

### 1.14.2.3 Final Labeling Text

#### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

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

See [full prescribing information](#) for complete boxed warning.

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

#### RECENT MAJOR CHANGES

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

#### INDICATIONS AND USAGE

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

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

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

#### DOSAGE AND ADMINISTRATION

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.

- The dose for NHL is 375 mg/m<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).

#### DOSAGE FORMS AND STRENGTHS

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

#### CONTRAINDICATIONS

None.

#### WARNINGS AND PRECAUTIONS

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

#### ADVERSE REACTIONS

- Lymphoid Malignancies: Common adverse reactions (≥25%) in clinical trials of NHL were: infusion reactions, fever, lymphopenia, chills, infection and asthenia. Common adverse reactions (≥25%) in clinical trials of CLL were: infusion reactions and neutropenia (6.1).
- Rheumatoid Arthritis (RA) - Common adverse reactions (≥10%) in clinical trials: upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis (6.2). Other important adverse reactions include infusion reactions, serious infections, and cardiovascular events (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](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: 02/2010

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

## 1 FULL PRESCRIBING INFORMATION

### 2 **WARNING: FATAL INFUSION REACTIONS, TUMOR LYSIS SYNDROME** 3 **(TLS), SEVERE MUCOCUTANEOUS REACTIONS, and** 4 **PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)**

#### 5 **Infusion Reactions**

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

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

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

#### 17 **Severe Mucocutaneous Reactions**

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

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

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

## 24 **1 INDICATIONS AND USAGE**

### 25 **1.1 Non-Hodgkin's Lymphoma (NHL)**

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

- 27 • Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a  
28 single agent
- 29 • Previously untreated follicular, CD20-positive, B-cell NHL in combination  
30 with CVP chemotherapy
- 31 • Non-progressing (including stable disease), low-grade, CD20-positive, B-cell  
32 NHL, as a single agent, after first-line CVP chemotherapy
- 33 • Previously untreated diffuse large B-cell, CD20-positive NHL in combination  
34 with CHOP or other anthracycline-based chemotherapy regimens

### 35 **1.2 Chronic Lymphocytic Leukemia (CLL)**

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

### 39 **1.3 Rheumatoid Arthritis (RA)**

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

### 43 **1.4 Limitations of Use**

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

## 45 2 DOSAGE AND ADMINISTRATION

### 46 2.1 Administration

47 DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

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

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

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

### 60 2.2 Recommended Dose for Non-Hodgkin's Lymphoma (NHL)

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

- 63 • **Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell**  
64 **NHL**  
65 Administer once weekly for 4 or 8 doses.
- 66 • **Retreatment for Relapsed or Refractory, Low-Grade or Follicular,**  
67 **CD20-Positive, B-Cell NHL**  
68 Administer once weekly for 4 doses.
- 69 • **Previously Untreated, Follicular, CD20-Positive, B-Cell NHL**  
70 Administer on Day 1 of each cycle of CVP chemotherapy, for up to 8 doses.
- 71 • **Non-progressing, Low-Grade, CD20-Positive, B-cell NHL, after first-line**  
72 **CVP chemotherapy**  
73 Following completion of 6–8 cycles of CVP chemotherapy, administer once  
74 weekly for 4 doses at 6-month intervals to a maximum of 16 doses.
- 75 • **Diffuse Large B-Cell NHL**  
76 Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions.

### 77 2.3 Recommended Dose for Chronic Lymphocytic Leukemia (CLL)

78 The recommended dose is:

- 79 • 375 mg/m<sup>2</sup> the day prior to the initiation of FC chemotherapy, then 500 mg/m<sup>2</sup>  
80 on Day 1 of cycles 2-6 (every 28 days).

### 81 2.4 Recommended Dose as a Component of Zevalin<sup>®</sup>

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

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

- 90 • Administer Rituxan as two-1000 mg intravenous infusions separated by  
91 2 weeks.

- 92 • Glucocorticoids administered as methylprednisolone 100 mg intravenous or its  
93 equivalent 30 minutes prior to each infusion are recommended to reduce the  
94 incidence and severity of infusion reactions.
- 95 • Subsequent courses should be administered every 24 weeks or based on clinical  
96 evaluation, but not sooner than every 16 weeks.
- 97 • Rituxan is given in combination with methotrexate.

## 98 **2.6 Recommended Concomitant Medications**

99 Premedicate before each infusion with acetaminophen and an antihistamine.

100 For RA patients, methylprednisolone 100 mg IV or its equivalent is recommended  
101 30 minutes prior to each infusion.

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

## 105 **2.7 Preparation for Administration**

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

## 113 **3 DOSAGE FORMS AND STRENGTHS**

114 100 mg/10 mL single-use vial

115 500 mg/50 mL single-use vial

## 116 **4 CONTRAINDICATIONS**

117 None.

## 118 **5 WARNINGS AND PRECAUTIONS**

### 119 **5.1 Infusion Reactions**

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

126 Premedicate patients with an antihistamine and acetaminophen prior to dosing.  
127 For RA patients, methylprednisolone 100 mg IV or its equivalent is recommended  
128 30 minutes prior to each infusion. Institute medical management (e.g.  
129 glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions as  
130 needed. Depending on the severity of the infusion reaction and the required  
131 interventions, temporarily or permanently discontinue Rituxan. Resume infusion at a  
132 minimum 50% reduction in rate after symptoms have resolved. Closely monitor the  
133 following patients: those with pre-existing cardiac or pulmonary conditions, those  
134 who experienced prior cardiopulmonary adverse reactions, and those with high  
135 numbers of circulating malignant cells ( $\geq 25,000/\text{mm}^3$ ). [See *Boxed Warning*,  
136 *Warnings and Precautions (5.7)*, *Adverse Reactions (6.1)*.]

### 137 **5.2 Tumor Lysis Syndrome (TLS)**

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

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

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

### 146 **5.3 Severe Mucocutaneous Reactions**

147 Mucocutaneous reactions, some with fatal outcome, can occur in patients treated  
148 with Rituxan. These reactions include paraneoplastic pemphigus, Stevens-Johnson  
149 syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal  
150 necrolysis. The onset of these reactions has varied from 1–13 weeks following  
151 Rituxan exposure. Discontinue Rituxan in patients who experience a severe  
152 mucocutaneous reaction. The safety of readministration of Rituxan to patients with  
153 severe mucocutaneous reactions has not been determined. [See *Boxed Warning,*  
154 *Adverse Reactions (6.1, 6.4)*.]

