

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

194 **5.8 Renal**

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

201 **5.9 Bowel Obstruction and Perforation**

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

207 **5.10 Immunization**

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

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

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

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

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

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

228 **5.11 Laboratory Monitoring**

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

236 **5.12 Concomitant Use with Biologic Agents and DMARDS other than Methotrexate in RA,**  
237 **WG and MPA**

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

244 **5.13 Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis**  
245 **Factor (TNF) Antagonists**

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

251 **5.14 Retreatment in Patients with Wegener’s Granulomatosis (WG) and Microscopic**  
252 **Polyangiitis (MPA)**

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

256 **6 ADVERSE REACTIONS**

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

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

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

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

273 **6.1 Clinical Trials Experience in Lymphoid Malignancies**

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

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

286 *Infusion Reactions*

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

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

#### 295 *Infections*

296 Serious infections (NCI CTCAE Grade 3 or 4), including sepsis, occurred in less than 5% of  
297 patients with NHL in the single-arm studies. The overall incidence of infections was 31% (bacterial  
298 19%, viral 10%, unknown 6%, and fungal 1%). [See *Warnings and Precautions (5.4), (5.5), (5.6).*]

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

#### 303 *Cytopenias and hypogammaglobulinemia*

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

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

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

313 Adverse reactions in Table 1 occurred in 356 patients with relapsed or refractory, low-grade or  
314 follicular, CD20-positive, B-cell NHL treated in single-arm studies of Rituxan administered as a  
315 single agent [see *Clinical Studies (14.1)*]. Most patients received Rituxan 375 mg/m<sup>2</sup> weekly for  
316 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.

318

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

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

322 In Study 4, patients in the R-CVP arm experienced a higher incidence of infusional toxicity and  
 323 neutropenia compared to patients in the CVP arm. The following adverse reactions occurred more  
 324 frequently ( $\geq 5\%$ ) in patients receiving R-CVP compared to CVP alone: rash (17% vs. 5%), cough  
 325 (15% vs. 6%), flushing (14% vs. 3%), rigors (10% vs. 2%), pruritus (10% vs. 1%), neutropenia (8%  
 326 vs. 3%), and chest tightness (7% vs. 1%). [*See Clinical Studies (14.2).*]

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

333 In Study 6, the following adverse reactions were reported more frequently ( $\geq 5\%$ ) in patients  
 334 receiving Rituxan following CVP compared to patients who received no further therapy: fatigue  
 335 (39% vs. 14%), anemia (35% vs. 20%), peripheral sensory neuropathy (30% vs. 18%), infections  
 336 (19% vs. 9%), pulmonary toxicity (18% vs. 10%), hepato-biliary toxicity (17% vs. 7%), rash and/or  
 337 pruritus (17% vs. 5%), arthralgia (12% vs. 3%), and weight gain (11% vs. 4%). Neutropenia was the  
 338 only Grade 3 or 4 adverse reaction that occurred more frequently ( $\geq 2\%$ ) in the Rituxan arm  
 339 compared with those who received no further therapy (4% vs. 1%). [*See Clinical Studies (14.3).*]

340 *DLBCL*

341 In Studies 7 and 8, [*see Clinical Studies (14.3)*], the following adverse reactions, regardless of  
 342 severity, were reported more frequently ( $\geq 5\%$ ) in patients age  $\geq 60$  years receiving R-CHOP as  
 343 compared to CHOP alone: pyrexia (56% vs. 46%), lung disorder (31% vs. 24%), cardiac disorder  
 344 (29% vs. 21%), and chills (13% vs. 4%). Detailed safety data collection in these studies was  
 345 primarily limited to Grade 3 and 4 adverse reactions and serious adverse reactions.

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

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

354 *CLL*

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

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

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

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

## 371 **6.2 Clinical Trials Experience in Rheumatoid Arthritis**

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

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

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

380 In placebo-controlled studies, patients received 2 x 500 mg or 2 x 1000 mg intravenous infusions  
381 of Rituxan or placebo, in combination with methotrexate, during a 24-week period. From these  
382 studies, 938 patients treated with Rituxan (2 x 1000 mg) or placebo have been pooled (see Table 2).  
383 Adverse reactions reported in  $\geq 5\%$  of patients were hypertension, nausea, upper respiratory tract  
384 infection, arthralgia, pyrexia and pruritus (see Table 2). The rates and types of adverse reactions in  
385 patients who received Rituxan 2 x 500 mg were similar to those observed in patients who received  
386 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 N=398 n (%)	Rituxan+MTX N=540 n (%)
Hypertension	21 (5)	43 (8)
Nausea	19 (5)	41 (8)
Upper Respiratory Tract Infection	23 (6)	37 (7)
Arthralgia	14 (4)	31 (6)
Pyrexia	8 (2)	27 (5)
Pruritus	5 (1)	26 (5)
Chills	9 (2)	16 (3)
Dyspepsia	3 (<1)	16 (3)
Rhinitis	6 (2)	14 (3)
Paresthesia	3 (<1)	12 (2)
Urticaria	3 (<1)	12 (2)
Abdominal Pain Upper	4 (1)	11 (2)
Throat Irritation	0 (0)	11 (2)
Anxiety	5 (1)	9 (2)
Migraine	2 (<1)	9 (2)
Asthenia	1 (<1)	9 (2)

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

\*\*Coded using MedDRA.

