

1.14.1.3 **Draft 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, RA (1.2)	10/2009
Dosage and Administration, RA (2.4)	10/2009
Dosage and Administration, Recommended Concomitant Medications (2.5)	10/2009
Warnings and Precautions, Infusion Reactions (5.1)	10/2009
Warnings and Precautions, Infections (5.6)	09/2009
Warnings and Precautions, Immunizations (5.10)	09/2009
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 the following:

- Non-Hodgkin's Lymphoma (NHL) (1.1)
- 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 (1.2)

-----**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 as a component of Zevalin<sup>®</sup> (Ibritumomab tiuxetan) Therapeutic Regimen is 250 mg/m<sup>2</sup> (2.3).
- 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 (2.4).

-----**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 prophylaxis 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).
- 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**-----

- Non-Hodgkin's Lymphoma (NHL) - Common adverse reactions (≥25%) in clinical trials were: infusion reactions, fever, lymphopenia, chills, infection and asthenia (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).

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 10/2009**

**FULL PRESCRIBING INFORMATION: CONTENTS\***

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

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- 12.1 Mechanism of Action
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- 14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20 Positive, B-Cell NHL
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- 14.3 Non-Progressing, Low-Grade, CD20-Positive, B-Cell NHL Following First-Line CVP Chemotherapy
- 14.4 Diffuse Large B-Cell NHL (DLBCL)
- 14.5 Rheumatoid Arthritis (RA)

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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 (TLS),** 3 **SEVERE MUCOCUTANEOUS REACTIONS, and** 4 **PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)**

#### 5 **Infusion Reactions**

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

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

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

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

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

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

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

## 22 1 INDICATIONS AND USAGE

### 23 **1.1 Non-Hodgkin's Lymphoma (NHL)**

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

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

### 32 **1.2 Rheumatoid Arthritis**

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

## 37 2 DOSAGE AND ADMINISTRATION

### 38 **2.1 Administration**

39 **DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.**

40 Premedicate before each infusion [see Dosage and Administration (2.5)]. Administer only as an  
41 intravenous (IV) infusion [see Dosage and Administration (2.5)].

- 42 • **First Infusion:** Initiate infusion at a rate of 50 mg/hr. In the absence of infusion toxicity,  
43 increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

- 44 • **Subsequent Infusions:** Initiate infusion at a rate of 100 mg/hr. In the absence of infusion  
45 toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of  
46 400 mg/hr.
- 47 • Interrupt the infusion or slow the infusion rate for infusion reactions [see *Boxed Warning,*  
48 *Warnings and Precautions (5.1)*]. Continue the infusion at one-half the previous rate upon  
49 improvement of symptoms.

## 50 **2.2 Recommended Dose for Non-Hodgkin's Lymphoma (NHL)**

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

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

## 65 **2.3 Recommended Dose as a Component of Zevalin<sup>®</sup>**

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

## 71 **2.4 Recommended Dose for Rheumatoid Arthritis**

- 72 • Administer Rituxan as two 1000 mg intravenous infusions separated by 2 weeks.
- 73 • Glucocorticoids administered as methylprednisolone 100 mg IV or its equivalent 30 minutes  
74 prior to each infusion are recommended to reduce the incidence and severity of infusion  
75 reactions.
- 76 • Subsequent courses should be administered every 24 weeks or based on clinical evaluation, but  
77 not sooner than every 16 weeks.
- 78 • Rituxan is given in combination with methotrexate.

## 79 **2.5 Recommended Concomitant Medications**

80 Premedicate before each infusion with acetaminophen and an antihistamine. For RA patients,  
81 methylprednisolone 100 mg IV or its equivalent is recommended 30 minutes prior to each infusion.

## 82 **2.6 Preparation for Administration**

83 Use appropriate aseptic technique. Parenteral drug products should be inspected visually for  
84 particulate matter and discoloration prior to administration. Do not use vial if particulates or  
85 discoloration is present. Withdraw the necessary amount of Rituxan and dilute to a final  
86 concentration of 1 to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride, USP, or

87 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Do not mix or dilute with  
88 other drugs. Discard any unused portion left in the vial.