### 155 **5.4 Progressive Multifocal Leukoencephalopathy (PML)**

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

163 Consider the diagnosis of PML in any patient presenting with new-onset  
164 neurologic manifestations. Evaluation of PML includes, but is not limited to,  
165 consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue  
166 Rituxan and consider discontinuation or reduction of any concomitant chemotherapy  
167 or immunosuppressive therapy in patients who develop PML. [See *Boxed Warning,*  
168 *Adverse Reactions (6.4)*.]

### 169 **5.5 Hepatitis B Virus (HBV) Reactivation**

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

174 Screen patients at high risk of HBV infection before initiation of Rituxan. Closely  
175 monitor carriers of hepatitis B for clinical and laboratory signs of active HBV  
176 infection for several months following Rituxan therapy. Discontinue Rituxan and any  
177 concomitant chemotherapy in patients who develop viral hepatitis, and institute  
178 appropriate treatment including antiviral therapy. Insufficient data exist regarding the  
179 safety of resuming Rituxan in patients who develop hepatitis subsequent to HBV  
180 reactivation. [See *Adverse Reactions (6.4)*.]

### 181 **5.6 Infections**

182 Serious, including fatal, bacterial, fungal, and new or reactivated viral infections  
183 can occur during and up to one year following the completion of Rituxan-based  
184 therapy. New or reactivated viral infections included cytomegalovirus, herpes  
185 simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B  
186 and C. Discontinue Rituxan for serious infections and institute appropriate anti-  
187 infective therapy. [See *Adverse Reactions (6.1, 6.4)*.]

188 **5.7 Cardiovascular**

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

193 **5.8 Renal**

194 Severe, including fatal, renal toxicity can occur after Rituxan administration in  
195 patients with NHL. Renal toxicity has occurred in patients who experience tumor  
196 lysis syndrome and in patients with NHL administered concomitant cisplatin therapy  
197 during clinical trials. The combination of cisplatin and Rituxan is not an approved  
198 treatment regimen. Monitor closely for signs of renal failure and discontinue Rituxan  
199 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,  
203 can occur in patients receiving Rituxan in combination with chemotherapy. In  
204 postmarketing reports, the mean time to documented gastrointestinal perforation was  
205 6 (range 1–77) days in patients with NHL. Perform a thorough diagnostic evaluation  
206 and institute appropriate treatment for complaints of abdominal pain. [*See Adverse*  
207 *Reactions (6.4).*]

208 **5.10 Immunization**

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

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

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

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

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

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

230 **5.11 Laboratory Monitoring**

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

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

### 239 **5.12 Concomitant Use with Biologic Agents and DMARDs other than** 240 **Methotrexate in RA**

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

### 245 **5.13 Use in RA Patients Who Have Not Had Prior Inadequate Response to** 246 **Tumor Necrosis Factor (TNF) Antagonists**

247 While the efficacy of Rituxan was supported in four controlled trials in patients  
248 with RA with prior inadequate responses to non-biologic DMARDs, and in a  
249 controlled trial in MTX-naïve patients, a favorable risk-benefit relationship has not  
250 been established in these populations. The use of Rituxan in patients with RA who  
251 have not had prior inadequate response to one or more TNF antagonists is not  
252 recommended [*see Clinical Studies (14.6)*].

## 253 **6 ADVERSE REACTIONS**

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

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

267  
268 The most common adverse reactions of Rituxan (incidence  $\geq 25\%$ ) observed in  
269 clinical trials of patients with NHL were infusion reactions, fever, lymphopenia,  
270 chills, infection, and asthenia.

271 The most common adverse reactions of Rituxan (incidence  $\geq 25\%$ ) observed in  
272 clinical trials of 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  
275 reaction rates observed in the clinical trials of a drug cannot be directly compared to  
276 rates in the clinical trials of another drug and may not reflect the rates observed in  
277 practice.

278 The data described below reflect exposure to Rituxan in 2282 patients, with  
279 exposures ranging from a single infusion up to 6–8 months. Rituxan was studied in  
280 both single-agent and active-controlled trials ( $n = 356$  and  $n = 1926$ ). The population  
281 included 679 patients with low-grade follicular lymphoma, 927 patients with DLBCL,  
282 and 676 patients with CLL. Most NHL patients received Rituxan as an infusion of  
283  $375 \text{ mg/m}^2$  per infusion, given as a single agent weekly for up to 8 doses, in  
284 combination with chemotherapy for up to 8 doses, or following chemotherapy for up  
285 to 16 doses. CLL patients received Rituxan  $375 \text{ mg/m}^2$  as an initial infusion followed



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

### 289 *Infusion Reactions*

290 In the majority of patients with NHL, infusion reactions consisting of fever,  
291 chills/rigors, nausea, pruritus, angioedema, hypotension, headache, bronchospasm,  
292 urticaria, rash, vomiting, myalgia, dizziness, or hypertension occurred during the first  
293 Rituxan infusion. Infusion reactions typically occurred within 30 to 120 minutes of  
294 beginning the first infusion and resolved with slowing or interruption of the Rituxan  
295 infusion and with supportive care (diphenhydramine, acetaminophen, and intravenous  
296 saline). The incidence of infusion reactions was highest during the first infusion  
297 (77%) and decreased with each subsequent infusion. [See *Boxed Warning, Warnings*  
298 *and Precautions (5.1).*]

### 299 *Infections*

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

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

### 308 *Cytopenias and hypogammaglobulinemia*

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

316 In studies of monotherapy, Rituxan-induced B-cell depletion occurred in 70% to  
317 80% of patients with NHL. Decreased IgM and IgG serum levels occurred in 14% of  
318 these patients.

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

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

**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>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
<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.