387

### 388 *Infusion Reactions*

389 In the Rituxan RA pooled placebo-controlled studies, 32% of Rituxan-treated patients experienced  
390 an adverse reaction during or within 24 hours following their first infusion, compared to 23% of  
391 placebo-treated patients receiving their first infusion. The incidence of adverse reactions during the  
392 24-hour period following the second infusion, Rituxan or placebo, decreased to 11% and 13%,  
393 respectively. Acute infusion reactions (manifested by fever, chills, rigors, pruritus, urticaria/rash,  
394 angioedema, sneezing, throat irritation, cough, and/or bronchospasm, with or without associated  
395 hypotension or hypertension) were experienced by 27% of Rituxan-treated patients following their  
396 first infusion, compared to 19% of placebo-treated patients receiving their first placebo infusion.  
397 The incidence of these acute infusion reactions following the second infusion of Rituxan or placebo  
398 decreased to 9% and 11%, respectively. Serious acute infusion reactions were experienced by <1%  
399 of patients in either treatment group. Acute infusion reactions required dose modification (stopping,  
400 slowing, or interruption of the infusion) in 10% and 2% of patients receiving rituximab or placebo,  
401 respectively, after the first course. The proportion of patients experiencing acute infusion reactions  
402 decreased with subsequent courses of Rituxan. The administration of intravenous glucocorticoids  
403 prior to Rituxan infusions reduced the incidence and severity of such reactions, however, there was  
404 no clear benefit from the administration of oral glucocorticoids for the prevention of acute infusion

405 reactions. Patients in clinical studies also received antihistamines and acetaminophen prior to  
406 Rituxan infusions.

#### 407 *Infections*

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

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

414 In the experience with Rituxan in 2578 RA patients, the rate of serious infections was 4.31 per  
415 100 patient years. The most common serious infections ( $\geq 0.5\%$ ) were pneumonia or lower  
416 respiratory tract infections, cellulitis and urinary tract infections. Fatal serious infections included  
417 pneumonia, sepsis and colitis. Rates of serious infection remained stable in patients receiving  
418 subsequent courses. In 185 Rituxan-treated RA patients with active disease, subsequent treatment  
419 with a biologic DMARD, the majority of which were TNF antagonists, did not appear to increase the  
420 rate of serious infection. Thirteen serious infections were observed in 186.1 patient years (6.99 per  
421 100 patient years) prior to exposure and 10 were observed in 182.3 patient years (5.49 per  
422 100 patient years) after exposure.

#### 423 *Cardiac Adverse Reactions*

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

428 In the experience with Rituxan in 2578 RA patients, the rate of serious cardiac reactions was  
429 1.93 per 100 patient years. The rate of myocardial infarction (MI) was 0.56 per 100 patient years  
430 (28 events in 26 patients), which is consistent with MI rates in the general RA population. These  
431 rates did not increase over three courses of Rituxan.

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

#### 435 *Hypophosphatemia and hyperuricemia*

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

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

#### 445 *Retreatment in Patients with RA*

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

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

### 455 **6.3 Clinical Trials Experience in Wegener's Granulomatosis (WG) and Microscopic** 456 **Polyangiitis (MPA)**

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

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

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

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

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

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

477

478 *Infusion Reactions*

479 Infusion-related reactions in the active-controlled, double-blind study were defined as any adverse  
480 event occurring within 24 hours of an infusion and considered to be infusion-related by  
481 investigators. Among the 99 patients treated with Rituxan, 12% experienced at least one infusion  
482 related reaction, compared with 11% of the 98 patients in the cyclophosphamide group.  
483 Infusion-related reactions included cytokine release syndrome, flushing, throat irritation, and tremor.  
484 In the Rituxan group, the proportion of patients experiencing an infusion related reaction was 12%,  
485 5%, 4%, and 1% following the first, second, third, and fourth infusions, respectively. Patients were  
486 pre-medicated with antihistamine and acetaminophen before each Rituxan infusion and were on  
487 background oral corticosteroids which may have mitigated or masked an infusion reaction; however,  
488 there is insufficient evidence to determine whether premedication diminishes the frequency or  
489 severity of infusion reactions.

490 *Infections*

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

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

#### 498 *Retreatment in Patients with WG and MPA*

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

#### 503 **6.4 Immunogenicity**

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

510 Using an ELISA assay, anti-human anti-chimeric antibody (HACA) was detected in 4 of  
511 356 (1.1%) patients with low-grade or follicular NHL receiving single-agent Rituxan. Three of the  
512 four patients had an objective clinical response.

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

519 A total of 23/99 (23%) Rituxan-treated patients with WG and MPA tested positive for HACA by  
520 18 months. The clinical relevance of HACA formation in Rituxan-treated patients is unclear.

#### 521 **6.5 Postmarketing Experience**

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

- 527 • Hematologic: prolonged pancytopenia, marrow hypoplasia, and late-onset neutropenia,  
528 hyperviscosity syndrome in Waldenstrom's macroglobulinemia, prolonged  
529 hypogammaglobulinemia [*see Warnings and Precautions (5.6)*].
- 530 • Cardiac: fatal cardiac failure.
- 531 • Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like  
532 syndrome, serum sickness, polyarticular arthritis, and vasculitis with rash.
- 533 • Infection: viral infections, including progressive multifocal leukoencephalopathy (PML),  
534 increase in fatal infections in HIV-associated lymphoma, and a reported increased incidence  
535 of Grade 3 and 4 infections [*see Warnings and Precautions (5.6)*].
- 536 • Neoplasia: disease progression of Kaposi's sarcoma.
- 537 • Skin: severe mucocutaneous reactions.
- 538 • Gastrointestinal: bowel obstruction and perforation.
- 539 • Pulmonary: fatal bronchiolitis obliterans and fatal interstitial lung disease.
- 540 • Nervous system: Posterior Reversible Encephalopathy Syndrome (PRES) / Reversible  
541 Posterior Leukoencephalopathy Syndrome (RPLS).