### 89 **3 DOSAGE FORMS AND STRENGTHS**

90 100 mg/10 mL single-use vial

91 500 mg/50 mL single-use vial

### 92 **4 CONTRAINDICATIONS**

93 None.

### 94 **5 WARNINGS AND PRECAUTIONS**

#### 95 **5.1 Infusion Reactions**

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

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

#### 110 **5.2 Tumor Lysis Syndrome (TLS)**

111 Rapid reduction in tumor volume followed by acute renal failure, hyperkalemia, hypocalcemia,  
112 hyperuricemia, or hyperphosphatemia, can occur within 12–24 hours after the first infusion. Fatal  
113 TLS cases have occurred after administration of Rituxan. A high number of circulating malignant  
114 cells ( $\geq 25,000/\text{mm}^3$ ) or high tumor burden confers a greater risk of TLS after rituximab. Consider  
115 prophylaxis for TLS in patients at high risk. Correct electrolyte abnormalities, monitor renal  
116 function and fluid balance, and administer supportive care, including dialysis as indicated. [See  
117 *Boxed Warning*.]

#### 118 **5.3 Severe Mucocutaneous Reactions**

119 Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with Rituxan.  
120 These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis,  
121 vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has varied  
122 from 1–13 weeks following Rituxan exposure. Discontinue Rituxan in patients who experience a  
123 severe mucocutaneous reaction. The safety of readministration of Rituxan to patients with severe  
124 mucocutaneous reactions has not been determined. [See *Boxed Warning*, *Adverse Reactions* (6.1,  
125 6.4).]

#### 126 **5.4 Progressive Multifocal Leukoencephalopathy (PML)**

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

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

### 138 **5.5 Hepatitis B Virus (HBV) Reactivation**

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

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

### 149 **5.6 Infections**

150 Rituxan is not recommended for treatment of patients with severe active infections.

151 The following additional serious viral infections, either new, reactivated, or exacerbated, have  
152 been identified in clinical studies or postmarketing reports. The majority of patients received  
153 Rituxan in combination with chemotherapy or as part of a hematopoietic stem cell transplant. These  
154 viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster  
155 virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred as late as one  
156 year following discontinuation of Rituxan and have resulted in death. [See *Adverse Reactions (6.1,*  
157 *6.4).*]

### 158 **5.7 Cardiovascular**

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

### 162 **5.8 Renal**

163 Severe, including fatal, renal toxicity can occur after Rituxan administration in patients with  
164 hematologic malignancies. Renal toxicity has occurred in patients with high numbers of circulating  
165 malignant cells ( $\geq 25,000/\text{mm}^3$ ) or high tumor burden who experience tumor lysis syndrome and in  
166 patients with NHL administered concomitant cisplatin therapy during clinical trials. The  
167 combination of cisplatin and Rituxan is not an approved treatment regimen. Use extreme caution if  
168 this non-approved combination is used in clinical trials and monitor closely for signs of renal failure.  
169 Consider discontinuation of Rituxan for patients with a rising serum creatinine or oliguria.

### 170 **5.9 Bowel Obstruction and Perforation**

171 Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in  
172 patients receiving Rituxan in combination with chemotherapy. In postmarketing reports, the mean  
173 time to documented gastrointestinal perforation was 6 (range 1–77) days in patients with NHL.  
174 Perform a thorough diagnostic evaluation and institute appropriate treatment for complaints of  
175 abdominal pain, especially early in the course of Rituxan therapy. [See *Adverse Reactions (6.4).*]

### 176 **5.10 Immunization**

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

179 For RA patients, physicians should follow current immunization guidelines and administer non-



180 live vaccines at least 4 weeks prior to a course of Rituxan.

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

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

190 A positive response to tetanus toxoid vaccine (a T-cell dependent antigen with existing immunity)  
191 was similar in patients treated with Rituxan plus MTX compared to patients on MTX alone (39% vs.  
192 42%). The proportion of patients maintaining a positive Candida skin test (to evaluate delayed type  
193 hypersensitivity) was also similar (77% of patients on Rituxan plus MTX vs. 70% of patients on  
194 MTX alone).