325

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

#### 328 *Previously Untreated Low-Grade NHL*

329 In Study 4, patients in the R-CVP arm experienced a higher incidence of infusional  
330 toxicity and neutropenia compared to patients in the CVP arm. The following  
331 adverse reactions occurred more frequently ( $\geq 5\%$ ) in patients receiving R-CVP  
332 compared to CVP alone: rash (17% vs. 5%), cough (15% vs. 6%), flushing (14% vs.  
333 3%), rigors (10% vs. 2%), pruritus (10% vs. 1%), neutropenia (8% vs. 3%), and chest  
334 tightness (7% vs. 1%). [*See Clinical Studies (14.2).*]

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

#### 344 *DLBCL*

345 In Studies 6 and 7, [*see Clinical Studies (14.4)*], the following adverse reactions,  
346 regardless of severity, were reported more frequently ( $\geq 5\%$ ) in patients age  
347  $\geq 60$  years receiving R-CHOP as compared to CHOP alone: pyrexia (56% vs. 46%),  
348 lung disorder (31% vs. 24%), cardiac disorder (29% vs. 21%), and chills (13% vs.  
349 4%). Detailed safety data collection in these studies was primarily limited to Grade 3  
350 and 4 adverse reactions and serious adverse reactions.

351 In Study 7, a review of cardiac toxicity determined that supraventricular  
352 arrhythmias or tachycardia accounted for most of the difference in cardiac disorders  
353 (4.5% for R-CHOP vs. 1.0% for CHOP).

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

### 359 *CLL*

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

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

368 In Study 9, the following Grade 3 and 4 adverse reactions occurred more  
369 frequently in R-FC-treated patients compared to FC-treated patients: infusion  
370 reactions (9% in R-FC arm), neutropenia (30% vs. 19%), febrile neutropenia  
371 (9% vs. 6%), leukopenia (23% vs. 12%), and pancytopenia (3% vs. 1%).

372 In Study 10, the following Grade 3 or 4 adverse reactions occurred more frequently  
373 in R-FC-treated patients compared to FC-treated patients: infusion reactions (7% in  
374 R-FC arm), neutropenia (49% vs. 44%), febrile neutropenia (15% vs. 12%),  
375 thrombocytopenia (11% vs. 9%), hypotension (2% vs. 0%), and hepatitis B  
376 (2% vs. < 1%). Fifty-nine percent of R-FC-treated patients experienced an infusion  
377 reaction of any severity.

## 378 **6.2 Clinical Trials Experience in Rheumatoid Arthritis**

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

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

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

388 In placebo-controlled studies, patients received 2 × 500 mg or 2 × 1000 mg  
389 intravenous infusions of Rituxan or placebo, in combination with methotrexate,  
390 during a 24-week period. From these studies, 938 patients treated with Rituxan  
391 (2 × 1000 mg) or placebo have been pooled (see [Table 2](#)). Adverse reactions reported  
392 in ≥5% of patients were hypertension, nausea, upper respiratory tract infection,  
393 arthralgia, pyrexia and pruritus (see [Table 2](#)). The rates and types of adverse reactions  
394 in patients who received Rituxan 2 × 500 mg were similar to those observed in  
395 patients who received Rituxan 2 × 1000 mg.  
396

**Table 2\***

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

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

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

\*\*Coded using MedDRA.

397

### 398 *Infusion Reactions*

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

420 *Infections*

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

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

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

437 *Cardiac Adverse Reactions*

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

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

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

452 *Hypophosphatemia and hyperuricemia*

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

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

463 *Retreatment in Patients with RA*

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

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

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

### 474 **6.3 Immunogenicity**

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

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

485 A total of 273/2578 (11%) patients with RA tested positive for HACA at any time  
486 after receiving Rituxan. HACA positivity was not associated with increased infusion  
487 reactions or other adverse reactions. Upon further treatment, the proportions of  
488 patients with infusion reactions were similar between HACA positive and negative  
489 patients, and most reactions were mild to moderate. Four HACA positive patients  
490 had serious infusion reactions, and the temporal relationship between HACA  
491 positivity and infusion reaction was variable. The clinical relevance of HACA  
492 formation in Rituxan-treated patients is unclear.

### 493 **6.4 Postmarketing Experience**

494 The following adverse reactions have been identified during post-approval use of  
495 Rituxan in hematologic malignancies. Because these reactions are reported  
496 voluntarily from a population of uncertain size, it is not always possible to reliably  
497 estimate their frequency or establish a causal relationship to drug exposure.  
498 Decisions to include these reactions in labeling are typically based on one or more of  
499 the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or  
500 (3) strength of causal connection to Rituxan.

- 501 • Hematologic: prolonged pancytopenia, marrow hypoplasia, and late-onset  
502 neutropenia, hyperviscosity syndrome in Waldenstrom's macroglobulinemia.
- 503 • Cardiac: fatal cardiac failure.
- 504 • Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis,  
505 pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis, and  
506 vasculitis with rash.
- 507 • Infection: viral infections, including progressive multifocal  
508 leukoencephalopathy (PML), increase in fatal infections in HIV-associated  
509 lymphoma, and a reported increased incidence of Grade 3 and 4 infections in  
510 patients with previously treated lymphoma without known HIV infection.
- 511 • Neoplasia: disease progression of Kaposi's sarcoma.
- 512 • Skin: severe mucocutaneous reactions.
- 513 • Gastrointestinal: bowel obstruction and perforation.
- 514 • Pulmonary: fatal bronchiolitis obliterans and pneumonitis (including  
515 interstitial pneumonitis).

516 **7 DRUG INTERACTIONS**

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

521 **8 USE IN SPECIFIC POPULATIONS**

522 **8.1 Pregnancy**

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

527 Non-Hodgkin's lymphoma and moderate-severe rheumatoid arthritis are serious  
528 conditions that require treatment. Rituximab should be used during pregnancy only if  
529 the potential benefit to the mother justifies the potential risk to the fetus.

530 Reproduction studies in cynomolgus monkeys at maternal exposures similar to  
531 human therapeutic exposures showed no evidence of teratogenic effects. However,  
532 B-cell lymphoid tissue was reduced in the offspring of treated dams. The B-cell  
533 counts returned to normal levels, and immunologic function was restored within  
534 6 months of birth.

535 **8.3 Nursing Mothers**

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

542 **8.4 Pediatric Use**

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

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

549 **8.5 Geriatric Use**

550 *Diffuse Large B-Cell NHL*

551 Among patients with DLBCL evaluated in three randomized, active-controlled  
552 trials, 927 patients received Rituxan in combination with chemotherapy. Of these,  
553 396 (43%) were age 65 or greater and 123 (13%) were age 75 or greater. No overall  
554 differences in effectiveness were observed between these patients and younger  
555 patients. Cardiac adverse reactions, mostly supraventricular arrhythmias, occurred  
556 more frequently among elderly patients. Serious pulmonary adverse reactions were  
557 also more common among the elderly, including pneumonia and pneumonitis.