542 **7 DRUG INTERACTIONS**

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

547 **8 USE IN SPECIFIC POPULATIONS**

548 **8.1 Pregnancy**

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

553 Non-Hodgkin's lymphoma, moderate-severe rheumatoid arthritis, Wegener's Granulomatosis and  
554 Microscopic Polyangiitis are serious conditions that require treatment. Rituximab should be used  
555 during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.  
556 Reproduction studies in cynomolgus monkeys at maternal exposures similar to human therapeutic  
557 exposures showed no evidence of teratogenic effects. However, B-cell lymphoid tissue was reduced  
558 in the offspring of treated dams. The B-cell counts returned to normal levels, and immunologic  
559 function was restored within 6 months of birth [*see Non-Clinical Toxicology (13.2)*].

560 **8.3 Nursing Mothers**

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

566 **8.4 Pediatric Use**

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

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

571 **8.5 Geriatric Use**

572 *Diffuse Large B-Cell NHL*

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

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

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

587 *Chronic Lymphocytic Leukemia*

588 Among patients with CLL evaluated in two randomized active-controlled trials, 243 of  
589 676 Rituxan-treated patients (36%) were 65 years of age or older; of these, 100 Rituxan-treated  
590 patients (15%) were 70 years of age or older.

591 In exploratory analyses defined by age, there was no observed benefit from the addition of  
592 Rituxan to fludarabine and cyclophosphamide among patients 70 years of age or older in Study 10 or  
593 in Study 11; there was also no observed benefit from the addition of Rituxan to fludarabine and  
594 cyclophosphamide among patients 65 years of age or older in Study 11 [*see Clinical Studies (14.4)*].  
595 Patients 70 years or older received lower dose intensity of fludarabine and cyclophosphamide  
596 compared to younger patients, regardless of the addition of Rituxan. In Study 10, the dose intensity  
597 of Rituxan was similar in older and younger patients, however in Study 11 older patients received a  
598 lower dose intensity of Rituxan.

599 The incidence of Grade 3 and 4 adverse reactions was higher among patients receiving R-FC who  
600 were 70 years or older compared to younger patients for neutropenia [44% vs. 31% (Study 10); 56%  
601 vs. 39% (Study 11)], febrile neutropenia [16% vs. 6% (Study 10)], anemia [5% vs. 2% (Study 10);  
602 21% vs. 10% (Study 11)], thrombocytopenia [19% vs. 8% (Study 11)], pancytopenia [7% vs. 2%  
603 (Study 10); 7% vs. 2% (Study 11)] and infections [30% vs. 14% (Study 11)].

#### 604 *Rheumatoid Arthritis*

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

#### 609 *Wegener's Granulomatosis and Microscopic Polyangiitis*

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

## 616 **10 OVERDOSAGE**

617 There has been no experience with overdosage in human clinical trials. Single doses of up to  
618 500 mg/m<sup>2</sup> have been administered in clinical trials.

## 619 **11 DESCRIPTION**

620 Rituxan<sup>®</sup> (rituximab) is a genetically engineered chimeric murine/human monoclonal IgG<sub>1</sub> kappa  
621 antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of  
622 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

623 Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a  
624 nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final  
625 product. Rituxan is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous  
626 administration. Rituxan is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or  
627 500 mg/50 mL single-use vials. The product is formulated in polysorbate 80 (0.7 mg/mL), sodium  
628 citrate dihydrate (7.35 mg/mL), sodium chloride (9 mg/mL) and Water for Injection. The pH is 6.5.

## 629 **12 CLINICAL PHARMACOLOGY**

### 630 **12.1 Mechanism of Action**

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

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

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

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

## 652 **12.2 Pharmacodynamics**

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

654 In NHL patients, administration of Rituxan resulted in depletion of circulating and tissue-based  
655 B cells. Among 166 patients in Study 1, circulating CD19-positive B cells were depleted within the  
656 first three weeks with sustained depletion for up to 6 to 9 months post treatment in 83% of patients.  
657 B-cell recovery began at approximately 6 months and median B-cell levels returned to normal by  
658 12 months following completion of treatment.

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

### 662 *Rheumatoid Arthritis*

663 In RA patients, treatment with Rituxan induced depletion of peripheral B lymphocytes, with the  
664 majority of patients demonstrating near complete depletion (CD19 counts below the lower limit of  
665 quantification, 20 cells/ $\mu$ l) within 2 weeks after receiving the first dose of Rituxan. The majority of  
666 patients showed peripheral B-cell depletion for at least 6 months. A small proportion of patients  
667 (~4%) had prolonged peripheral B-cell depletion lasting more than 3 years after a single course of  
668 treatment.

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

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

### 681 *Wegener's Granulomatosis and Microscopic Polyangiitis*

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

686 **12.3 Pharmacokinetics**

687 *Non-Hodgkins Lymphoma (NHL)*

688 Pharmacokinetics were characterized in 203 NHL patients receiving 375 mg/m<sup>2</sup> Rituxan weekly  
689 by intravenous infusion for 4 doses. Rituximab was detectable in the serum of patients 3 to  
690 6 months after completion of treatment.

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

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

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

702 *Rheumatoid Arthritis*

703 Following administration of 2 doses of Rituxan in patients with RA, the mean (± S.D.; % CV)  
704 concentrations after the first infusion (C<sub>max</sub> first) and second infusion (C<sub>max</sub> second) were  
705 157 (± 46; 29%) and 183 (± 55; 30%) mcg/mL, and 318 (± 86; 27%) and 381 (± 98; 26%)  
706 mcg/mL for the 2 × 500 mg and 2 × 1000 mg doses, respectively.