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

### 197 **5.11 Laboratory Monitoring**

198 Because Rituxan binds to all CD20-positive B lymphocytes (malignant and non-malignant),  
199 obtain complete blood counts (CBC) and platelet counts at regular intervals during Rituxan therapy  
200 and more frequently in patients who develop cytopenias [*see Adverse Reactions (6.1)*]. The duration  
201 of cytopenias caused by Rituxan can extend months beyond the treatment period.

### 202 **5.12 Concomitant Use with Biologic Agents and DMARDs other than Methotrexate in RA**

203 Limited data are available on the safety of the use of biologic agents or DMARDs other than  
204 methotrexate in patients exhibiting peripheral B-cell depletion following treatment with Rituxan.  
205 Observe patients closely for signs of infection if biologic agents and/or DMARDs are used  
206 concomitantly.

### 207 **5.13 Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis 208 Factor (TNF) Antagonists**

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

## 215 **6 ADVERSE REACTIONS**

216 The following adverse reactions are discussed in greater detail in other sections of the labeling:

- 217 • Infusion reactions [*see Warnings and Precautions (5.1)*]
- 218 • Tumor lysis syndrome [*see Warnings and Precautions (5.2)*]
- 219 • Mucocutaneous reactions [*see Warnings and Precautions (5.3)*]
- 220 • Progressive multifocal leukoencephalopathy [*see Warnings and Precautions (5.4)*]
- 221 • Hepatitis B reactivation with fulminant hepatitis [*see Warnings and Precautions (5.5)*]
- 222 • Other viral infections [*see Warnings and Precautions (5.6)*]
- 223 • Cardiac arrhythmias [*see Warnings and Precautions (5.7)*]
- 224 • Renal toxicity [*see Warnings and Precautions (5.8)*]
- 225 • Bowel obstruction and perforation [*see Warnings and Precautions (5.9)*]

226 The most common adverse reactions of Rituxan (incidence  $\geq 25\%$ ) observed in patients with  
227 NHL are infusion reactions, fever, chills, infection, asthenia, and lymphopenia.

228 The most important serious adverse reactions of Rituxan are infusion reactions, tumor lysis  
229 syndrome, mucocutaneous toxicities, hepatitis B reactivation with fulminant hepatitis, PML, other  
230 viral infections, cardiac arrhythmias, renal toxicity, and bowel obstruction and perforation.

### 231 **6.1 Clinical Trials Experience Non-Hodgkin's Lymphoma**

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

235 The data described below reflect exposure to Rituxan in 1606 patients, with exposures ranging  
236 from a single infusion up to 6–8 months. Rituxan was studied in both single-agent and  
237 active-controlled trials ( $n = 356$  and  $n = 1250$ ). These data were obtained in adults with low-grade,  
238 follicular, or DLBCL NHL. Most patients received Rituxan as an infusion of  $375 \text{ mg/m}^2$  per  
239 infusion, given as a single agent weekly for up to 8 doses, in combination with chemotherapy for up  
240 to 8 doses, or following chemotherapy for up to 16 doses.

#### 241 *Infusion Reactions*

242 In the majority of patients with NHL, infusion reactions consisting of fever, chills/rigors, nausea,  
243 pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia,  
244 dizziness, or hypertension occurred during the first Rituxan infusion. Infusion reactions typically  
245 occurred within 30 to 120 minutes of beginning the first infusion and resolved with slowing or  
246 interruption of the Rituxan infusion and with supportive care (diphenhydramine, acetaminophen, and  
247 intravenous saline). The incidence of infusion reactions was highest during the first infusion (77%)  
248 and decreased with each subsequent infusion. [See *Boxed Warning, Warnings and Precautions*  
249 (5.1).]