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

559 Clinical studies of Rituxan in low-grade or follicular, CD20-positive, B-cell NHL  
560 did not include sufficient numbers of patients aged 65 and over to determine whether  
561 they respond differently from younger subjects.



562 *Chronic Lymphocytic Leukemia*

563 Among patients with CLL evaluated in two randomized active-controlled trials,  
564 243 of 676 Rituxan-treated patients (36%) were 65 years of age or older; of these,  
565 100 Rituxan-treated patients (15%) were 70 years of age or older.

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

575 The incidence of Grade 3 and 4 adverse reactions was higher among patients  
576 receiving R-FC who were 70 years or older compared to younger patients for  
577 neutropenia [44% vs. 31% (Study 9); 56% vs. 39% (Study 10)], febrile neutropenia  
578 [16% vs. 6% (Study 9)], anemia [5% vs. 2% (Study 9); 21% vs. 10% (Study 10)],  
579 thrombocytopenia [19% vs. 8% (Study 10)], pancytopenia [7% vs. 2% (Study 9);  
580 7% vs. 2% (Study 10)] and infections [30% vs. 14% (Study 10)].

581 *Rheumatoid Arthritis*

582 Among the 2578 patients in global RA studies completed to date, 12% were  
583 65–75 years old and 2% were 75 years old and older. The incidences of adverse  
584 reactions were similar between older and younger patients. The rates of serious  
585 adverse reactions, including serious infections, malignancies, and cardiovascular  
586 events were higher in older patients.

587 **10 OVERDOSAGE**

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

590 **11 DESCRIPTION**

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

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

602 **12 CLINICAL PHARMACOLOGY**

603 **12.1 Mechanism of Action**

604 Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted  
605 differentiation antigen, Bp35), a hydrophobic transmembrane protein with a  
606 molecular weight of approximately 35 kD located on pre-B and mature B  
607 lymphocytes. The antigen is expressed on > 90% of B-cell non-Hodgkin's  
608 lymphomas (NHL), but the antigen is not found on hematopoietic stem cells,  
609 pro-B-cells, normal plasma cells or other normal tissues. CD20 regulates an early

610 step(s) in the activation process for cell cycle initiation and differentiation, and  
611 possibly functions as a calcium ion channel. CD20 is not shed from the cell surface  
612 and does not internalize upon antibody binding. Free CD20 antigen is not found in  
613 the circulation.

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

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

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

## 629 **12.2 Pharmacodynamics**

630 In NHL patients, administration of Rituxan resulted in depletion of circulating and  
631 tissue-based B cells. Among 166 patients in Study 1, circulating CD19-positive B  
632 cells were depleted within the first three weeks with sustained depletion for up to  
633 6 to 9 months posttreatment in 83% of patients. B-cell recovery began at  
634 approximately 6 months and median B-cell levels returned to normal by 12 months  
635 following completion of treatment.

636 There were sustained and statistically significant reductions in both IgM and IgG  
637 serum levels observed from 5 through 11 months following rituximab administration;  
638 14% of patients had IgM and/or IgG serum levels below the normal range.

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

646 Total serum immunoglobulin levels, IgM, IgG, and IgA were reduced at 6 months  
647 with the greatest change observed in IgM. At Week 24 of the first course of Rituxan  
648 treatment, small proportions of patients experienced decreases in IgM (10%), IgG  
649 (2.8%), and IgA (0.8%) levels below the lower limit of normal (LLN). In the  
650 experience with Rituxan in RA patients during repeated Rituxan treatment, 23.3%,  
651 5.5%, and 0.5% of patients experienced decreases in IgM, IgG, and IgA  
652 concentrations below LLN at any time after receiving Rituxan, respectively. The  
653 clinical consequences of decreases in immunoglobulin levels in RA patients treated  
654 with Rituxan are unclear.

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

659 **12.3 Pharmacokinetics**

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

663 The pharmacokinetic profile of rituximab when administered as 6 infusions of  
664 375 mg/m<sup>2</sup> in combination with 6 cycles of CHOP chemotherapy was similar to that  
665 seen with rituximab alone.

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

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

676 Following administration of 2 doses of Rituxan in patients with RA, the mean  
677 ( $\pm$  S.D.; % CV) concentrations after the first infusion (C<sub>max</sub> first) and second  
678 infusion (C<sub>max</sub> second) were 157 ( $\pm$  46; 29%) and 183 ( $\pm$  55; 30%) mcg/mL, and  
679 318 ( $\pm$  86; 27%) and 381 ( $\pm$  98; 26%) mcg/mL for the 2  $\times$  500 mg and 2  $\times$  1000 mg  
680 doses, respectively.

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

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

689 **13 NONCLINICAL TOXICOLOGY**

690 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

694 **13.2 Animal Toxicology and/or Pharmacology**

695 *Reproductive Toxicology Studies*

696 An embryo-fetal developmental toxicity study was performed on pregnant  
697 cynomolgus monkeys. Pregnant animals received rituximab via the intravenous route  
698 during early gestation (organogenesis period; post-coitum days 20 through 50).  
699 Rituximab was administered as loading doses on post-coitum (PC) days 20, 21 and  
700 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on PC Days 29, 36, 43 and 50, at  
701 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the  
702 exposure (based on AUC) of those achieved following a dose of 2 grams in humans.  
703 Rituximab crosses the monkey placenta. Exposed offspring did not exhibit any  
704 teratogenic effects but did have decreased lymphoid tissue B cells.

705 A subsequent pre- and postnatal reproductive toxicity study in cynomolgus  
706 monkeys was completed to assess developmental effects including the recovery of  
707 B cells and immune function in infants exposed to rituximab in utero. Animals were

708 treated with a loading dose of 0, 15, or 75 mg/kg every day for 3 days, followed by  
709 weekly dosing with 0, 20, or 100 mg/kg dose. Subsets of pregnant females were  
710 treated from PC Day 20 through postpartum Day 78, PC Day 76 through PC Day 134,  
711 and from PC Day 132 through delivery and postpartum Day 28. Regardless of the  
712 timing of treatment, decreased B cells and immunosuppression were noted in the  
713 offspring of rituximab-treated pregnant animals. The B-cell counts returned to  
714 normal levels, and immunologic function was restored within 6 months postpartum.