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

711 *Wegener's Granulomatosis and Microscopic Polyangiitis*

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

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

722 **13 NONCLINICAL TOXICOLOGY**

723 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

726 **13.2 Animal Toxicology and/or Pharmacology**

727 *Reproductive Toxicology Studies*

728 An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys.  
729 Pregnant animals received rituximab via the intravenous route during early gestation (organogenesis  
730 period; post-coitum days 20 through 50). Rituximab was administered as loading doses on post-  
731 coitum (PC) days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on PC Days 29, 36,  
732 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the exposure  
733 (based on AUC) of those achieved following a dose of 2 grams in humans. Rituximab crosses the

734 monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have decreased  
735 lymphoid tissue B cells.

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

## 745 **14 CLINICAL STUDIES**

### 746 **14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**

747 The safety and effectiveness of Rituxan in relapsed, refractory CD20+ NHL were demonstrated in  
748 3 single-arm studies enrolling 296 patients.

#### 749 *Study 1*

750 A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or  
751 refractory, low-grade or follicular, B-cell NHL who received 375 mg/m<sup>2</sup> of Rituxan given as an  
752 intravenous infusion weekly for 4 doses. Patients with tumor masses > 10 cm or with  
753 > 5000 lymphocytes/μL in the peripheral blood were excluded from the study.

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

#### 757 *Study 2*

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

#### 760 *Study 3*

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

#### 766 *Bulky Disease*

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

770

**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> (Months) [Range]	11.2 [1.9 to 42.1+]	13.4 [2.5 to 36.5+]	6.9 [2.8 to 25.0+]	15.0 [3.0 to 25.1+]

<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.

771

772 **14.2 Previously Untreated, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**

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

775 *Study 4*

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

781 Twenty-six percent of the study population was >60 years of age, 99% had Stage III or IV disease,  
782 and 50% had an International Prognostic Index (IPI) score ≥2. The results for PFS as determined by  
783 a blinded, independent assessment of progression are presented in Table 5. The point estimates may  
784 be influenced by the presence of informative censoring. The PFS results based on investigator  
785 assessment of progression were similar to those obtained by the independent review assessment.  
786

**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.

787

788 *Study 5*

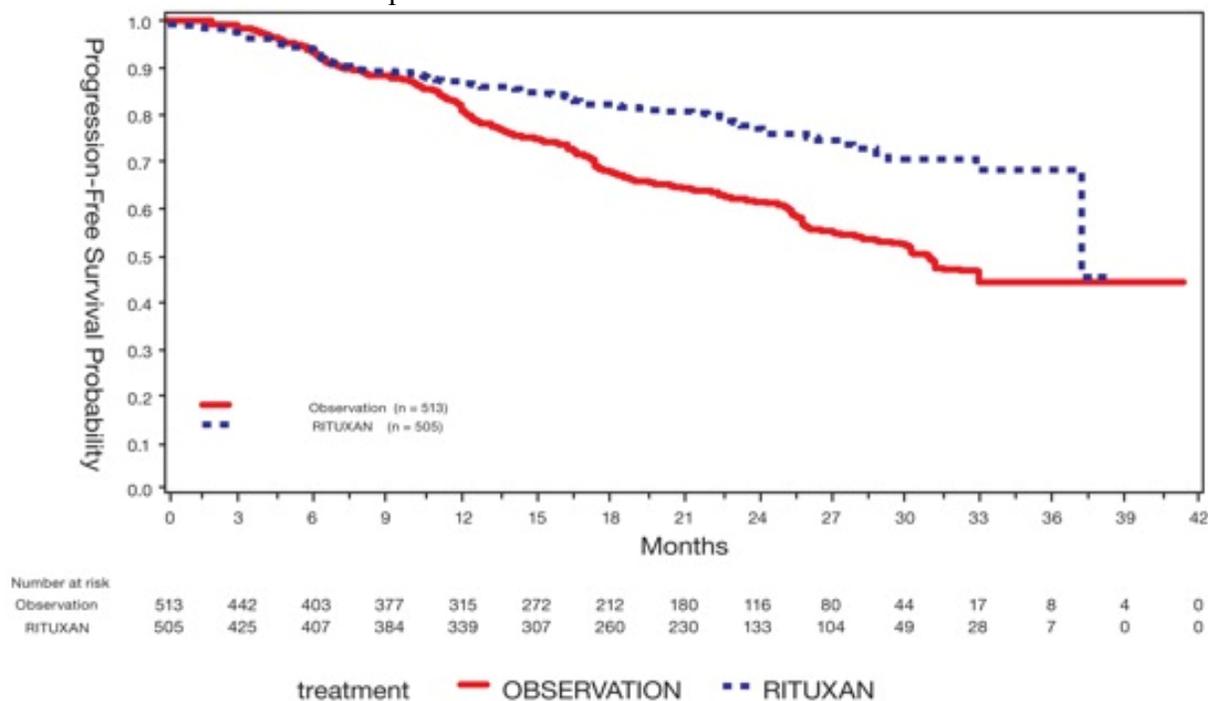
789 An open-label, multicenter, randomized (1:1) study was conducted in 1,018 patients with  
790 previously untreated follicular NHL who achieved a response (CR or PR) to Rituxan in combination  
791 with chemotherapy. Patients were randomized to Rituxan as single-agent maintenance therapy,

792 375 mg/m<sup>2</sup> every 8 weeks for up to 12 doses or to observation. Rituxan was initiated at 8 weeks  
 793 following completion of chemotherapy. The main outcome measure of the study was  
 794 progression-free survival (PFS), defined as the time from randomization in the  
 795 maintenance/observation phase to progression, relapse, or death, as determined by independent  
 796 review.