#### 250 *Infections*

251 Serious infections (NCI CTCAE Grade 3 or 4), including sepsis, occurred in less than 5% of  
252 patients with NHL in the single-arm studies. The overall incidence of infections was 31% (bacterial  
253 19%, viral 10%, unknown 6%, and fungal 1%). [See *Warnings and Precautions* (5.4), (5.5), (5.6).]

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

#### 258 *Cytopenias and hypogammaglobulinemia*

259 In patients with NHL receiving rituximab monotherapy, NCI-CTC Grade 3 and 4 cytopenias were  
260 reported in 48% of patients. These included lymphopenia (40%), neutropenia (6%), leukopenia  
261 (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days  
262 (range, 1–588 days) and of neutropenia was 13 days (range, 2–116 days). A single occurrence of  
263 transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following  
264 Rituxan therapy occurred during the single-arm studies.

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

#### 267 *Single-Agent Rituxan*

268 Adverse reactions in [Table 1](#) occurred in 356 patients with relapsed or refractory, low-grade or  
269 follicular, CD20-positive, B-cell NHL treated in single-arm studies of Rituxan administered as a  
270 single agent [see *Clinical Studies* (14.1)]. Most patients received Rituxan  $375 \text{ mg/m}^2$  weekly for  
271 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.

273

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

276 *Rituxan in Combination with Chemotherapy*

277 Adverse reactions information below is based on 1250 patients who received Rituxan in  
 278 combination with chemotherapy or following chemotherapy.

279 *Rituxan in Combination with Chemotherapy for Low-Grade NHL*

280 In Study 4, patients in the R-CVP arm experienced a higher incidence of infusional toxicity and  
 281 neutropenia compared to patients in the CVP arm. The following adverse reactions occurred more  
 282 frequently ( $\geq 5\%$ ) in patients receiving R-CVP compared to CVP alone: rash (17% vs. 5%), cough  
 283 (15% vs. 6%), flushing (14% vs. 3%), rigors (10% vs. 2%), pruritus (10% vs. 1%), neutropenia (8%  
 284 vs. 3%), and chest tightness (7% vs. 1%). [See *Clinical Studies (14.2)*.]

285 In Study 5, the following adverse reactions were reported more frequently ( $\geq 5\%$ ) in patients  
 286 receiving Rituxan following CVP compared to patients who received no further therapy: fatigue  
 287 (39% vs. 14%), anemia (35% vs. 20%), peripheral sensory neuropathy (30% vs. 18%), infections  
 288 (19% vs. 9%), pulmonary toxicity (18% vs. 10%), hepato-biliary toxicity (17% vs. 7%), rash and/or  
 289 pruritus (17% vs. 5%), arthralgia (12% vs. 3%), and weight gain (11% vs. 4%). Neutropenia was the  
 290 only Grade 3 or 4 adverse reaction that occurred more frequently ( $\geq 2\%$ ) in the Rituxan arm  
 291 compared with those who received no further therapy (4% vs. 1%). [See *Clinical Studies (14.3)*.]

292 *Rituxan in Combination with Chemotherapy for DLBCL*

293 In Studies 6 and 7 [see *Clinical Studies (14.4)*], the following adverse reactions, regardless of  
 294 severity, were reported more frequently ( $\geq 5\%$ ) in patients age  $\geq 60$  years receiving R-CHOP as  
 295 compared to CHOP alone: pyrexia (56% vs. 46%), lung disorder (31% vs. 24%), cardiac disorder

296 (29% vs. 21%), and chills (13% vs. 4%). Detailed safety data collection in these studies was  
297 primarily limited to Grade 3 and 4 adverse reactions and serious adverse reactions.

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

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

## 306 **6.2 Clinical Trials Experience Rheumatoid Arthritis**

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

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

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

315 In placebo-controlled studies, patients received 2 x 500 mg or 2 x 1000 mg intravenous infusions  
316 of Rituxan or placebo, in combination with methotrexate, during a 24-week period. From these  
317 studies, 938 patients treated with Rituxan (2 x 1000 mg) or placebo have been pooled (see [Table 2](#)).  
318 Adverse reactions reported in  $\geq 5\%$  of patients were hypertension, nausea, upper respiratory tract  
319 infection, arthralgia, pyrexia and pruritus (see [Table 2](#)). The rates and types of adverse reactions in  
320 patients who received Rituxan 2 x 500 mg were similar to those observed in patients who received  
321 Rituxan 2 x 1000 mg.  
322

**Table 2\***

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

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

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

\*\*Coded using MedDRA.