## 715 **14 CLINICAL STUDIES**

### 716 **14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell** 717 **NHL**

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

#### 720 *Study 1*

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

726 Results are summarized in [Table 3](#). The median time to onset of response was  
727 50 days. Disease-related signs and symptoms (including B-symptoms) resolved in  
728 64% (25/39) of those patients with such symptoms at study entry.

#### 729 *Study 2*

730 In a multicenter, single-arm study, 37 patients with relapsed or refractory,  
731 low-grade NHL received 375 mg/m<sup>2</sup> of Rituxan weekly for 8 doses. Results are  
732 summarized in [Table 3](#).

#### 733 *Study 3*

734 In a multicenter, single-arm study, 60 patients received 375 mg/m<sup>2</sup> of Rituxan  
735 weekly for 4 doses. All patients had relapsed or refractory, low-grade or follicular,  
736 B-cell NHL and had achieved an objective clinical response to Rituxan administered  
737 3.8–35.6 months (median 14.5 months) prior to retreatment with Rituxan. Of these  
738 60 patients, 5 received more than one additional course of Rituxan. Results are  
739 summarized in [Table 3](#).

#### 740 *Bulky Disease*

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

744

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

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

745

746 **14.2 Previously Untreated, Follicular, CD20-Positive, B-Cell NHL**

747 *Study 4*

748 A total of 322 patients with previously untreated follicular NHL were randomized  
749 (1:1) to receive up to eight 3-week cycles of CVP chemotherapy alone (CVP) or in  
750 combination with Rituxan 375 mg/m<sup>2</sup> on Day 1 of each cycle (R-CVP) in an  
751 open-label, multicenter study. The main outcome measure of the study was  
752 progression-free survival (PFS) defined as the time from randomization to the first of  
753 progression, relapse, or death.

754 Twenty-six percent of the study population was > 60 years of age, 99% had  
755 Stage III or IV disease, and 50% had an International Prognostic Index (IPI) score  
756 ≥ 2. The results for PFS as determined by a blinded, independent assessment of  
757 progression are presented in Table 4. The point estimates may be influenced by the  
758 presence of informative censoring. The PFS results based on investigator assessment  
759 of progression were similar to those obtained by the independent review assessment.  
760

**Table 4**  
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.

761

762 **14.3 Non-Progressing Low-Grade, CD20-Positive, B-Cell NHL Following**  
763 **First-Line CVP Chemotherapy**

764 *Study 5*

765 A total of 322 patients with previously untreated low-grade, B-cell NHL who did  
766 not progress after 6 or 8 cycles of CVP chemotherapy were enrolled in an open-label,  
767 multicenter, randomized trial. Patients were randomized (1:1) to receive Rituxan,  
768 375 mg/m<sup>2</sup> intravenous infusion, once weekly for 4 doses every 6 months for up to  
769 16 doses or no further therapeutic intervention. The main outcome measure of the  
770 study was progression-free survival defined as the time from randomization to

771 progression, relapse, or death. Thirty-seven percent of the study population was  
772 > 60 years of age, 99% had Stage III or IV disease, and 63% had an IPI score  $\geq 2$ .

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

#### 776 **14.4 Diffuse Large B-Cell NHL (DLBCL)**

777 The safety and effectiveness of Rituxan were evaluated in three randomized,  
778 active-controlled, open-label, multicenter studies with a collective enrollment of  
779 1854 patients. Patients with previously untreated diffuse large B-cell NHL received  
780 Rituxan in combination with cyclophosphamide, doxorubicin, vincristine, and  
781 prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

##### 782 *Study 6*

783 A total of 632 patients age  $\geq 60$  years with DLBCL (including primary mediastinal  
784 B-cell lymphoma) were randomized in a 1:1 ratio to treatment with CHOP or  
785 R-CHOP. Patients received 6 or 8 cycles of CHOP, each cycle lasting 21 days. All  
786 patients in the R-CHOP arm received 4 doses of Rituxan 375 mg/m<sup>2</sup> on Days -7 and  
787 -3 (prior to Cycle 1) and 48-72 hours prior to Cycles 3 and 5. Patients who received  
788 8 cycles of CHOP also received Rituxan prior to Cycle 7. The main outcome  
789 measure of the study was progression-free survival, defined as the time from  
790 randomization to the first of progression, relapse, or death. Responding patients  
791 underwent a second randomization to receive Rituxan or no further therapy.

792 Among all enrolled patients, 62% had centrally confirmed DLBCL histology, 73%  
793 had Stage III-IV disease, 56% had IPI scores  $\geq 2$ , 86% had ECOG performance  
794 status of  $< 2$ , 57% had elevated LDH levels, and 30% had two or more extranodal  
795 disease sites involved. Efficacy results are presented in [Table 5](#). These results reflect  
796 a statistical approach which allows for an evaluation of Rituxan administered in the  
797 induction setting that excludes any potential impact of Rituxan given after the second  
798 randomization.

799 Analysis of results after the second randomization in Study 6 demonstrates that for  
800 patients randomized to R-CHOP, additional Rituxan exposure beyond induction was  
801 not associated with further improvements in progression-free survival or overall  
802 survival.

##### 803 *Study 7*

804 A total of 399 patients with DLBCL, age  $\geq 60$  years, were randomized in a  
805 1:1 ratio to receive CHOP or R-CHOP. All patients received up to eight 3-week  
806 cycles of CHOP induction; patients in the R-CHOP arm received Rituxan 375 mg/m<sup>2</sup>  
807 on Day 1 of each cycle. The main outcome measure of the study was event-free  
808 survival, defined as the time from randomization to relapse, progression, change in  
809 therapy, or death from any cause. Among all enrolled patients, 80% had Stage III or  
810 IV disease, 60% of patients had an age-adjusted IPI  $\geq 2$ , 80% had ECOG  
811 performance status scores  $< 2$ , 66% had elevated LDH levels, and 52% had  
812 extranodal involvement in at least two sites. Efficacy results are presented in [Table 5](#).