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

801 PFS was longer in patients randomized to Rituxan as single agent maintenance therapy (HR: 0.54,  
 802 95% CI: 0.42, 0.70). The PFS results based on investigator assessment of progression were similar  
 803 to those obtained by the independent review assessment.  
 804

805 **Figure 1**  
 806 Kaplan-Meier Plot of IRC Assessed PFS



807  
 808

809 **Study 6**

810 A total of 322 patients with previously untreated low-grade, B-cell NHL who did not progress  
 811 after 6 or 8 cycles of CVP chemotherapy were enrolled in an open-label, multicenter, randomized  
 812 trial. Patients were randomized (1:1) to receive Rituxan, 375 mg/m<sup>2</sup> intravenous infusion, once  
 813 weekly for 4 doses every 6 months for up to 16 doses or no further therapeutic intervention. The  
 814 main outcome measure of the study was progression-free survival defined as the time from  
 815 randomization to progression, relapse, or death. Thirty-seven percent of the study population was  
 816 >60 years of age, 99% had Stage III or IV disease, and 63% had an IPI score ≥2.

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

820 **14.3 Diffuse Large B-Cell NHL (DLBCL)**

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

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

#### 826 *Study 7*

827 A total of 632 patients age  $\geq 60$  years with DLBCL (including primary mediastinal B-cell  
828 lymphoma) were randomized in a 1:1 ratio to treatment with CHOP or R-CHOP. Patients received  
829 6 or 8 cycles of CHOP, each cycle lasting 21 days. All patients in the R-CHOP arm received 4 doses  
830 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  
831 5. Patients who received 8 cycles of CHOP also received Rituxan prior to Cycle 7. The main  
832 outcome measure of the study was progression-free survival, defined as the time from randomization  
833 to the first of progression, relapse, or death. Responding patients underwent a second randomization  
834 to receive Rituxan or no further therapy.

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

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

#### 844 *Study 8*

845 A total of 399 patients with DLBCL, age  $\geq 60$  years, were randomized in a 1:1 ratio to receive  
846 CHOP or R-CHOP. All patients received up to eight 3-week cycles of CHOP induction; patients in  
847 the R-CHOP arm received Rituxan  $375 \text{ mg/m}^2$  on Day 1 of each cycle. The main outcome measure  
848 of the study was event-free survival, defined as the time from randomization to relapse, progression,  
849 change in therapy, or death from any cause. Among all enrolled patients, 80% had Stage III or IV  
850 disease, 60% of patients had an age-adjusted IPI  $\geq 2$ , 80% had ECOG performance status scores  
851  $< 2$ , 66% had elevated LDH levels, and 52% had extranodal involvement in at least two sites.  
852 Efficacy results are presented in Table 6.

#### 853 *Study 9*

854 A total of 823 patients with DLBCL, aged 18–60 years, were randomized in a 1:1 ratio to receive  
855 an anthracycline-containing chemotherapy regimen alone or in combination with Rituxan. The main  
856 outcome measure of the study was time to treatment failure, defined as time from randomization to  
857 the earliest of progressive disease, failure to achieve a complete response, relapse, or death. Among  
858 all enrolled patients, 28% had Stage III–IV disease, 100% had IPI scores of  $\leq 1$ , 99% had ECOG  
859 performance status of  $< 2$ , 29% had elevated LDH levels, 49% had bulky disease, and 34% had  
860 extranodal involvement. Efficacy results are presented in Table 6.  
861

**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.

862

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

865 **14.4 Chronic Lymphocytic Leukemia (CLL)**

866 The safety and effectiveness of Rituxan were evaluated in two randomized (1:1) multicenter  
867 open-label studies comparing FC alone or in combination with Rituxan for up to 6 cycles in patients  
868 with previously untreated CLL [Study 10 (n = 817)] or previously treated CLL [Study 11 (n = 552)].  
869 Patients received fludarabine 25 mg/m<sup>2</sup>/day and cyclophosphamide 250 mg/m<sup>2</sup>/day on days 1, 2 and  
870 3 of each cycle, with or without Rituxan. In both studies, seventy-one percent of CLL patients  
871 received 6 cycles and 90% received at least 3 cycles of Rituxan-based therapy.

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

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

882

**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.

883  
884  
885  
886  
887

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

**Table 8**  
Efficacy Results in Studies 10 and 11 in Subgroups Defined by Age<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.

888  
889

## 14.5 Rheumatoid Arthritis (RA)

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

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

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

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

906 patients achieving ACR 20, 50, and 70 responses at Week 24, before the re-treatment course, and at  
 907 Week 48, after retreatment, are shown in Table 9.  
 908

**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)
ACR20				ACR20			
Week 24	18%	51%	33% (26%, 41%)	Week 24	48%	45%	NA
				Week 48	45%	54%	11% (2%, 20%)
ACR50				ACR50			
Week 24	5%	27%	21% (15%, 27%)	Week 24	27%	21%	NA
				Week 48	26%	29%	4% (-4%, 13%)
ACR70				ACR70			
Week 24	1%	12%	11% (7%, 15%)	Week 24	11%	8%	NA
				Week 48	13%	14%	1% (-5%, 8%)

<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).