323

324 *Infusion Reactions*

325 In the Rituxan RA pooled placebo-controlled studies, 32% of Rituxan-treated patients experienced  
 326 an adverse reaction during or within 24 hours following their first infusion, compared to 23% of  
 327 placebo-treated patients receiving their first infusion. The incidence of adverse reactions during the  
 328 24-hour period following the second infusion, Rituxan or placebo, decreased to 11% and 13%,  
 329 respectively. Acute infusion reactions (manifested by fever, chills, rigors, pruritus, urticaria/rash,  
 330 angioedema, sneezing, throat irritation, cough, and/or bronchospasm, with or without associated  
 331 hypotension or hypertension) were experienced by 27% of Rituxan-treated patients following their  
 332 first infusion, compared to 19% of placebo-treated patients receiving their first placebo infusion.  
 333 The incidence of these acute infusion reactions following the second infusion of Rituxan or placebo  
 334 decreased to 9% and 11%, respectively. Serious acute infusion reactions were experienced by < 1%  
 335 of patients in either treatment group. Acute infusion reactions required dose modification (stopping,  
 336 slowing, or interruption of the infusion) in 10% and 2% of patients receiving Rituxan or placebo,  
 337 respectively, after the first course. The proportion of patients experiencing acute infusion reactions  
 338 decreased with subsequent courses of Rituxan. The administration of intravenous glucocorticoids  
 339 prior to Rituxan infusions reduced the incidence and severity of such reactions, however, there was  
 340 no clear benefit from the administration of oral glucocorticoids for the prevention of acute infusion

341 reactions. Patients in clinical studies also received antihistamines and acetaminophen prior to  
342 Rituxan infusions.

### 343 *Infections*

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

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

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

### 359 *Cardiac Adverse Reactions*

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

364 In the experience with Rituxan in 2578 RA patients, the rate of serious cardiac reactions was 1.93  
365 per 100 patient years. The rate of myocardial infarction (MI) was 0.56 per 100 patient years  
366 (28 events in 26 patients), which is consistent with MI rates in the general RA population. These  
367 rates did not increase over three courses of Rituxan.

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

### 371 *Hypophosphatemia and hyperuricemia*

372 In the pooled, placebo-controlled studies, newly occurring hypophosphatemia ( $< 2.0$  mg/dl) was  
373 observed in 12% ( $67/540$ ) of patients on Rituxan versus 10% ( $39/398$ ) of patients on placebo.  
374 Hypophosphatemia was more common in patients who received corticosteroids. Newly occurring  
375 hyperuricemia ( $> 10$  mg/dl) was observed in 1.5% ( $8/540$ ) of patients on Rituxan versus 0.3%  
376 ( $1/398$ ) of patients on placebo.

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

### 381 *Retreatment in Patients with RA*

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



388 In RA Study 2, where all patients initially received Rituxan, the safety profile of patients who  
389 were retreated with Rituxan was similar to those who were retreated with placebo [*see Clinical*  
390 *Studies (14.5), and Dosage and Administration (2.2).*]

### 391 **6.3 Immunogenicity**

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

398 Using an ELISA assay, anti-human anti-chimeric antibody (HACA) was detected in 4 of  
399 356 (1.1%) patients with low-grade or follicular NHL receiving single-agent Rituxan. Three of the  
400 four patients had an objective clinical response.

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

### 408 **6.4 Postmarketing Experience**

409 The following adverse reactions have been identified during post-approval use of Rituxan in  
410 hematologic malignancies. Because these reactions are reported voluntarily from a population of  
411 uncertain size, it is not always possible to reliably estimate their frequency or establish a causal  
412 relationship to drug exposure.