##### 813 *Study 8*

814 A total of 823 patients with DLBCL, aged 18-60 years, were randomized in a  
815 1:1 ratio to receive an anthracycline-containing chemotherapy regimen alone or in  
816 combination with Rituxan. The main outcome measure of the study was time to  
817 treatment failure, defined as time from randomization to the earliest of progressive  
818 disease, failure to achieve a complete response, relapse, or death. Among all enrolled

819 patients, 28% had Stage III–IV disease, 100% had IPI scores of  $\leq 1$ , 99% had ECOG  
 820 performance status of  $< 2$ , 29% had elevated LDH levels, 49% had bulky disease,  
 821 and 34% had extranodal involvement. Efficacy results are presented in Table 5.  
 822

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

	Study 6 (n = 632)		Study 7 (n = 399)		Study 8 (n = 823)	
	R-CHOP	CHOP	R-CHOP	CHOP	R-Chemo	Chemo
Main outcome	Progression-free survival (years)		Event-free survival (years)		Time to treatment failure (years)	
Median of main outcome measure	3.1	1.6	2.9	1.1	NE <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.

823

824 In Study 7, overall survival estimates at 5 years were 58% vs. 46% for R-CHOP  
 825 and CHOP, respectively.

826 **14.5 Chronic Lymphocytic Leukemia (CLL)**

827 The safety and effectiveness of Rituxan were evaluated in two randomized (1:1)  
 828 multicenter open-label studies comparing FC alone or in combination with Rituxan  
 829 for up to 6 cycles in patients with previously untreated CLL [Study 9 (n = 817)] or  
 830 previously treated CLL [Study 10 (n = 552)]. Patients received fludarabine  
 831 25 mg/m<sup>2</sup>/day and cyclophosphamide 250 mg/m<sup>2</sup>/day on days 1, 2 and 3 of each  
 832 cycle, with or without Rituxan. In both studies, seventy-one percent of CLL patients  
 833 received 6 cycles and 90% received at least 3 cycles of Rituxan-based therapy.

834 In Study 9, 30% of patients were 65 years or older, 31% were Binet stage C, 45%  
 835 had B symptoms, more than 99% had ECOG performance status (PS) 0–1, 74% were  
 836 male, and 100% were White. In Study 10, 44% of patients were 65 years or older,  
 837 28% had B symptoms, 82% received a prior alkylating drug, 18% received prior  
 838 fludarabine, 100% had ECOG PS 0–1, 67% were male and 98% were White.

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

844 [Table 6](#).

**Table 6**  
Efficacy Results in Studies 9 and 10

	Study 9*		Study 10*	
	(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

845

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

849

**Table 7**  
Efficacy Results in Studies 9 and 10 in Subgroups Defined by Age<sup>a</sup>

Age subgroup	Study 9		Study 10	
	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.

850

## 851 **14.6 Rheumatoid Arthritis (RA)**

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

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

859 In RA Study 1, patients were randomized to receive either Rituxan  
860 2 × 1000 mg + MTX or placebo + MTX for 24 weeks. Further courses of Rituxan  
861 2 × 1000 mg + MTX were administered in an open label extension study at a  
862 frequency determined by clinical evaluation, but no sooner than 16 weeks after the  
863 preceding course of Rituxan. In addition to the IV premedication, glucocorticoids  
864 were administered orally on a tapering schedule from baseline through Day 14. The  
865 proportions of patients achieving ACR 20, 50, and 70 responses at Week 24 of the  
866 placebo-controlled period are shown in Table 8.



867 In RA Study 2, all patients received the first course of Rituxan  
 868 2 × 1000 mg + MTX. Patients who experienced ongoing disease activity were  
 869 randomized to receive a second course of either Rituxan 2 × 1000 mg MTX or  
 870 placebo + MTX, the majority between Weeks 24–28. The proportions of patients  
 871 achieving ACR 20, 50, and 70 responses at Week 24, before the re-treatment course,  
 872 and at Week 48, after retreatment, are shown in Table 8.  
 873

**Table 8**  
 ACR Responses in Study 1 and Study 2 (Percent of Patients)  
 (Modified Intent-to-Treat Population)

Inadequate Response to TNF Antagonists							
Study 1 24 Week Placebo-Controlled (Week 24)				Study 2 Placebo-Controlled Retreatment (Week 24 and Week 48)			
Response	Placebo + MTX n = 201	Rituxan + MTX n = 298	Treatment Difference (Rituxan – Placebo) <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).

874  
 875 Improvement was also noted for all components of ACR response following  
 876 treatment with Rituxan, as shown in Table 9.  
 877

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

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

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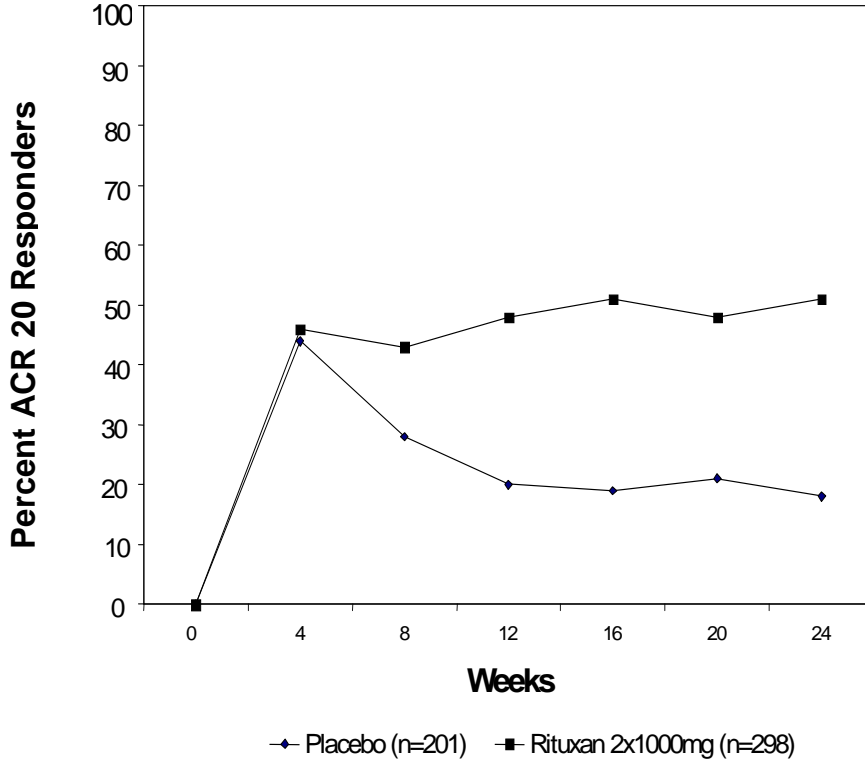
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The time course of ACR 20 response for Study 1 is shown in [Figure 1](#). Although both treatment groups received a brief course of intravenous and oral glucocorticoids, resulting in similar benefits at Week 4, higher ACR 20 responses were observed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