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

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

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

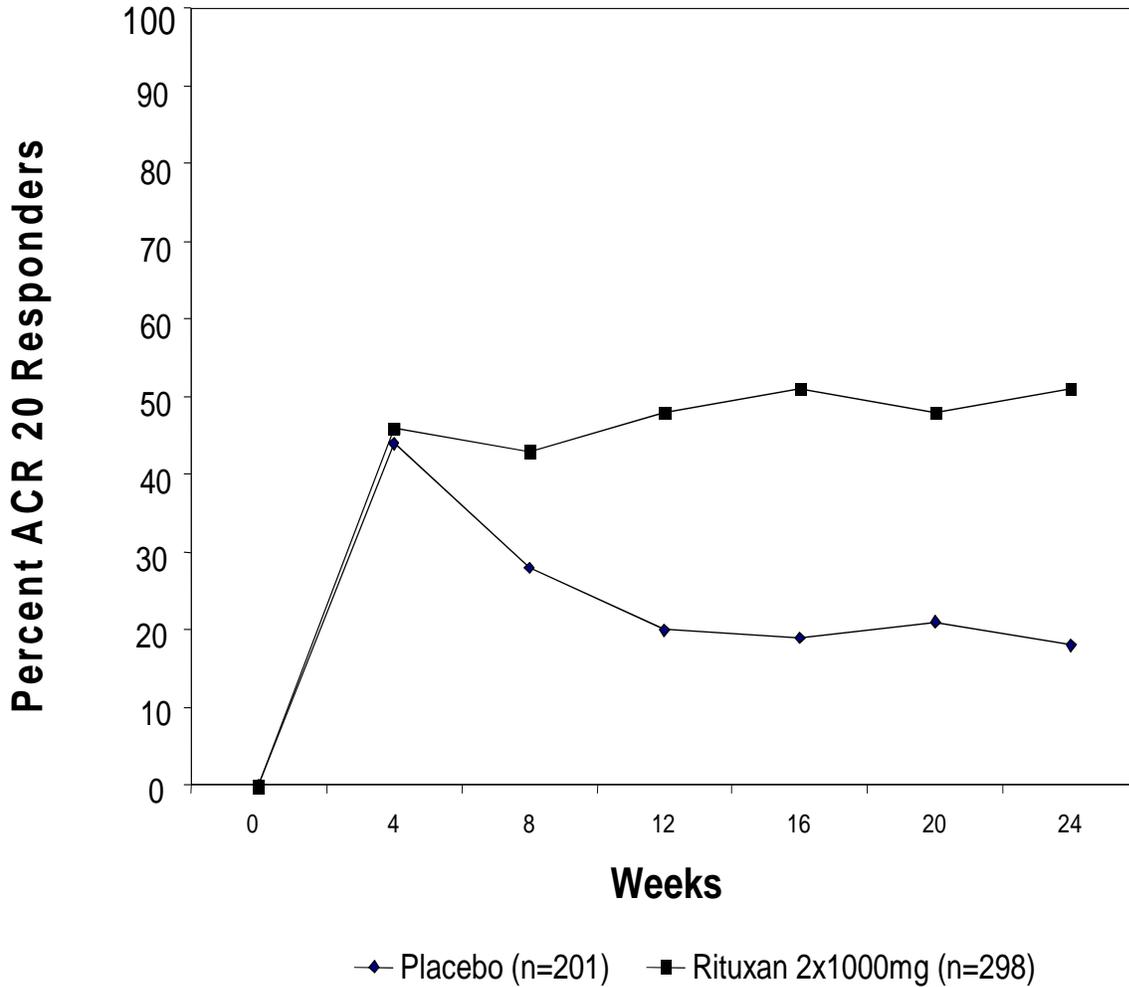
<sup>b</sup> Disability Index of the Health Assessment Questionnaire: 0=best, 3=worst.

912

913 The time course of ACR 20 response for Study 1 is shown in Figure 2. Although both treatment  
914 groups received a brief course of intravenous and oral glucocorticoids, resulting in similar benefits at  
915 Week 4, higher ACR 20 responses were observed for the Rituxan group by Week 8. A similar  
916 proportion of patients achieved these responses through Week 24 after a single course of treatment  
917 (2 infusions) with Rituxan. Similar patterns were demonstrated for ACR 50 and 70 responses.

918  
919  
920

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



921  
922  
923

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

924 *Radiographic Response*

925 In RA Study 1, structural joint damage was assessed radiographically and expressed as changes in  
926 Genant-modified Total Sharp Score (TSS) and its components, the erosion score (ES) and the joint  
927 space narrowing (JSN) score. Rituxan +MTX slowed the progression of structural damage  
928 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.

929

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

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

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

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

952 *Physical Function Response*

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

957 Physical function was assessed at Weeks 24 and 48 using the Health Assessment Questionnaire  
 958 Disability Index (HAQ-DI). From baseline to Week 24, a greater proportion of Rituxan-treated  
 959 patients had an improvement in HAQ-DI of at least 0.22 (a minimal clinically important difference)  
 960 and a greater mean HAQ-DI improvement compared to placebo, as shown in Table 12. HAQ-DI  
 961 results for the Rituxan 500 mg treatment group were similar to the Rituxan 1000 mg treatment  
 962 group; however radiographic responses were not assessed (see Dosing Precaution in the  
 963 Radiographic Responses section above). These improvements were maintained at 48 weeks.  
 964

**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.

965

966 **14.6 Wegener’s Granulomatosis (WG) and Microscopic Polyangiitis (MPA)**

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

976 Patients in both arms received 1000 mg of pulse intravenous methylprednisolone per day for 1 to  
 977 3 days within 14 days prior to initial infusion. Patients were randomized in a 1:1 ratio to receive  
 978 either Rituxan 375 mg/m<sup>2</sup> once weekly for 4 weeks or oral cyclophosphamide 2 mg/kg daily for 3 to  
 979 6 months in the remission induction phase. Patients were pre-medicated with antihistamine and  
 980 acetaminophen prior to Rituxan infusion. Following intravenous corticosteroid administration, all  
 981 patients received oral prednisone (1 mg/kg/day, not exceeding 80 mg/day) with pre-specified  
 982 tapering. Once remission was achieved or at the end of the 6 month remission induction period, the  
 983 cyclophosphamide group received azathioprine to maintain remission. The Rituxan group did not  
 984 receive additional therapy to maintain remission. The main outcome measure for both WG and  
 985 MPA patients was achievement of complete remission at 6 months defined as a BVAS/WG of 0, and  
 986 off glucocorticoid therapy. The pre-specified non-inferiority margin was a treatment difference of  
 987 20%. As shown in Table 13, the study demonstrated non-inferiority of Rituxan to  
 988 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.