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



885

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

887

888 *Radiographic Response*

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

**Table 10**  
Mean Radiographic Change From Baseline to 104 Weeks

Inadequate Response to TNF Antagonists				
Parameter	Rituxan 2 x 1000 mg + MTX <sup>b</sup>	Placebo + MTX <sup>c</sup>	Treatment Difference (Placebo – Rituxan)	95% CI
<u>Change during First Year</u>				
TSS	0.66	1.78	1.12	(0.48, 1.76)
ES	0.44	1.19	0.75	(0.32, 1.18)
JSN Score	0.22	0.59	0.37	(0.11, 0.63)
<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.

894

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

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

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

908 RA Study 3 is a randomized, double-blind, placebo-controlled study which  
909 evaluated the effect of placebo + MTX compared to Rituxan 2 x 500 mg + MTX and  
910 Rituxan 2 x 1000 mg + MTX treatment courses in MTX-naïve RA patients with  
911 moderately to severely active disease. Patients received a first course of two  
912 infusions of rituximab or placebo on Days 1 and 15. MTX was initiated at  
913 7.5 mg/week and escalated up to 20 mg/week by week 8 in all three treatment arms.  
914 After a minimum of 24 weeks, patients with ongoing disease activity were eligible to  
915 receive re-treatment with additional courses of their assigned treatment. After one  
916 year of treatment, the proportion of patients achieving ACR 20/50/70 responses were  
917 similar in both Rituxan dose groups and were higher than in the placebo group.  
918 However, with respect to radiographic scores, only the Rituxan 1000 mg treatment  
919 group demonstrated a statistically significant reduction in TSS: a change of 0.36 units  
920 compared to 1.08 units for the placebo group, a 67% reduction.

921 *Physical Function Response*

922 RA Study 4 is a randomized, double-blind, placebo-controlled study in adult RA  
923 patients with moderately to severely active disease with inadequate response to MTX.  
924 Patients were randomized to receive an initial course of Rituxan 500 mg, Rituxan  
925 1000 mg, or placebo in addition to background MTX.

926 Physical function was assessed at Weeks 24 and 48 using the Health Assessment  
927 Questionnaire Disability Index (HAQ-DI). From baseline to Week 24, a greater  
928 proportion of Rituxan-treated patients had an improvement in HAQ-DI of at least  
929 0.22 (a minimal clinically important difference) and a greater mean  
930 HAQ-DI improvement compared to placebo, as shown in Table 11. HAQ-DI results  
931 for the Rituxan 500 mg treatment group were similar to the Rituxan 1000 mg  
932 treatment group; however radiographic responses were not assessed (see Dosing  
933 Precaution in the Radiographic Responses section above). These improvements were  
934 maintained at 48 weeks.  
935

**Table 11**  
Improvement from Baseline in Health Assessment  
Questionnaire Disability Index (HAQ-DI) at Week 24 in Study 4

	Placebo + MTX n = 172	Rituxan 2 x 1000 mg + MTX n = 170	Treatment Difference (Rituxan – Placebo) <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.

936

937 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

942 Rituxan solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for  
943 24 hours. Rituxan solutions for infusion have been shown to be stable for an  
944 additional 24 hours at room temperature. However, since Rituxan solutions do not  
945 contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C). No  
946 incompatibilities between Rituxan and polyvinylchloride or polyethylene bags have  
947 been observed.

948 **17 PATIENT COUNSELING INFORMATION**

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

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

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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 system can get PML. Your chance of getting PML may be higher if you are treated with Rituxan alone or with other medicines that weaken your immune system. PML can result in death or severe disability. There is no known treatment, prevention, or cure for PML.

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

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

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

- kidney failure and the need for dialysis treatment

998           • abnormal heart rhythm

999           Your doctor may do blood tests to check you for TLS. Your doctor may give you  
1000           medicine to help prevent TLS.

1001       **4. Severe skin and mouth reactions.** Tell your doctor or get medical help right  
1002           away if you get any of these symptoms at anytime during your treatment with  
1003           Rituxan:

- 1004           • painful sores or ulcers on your skin, lips or in your mouth
- 1005           • blisters
- 1006           • peeling skin
- 1007           • rash
- 1008           • pustules

1009       See “**What are possible side effects of Rituxan?**” for more information about side  
1010           effects.

#### 1011       **What is Rituxan?**

1012       Rituxan is a prescription medicine used to treat:

- 1013       • **Non-Hodgkin’s Lymphoma (NHL):** alone or with other chemotherapy  
1014           medicines.
- 1015       • **Chronic Lymphocytic Leukemia (CLL):** with the chemotherapy medicines  
1016           fludarabine and cyclophosphamide.
- 1017       • **Rheumatoid Arthritis (RA):** with another prescription medicine called  
1018           methotrexate, to reduce the signs and symptoms of moderate to severe active RA  
1019           in adults, after treatment with at least one other medicine called a Tumor  
1020           Necrosis Factor (TNF) antagonist has been used and did not work well enough.