989

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

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

995 *Retreatment with Rituxan*

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

1000 **16 HOW SUPPLIED/STORAGE AND HANDLING**

1001 Rituxan vials [100 mg/10 mL single-use vials (NDC 50242-051-21) and 500 mg/50 mL single-use  
 1002 vials (NDC 50242-053-06)] are stable at 2°C–8°C (36°F–46°F). Do not use beyond expiration date  
 1003 stamped on carton. Rituxan vials should be protected from direct sunlight. Do not freeze or shake.

1004 Rituxan solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for 24 hours. Rituxan  
 1005 solutions for infusion have been shown to be stable for an additional 24 hours at room temperature.  
 1006 However, since Rituxan solutions do not contain a preservative, diluted solutions should be stored  
 1007 refrigerated (2°C–8°C). No incompatibilities between Rituxan and polyvinylchloride or  
 1008 polyethylene bags have been observed.

1009 **17 PATIENT COUNSELING INFORMATION**

1010 Patients should be provided the Rituxan Medication Guide and provided an opportunity to read  
 1011 prior to each treatment session. It is important that the patient’s overall health be assessed at each  
 1012 visit and the risks of Rituxan therapy and any questions resulting from the patient’s reading of the  
 1013 Medication Guide be discussed.

1014 Rituxan is detectable in serum for up to six months following completion of therapy. Individuals  
 1015 of childbearing potential should use effective contraception during treatment and for 12 months after  
 1016 Rituxan therapy.

1017

**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 02 2012

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**MEDICATION GUIDE**  
**Rituxan® (ri-tuk-san)**  
**(rituximab)**  
**for injection**

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

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

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

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

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

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

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

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

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

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

- kidney failure and the need for dialysis treatment
- abnormal heart rhythm

1059 Your doctor may do blood tests to check you for TLS. Your doctor may give you medicine to  
1060 help prevent TLS.

1061 **4. Severe skin and mouth reactions.** Tell your doctor or get medical help right away if you get  
1062 any of these symptoms at anytime during your treatment with Rituxan:

- 1063 • painful sores or ulcers on your skin, lips or in your mouth
- 1064 • blisters
- 1065 • peeling skin
- 1066 • rash
- 1067 • pustules

1068 See “**What are possible side effects of Rituxan?**” for more information about side effects.

#### 1069 **What is Rituxan?**

1070 Rituxan is a prescription medicine used to treat:

- 1071 • **Non-Hodgkin’s Lymphoma (NHL):** alone or with other chemotherapy medicines.
- 1072 • **Chronic Lymphocytic Leukemia (CLL):** with the chemotherapy medicines fludarabine and  
1073 cyclophosphamide.
- 1074 • **Rheumatoid Arthritis (RA):** with another prescription medicine called methotrexate, to reduce  
1075 the signs and symptoms of moderate to severe active RA in adults, after treatment with at least  
1076 one other medicine called a Tumor Necrosis Factor (TNF) antagonist has been used and did not  
1077 work well enough.
- 1078 • **Wegener’s Granulomatosis (WG) and Microscopic Polyangiitis (MPA):** with  
1079 glucocorticoids, to treat WG and MPA.

1080 People with serious infections should not receive Rituxan.

1081 It is not known if Rituxan is safe or effective in children.

1082

#### 1083 **What should I tell my doctor before receiving Rituxan?**

1084 Before receiving Rituxan, tell your doctor if you:

- 1085 • have had a severe infusion reaction to Rituxan in the past
- 1086 • have a history of heart problems, irregular heart beat or chest pain
- 1087 • have lung or kidney problems
- 1088 • have an infection or weakened immune system.
- 1089 • have or have had any severe infections including:
  - 1090 • Hepatitis B virus (HBV)
  - 1091 • Hepatitis C virus (HCV)
  - 1092 • Cytomegalovirus (CMV)
  - 1093 • Herpes simplex virus (HSV)
  - 1094 • Parvovirus B19
  - 1095 • Varicella zoster virus (chickenpox or shingles)
  - 1096 • West Nile Virus

- 1097 • have had a recent vaccination or are scheduled to receive vaccinations. You should not receive  
1098 certain vaccines before or after you receive Rituxan. Tell your doctor if anyone in your  
1099 household is scheduled to receive a vaccination. Some types of vaccines can spread to people  
1100 with a weakened immune system, and cause serious problems.
- 1101 • have taken Rituxan for WG or MPA in the past.
- 1102 • have any other medical conditions
- 1103 • are pregnant or planning to become pregnant. Rituxan may affect the white blood cell counts of  
1104 your unborn baby. It is not known if Rituxan may harm your unborn baby in other ways.
- 1105 Women who are able to become pregnant should use effective birth-control (contraception)  
1106 while using Rituxan and for 12 months after you finish treatment. Talk to your doctor about  
1107 effective birth control.
- 1108 • are breast-feeding or plan to breast-feed. It is not known if Rituxan passes into your breast milk.  
1109 You and your doctor should decide the best way to feed your baby if you receive Rituxan.