1021       People with serious infections should not receive Rituxan.

1022       It is not known if Rituxan is safe or effective in children.

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#### 1024       **What should I tell my doctor before receiving Rituxan?**

1025       Before receiving Rituxan, tell your doctor if you:

- 1026       • have had a severe infusion reaction to Rituxan in the past
- 1027       • have a history of heart problems, irregular heart beat or chest pain
- 1028       • have lung or kidney problems
- 1029       • have an infection or weakened immune system.
- 1030       • have or have had any severe infections including:
  - 1031           • Hepatitis B virus (HBV)
  - 1032           • Hepatitis C virus (HCV)
  - 1033           • Cytomegalovirus (CMV)
  - 1034           • Herpes simplex virus (HSV)
  - 1035           • Parvovirus B19
  - 1036           • Varicella zoster virus (chickenpox or shingles)



- 1037           • West Nile Virus
- 1038   • have had a recent vaccination or are scheduled to receive vaccinations. You  
1039    should not receive certain vaccines before or after you receive Rituxan. Tell your  
1040    doctor if anyone in your household is scheduled to receive a vaccination. Some  
1041    types of vaccines can spread to people with a weakened immune system, and  
1042    cause serious problems.
- 1043   • have any other medical conditions
- 1044   • are pregnant or planning to become pregnant. Rituxan may affect the white blood  
1045    cell counts of your unborn baby. It is not known if Rituxan may harm your  
1046    unborn baby in other ways.
- 1047    Women who are able to become pregnant should use effective birth-control  
1048    (contraception) while using Rituxan and for 12 months after you finish treatment.  
1049    Talk to your doctor about effective birth control.
- 1050   • are breast-feeding or plan to breast-feed. It is not known if Rituxan passes into  
1051    your breast milk. You and your doctor should decide the best way to feed your  
1052    baby if you receive Rituxan.

1053   Tell your doctor about all the medicines you take, including prescription and  
1054    nonprescription medicines, vitamins, and herbal supplements. Especially tell your  
1055    doctor if you take or have taken:

- 1056           • a Tumor Necrosis Factor (TNF) inhibitor medicine  
1057           • a Disease Modifying Anti-Rheumatic Drug (DMARD)

1058   If you are not sure if your medicine is one listed above, ask your doctor or  
1059    pharmacist.

1060   Know the medicines you take. Keep a list of them to show to your doctor and  
1061    pharmacist when you get a new medicine. Do not take any new medicine without  
1062    talking with your doctor.

### 1063   **How will I receive Rituxan?**

- 1064           • Rituxan is given by infusion through a needle placed in a vein (IV or  
1065            intravenous infusion), in your arm. Talk to your doctor about how you will  
1066            receive Rituxan.
- 1067           • Your doctor may prescribe medicines before each infusion of Rituxan to  
1068            reduce side effects of infusions such as fever and chills.
- 1069           • Your doctor should do regular blood tests to check for side effects to  
1070            Rituxan.

1071   Before each Rituxan treatment, your doctor or nurse will ask you questions about  
1072    your general health. Tell your doctor or nurse about any new symptoms.

### 1073   **What are the possible side effects of Rituxan?**

1074   Rituxan can cause serious and life-threatening side effects, including:

1075   See **“What is the most important information I should know about Rituxan?”**

- 1076   • **Hepatitis B virus (HBV) reactivation.** If you have had hepatitis B or are a  
1077    carrier of hepatitis B virus, receiving Rituxan could cause the virus to become an  
1078    active infection again. This may cause serious liver problems including liver

1079 failure, and death. You should not receive Rituxan if you have active hepatitis B  
1080 liver disease.

1081 • **Serious infections.** Serious infections that happen with Rituxan can lead to  
1082 death. Call your doctor right away if you have any symptoms of infection:

- 1083 ○ fever
- 1084 ○ cold symptoms, such as runny nose or sore throat that do not go away
- 1085 ○ flu symptoms, such as cough, tiredness, and body aches
- 1086 ○ earache or headache
- 1087 ○ pain during urination
- 1088 ○ white patches in the mouth or throat
- 1089 ○ cuts, scrapes or incisions that are red, warm, swollen or painful

1090 • **Heart problems.** Rituxan may cause chest pain and irregular heart beats which  
1091 may need treatment, or your doctor may decide to stop your treatment with  
1092 Rituxan.

1093 • **Kidney problems,** especially if you are receiving Rituxan for NHL. Your doctor  
1094 should do blood test to check how well your kidneys are working.

1095 • **Stomach and Serious bowel problems that can sometimes lead to death.**  
1096 Bowel problems, including blockage or tears in the bowel can happen if you  
1097 receive Rituxan with chemotherapy medicines to treat non-Hodgkin’s lymphoma.  
1098 Tell your doctor right away if you have any stomach area pain during treatment  
1099 with Rituxan.

1100 • **Low blood cell counts.** Your doctor may do blood test during treatment with  
1101 Rituxan to check you blood cell counts.

1102 ○ **White blood cells.** White blood cells fight against bacterial infections.  
1103 Low white blood cells can cause you to get infections, which may be  
1104 serious. See “Increased risk of infections” above for a list of symptoms  
1105 of infection.

1106 ○ **Red blood cells.** Red blood cells carry oxygen to your body tissues  
1107 and organs.

1108 ○ **Platelets.** Platelets are blood cells that help your blood to clot.

1109 **Common side effects during Rituxan treatment include:**

1110 • infusion reactions (see What is the most important information I should know  
1111 about Rituxan?)

1112 • chills

1113 • infections

1114 • body aches

1115 • tiredness

1116 • low white blood cells

1117 Other side effects with Rituxan include:

- 1118 • aching joints during or within hours of receiving an infusion
- 1119 • more frequent upper respiratory tract infection

1120 Tell your doctor about any side effect that bothers you or that does not go away.

1121 These are not all of the possible side effects with Rituxan. For more information, ask  
1122 your doctor or pharmacist.

1123 Call your doctor for medical advice about side effects. You may report side effects to  
1124 FDA at 1-800-FDA-1088.

### 1125 **General information about Rituxan**

1126 Medicines are sometimes prescribed for purposes other than those listed in a  
1127 Medication Guide. This Medication Guide provides a summary of the most important  
1128 information about Rituxan. If you would like more information talk with your doctor.  
1129 You can ask your doctor for information about Rituxan that is written for healthcare  
1130 professionals.

1131 For more information, go to [www.Rituxan.com](http://www.Rituxan.com) or call 1-877-474-8892.

### 1132 **What are the ingredients in Rituxan?**

1133 Active ingredient: rituximab

1134 Inactive ingredients: sodium chloride, sodium citrate dihydrate, polysorbate 80, and  
1135 water for injection.

1136 Jointly Marketed by: Biogen Idec Inc. and Genentech USA, Inc.

1137

1138 Manufactured by:

1139 Genentech, Inc.

1140 A Member of the Roche Group

1141 1 DNA Way

1142 South San Francisco, CA 94080-4990

1143 ©2010 Biogen Idec Inc. and Genentech, Inc.

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1145 This Medication Guide has been approved by the U.S. Food and Drug  
1146 Administration.

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