1110 Tell your doctor about all the medicines you take, including prescription and nonprescription  
1111 medicines, vitamins, and herbal supplements. Especially tell your doctor if you take or have taken:

- 1112 • a Tumor Necrosis Factor (TNF) inhibitor medicine  
1113 • a Disease Modifying Anti-Rheumatic Drug (DMARD)

1114 If you are not sure if your medicine is one listed above, ask your doctor or pharmacist.

1115 Know the medicines you take. Keep a list of them to show to your doctor and pharmacist when you  
1116 get a new medicine. Do not take any new medicine without talking with your doctor.

### 1117 **How will I receive Rituxan?**

- 1118 • Rituxan is given by infusion through a needle placed in a vein (intravenous infusion), in  
1119 your arm. Talk to your doctor about how you will receive Rituxan.
- 1120 • Your doctor may prescribe medicines before each infusion of Rituxan to reduce side effects  
1121 of infusions such as fever and chills.
- 1122 • Your doctor should do regular blood tests to check for side effects to Rituxan.

1123 Before each Rituxan treatment, your doctor or nurse will ask you questions about your general  
1124 health. Tell your doctor or nurse about any new symptoms.

### 1125 **What are the possible side effects of Rituxan?**

1126 Rituxan can cause serious and life-threatening side effects, including:

1127 See **“What is the most important information I should know about Rituxan?”**

- 1128 • **Hepatitis B virus (HBV) reactivation.** If you have had hepatitis B or are a carrier of hepatitis B  
1129 virus, receiving Rituxan could cause the virus to become an active infection again. Hepatitis B  
1130 reactivation may cause serious liver problems including liver failure, and death. You should not  
1131 receive Rituxan if you have active hepatitis B liver disease. Your doctor should monitor you for  
1132 hepatitis B infection during and for several months after you stop receiving Rituxan.
- 1133
- 1134 • **Serious infections.** Serious infections can happen during and after treatment with Rituxan, and  
1135 can lead to death. Rituxan can lower the ability of your immune system to fight infections.  
1136 Types of serious infections that can happen with Rituxan include bacterial, fungal, and viral  
1137 infections. After receiving Rituxan, some patients have developed low levels of certain  
1138 antibodies in their blood for a long period of time (longer than 11 months). Some of these

1139 patients with low antibody levels developed infections. Call your doctor right away if you have  
1140 any symptoms of infection:

- 1141           ○ fever
- 1142           ○ cold symptoms, such as runny nose or sore throat that do not go away
- 1143           ○ flu symptoms, such as cough, tiredness, and body aches
- 1144           ○ earache or headache
- 1145           ○ pain during urination
- 1146           ○ white patches in the mouth or throat
- 1147           ○ cuts, scrapes or incisions that are red, warm, swollen or painful
- 1148 • **Heart problems.** Rituxan may cause chest pain and irregular heart beats which may need  
1149 treatment, or your doctor may decide to stop your treatment with Rituxan.
- 1150 • **Kidney problems,** especially if you are receiving Rituxan for NHL. Your doctor should do  
1151 blood tests to check how well your kidneys are working.
- 1152 • **Stomach and Serious bowel problems that can sometimes lead to death.** Bowel problems,  
1153 including blockage or tears in the bowel can happen if you receive Rituxan with chemotherapy  
1154 medicines to treat non-Hodgkin’s lymphoma. Tell your doctor right away if you have any  
1155 stomach area pain during treatment with Rituxan.
- 1156 • **Low blood cell counts.** Your doctor may do blood tests during treatment with Rituxan to check  
1157 your blood cell counts.
  - 1158           ○ **White blood cells.** White blood cells fight against bacterial infections. Low white  
1159 blood cells can cause you to get infections, which may be serious. See “Increased  
1160 risk of infections” above for a list of symptoms of infection.
  - 1161           ○ **Red blood cells.** Red blood cells carry oxygen to your body tissues and organs.
  - 1162           ○ **Platelets.** Platelets are blood cells that help your blood to clot.

1163 **Common side effects during Rituxan treatment include:**

- 1164 • infusion reactions (see What is the most important information I should know about Rituxan?)
- 1165 • chills
- 1166 • infections
- 1167 • body aches
- 1168 • tiredness
- 1169 • low white blood cells

1170 Other side effects with Rituxan include:

- 1171 • aching joints during or within hours of receiving an infusion
- 1172 • more frequent upper respiratory tract infection

1173 Tell your doctor about any side effect that bothers you or that does not go away.

1174 These are not all of the possible side effects with Rituxan. For more information, ask your doctor or  
1175 pharmacist.

1176 Call your doctor for medical advice about side effects. You may report side effects to FDA at  
1177 1-800-FDA-1088.

1178 **General information about Rituxan**

1179 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This  
1180 Medication Guide provides a summary of the most important information about Rituxan. If you  
1181 would like more information, talk with your doctor. You can ask your doctor for information about  
1182 Rituxan that is written for healthcare professionals.

1183 For more information, go to [www.Rituxan.com](http://www.Rituxan.com) or call 1-877-474-8892.

1184 **What are the ingredients in Rituxan?**

1185 Active ingredient: rituximab

1186 Inactive ingredients: sodium chloride, sodium citrate dihydrate, polysorbate 80, and water for  
1187 injection.

1188 This Medication Guide has been approved by the U.S. Food and Drug Administration.

1189 Jointly Marketed by: Biogen Idec Inc. and Genentech USA, Inc.  
1190

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**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

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1192 This Medication Guide has been approved by the U.S. Food and Drug Administration.