413 Decisions to include these reactions in labeling are typically based on one or more of the  
414 following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of  
415 causal connection to Rituxan.

- 416 • Hematologic: prolonged pancytopenia, marrow hypoplasia, and late-onset neutropenia,  
417 hyperviscosity syndrome in Waldenstrom's macroglobulinemia.
- 418 • Cardiac: fatal cardiac failure.
- 419 • Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like  
420 syndrome, serum sickness, polyarticular arthritis, and vasculitis with rash.
- 421 • Infection: viral infections, including progressive multifocal leukoencephalopathy (PML),  
422 increase in fatal infections in HIV-associated lymphoma, and a reported increased incidence of  
423 Grade 3 and 4 infections in patients with previously treated lymphoma without known HIV  
424 infection.
- 425 • Neoplasia: disease progression of Kaposi's sarcoma.
- 426 • Skin: severe mucocutaneous reactions.
- 427 • Gastrointestinal: bowel obstruction and perforation.
- 428 • Pulmonary: fatal bronchiolitis obliterans and pneumonitis (including interstitial pneumonitis).

## 429 **7 DRUG INTERACTIONS**

430 Formal drug interaction studies have not been performed with Rituxan. In clinical trials of  
431 patients with RA, concomitant administration of methotrexate or cyclophosphamide did not alter the  
432 pharmacokinetics of rituximab.

433 **8 USE IN SPECIFIC POPULATIONS**

434 **8.1 Pregnancy**

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

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

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

446 **8.3 Nursing Mothers**

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

452 **8.4 Pediatric Use**

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

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

457 **8.5 Geriatric Use**

458 *Diffuse Large B-Cell NHL*

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

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

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

469 *Rheumatoid Arthritis*

470 Among the 2578 patients in global RA studies completed to date, 12% were 65–75 years old and  
471 2% were 75 years old and older. The incidences of adverse reactions were similar between older and  
472 younger patients. The rates of serious adverse reactions, including serious infections, malignancies,  
473 and cardiovascular events were higher in older patients.  
474

475 **10 OVERDOSAGE**

476 There has been no experience with overdosage in human clinical trials. Single doses of up to  
477 500 mg/m<sup>2</sup> have been given in dose-escalation clinical trials.  
478

479 **11 DESCRIPTION**

480 Rituxan<sup>®</sup> (rituximab) is a genetically engineered chimeric murine/human monoclonal IgG<sub>1</sub> kappa  
481 antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of  
482 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

483 Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a  
484 nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final  
485 product. Rituxan is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous  
486 administration. Rituxan is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or  
487 500 mg (50 mL) single-use vials. The product is formulated in 9 mg/mL sodium chloride,  
488 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Water for Injection. The pH  
489 is 6.5.  
490

491 **12 CLINICAL PHARMACOLOGY**

492 **12.1 Mechanism of Action**

493 Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation  
494 antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately  
495 35 kD located on pre-B and mature B lymphocytes. The antigen is expressed on > 90% of B-cell  
496 non-Hodgkin's lymphomas (NHL), but the antigen is not found on hematopoietic stem cells,  
497 pro-B-cells, normal plasma cells or other normal tissues. CD20 regulates an early step(s) in the  
498 activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion  
499 channel. CD20 is not shed from the cell surface and does not internalize upon antibody binding.  
500 Free CD20 antigen is not found in the circulation.

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

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

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

514 **12.2 Pharmacodynamics**

515 In NHL patients, administration of Rituxan resulted in depletion of circulating and tissue-based B  
516 cells. Among 166 patients in Study 1, circulating CD19-positive B cells were depleted within the

517 first three weeks with sustained depletion for up to 6 to 9 months posttreatment in 83% of patients.  
518 B-cell recovery began at approximately 6 months and median B-cell levels returned to normal by  
519 12 months following completion of treatment.

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

523 In RA patients, treatment with Rituxan induced depletion of peripheral B lymphocytes, with the  
524 majority of patients demonstrating near complete depletion (CD19 counts below the lower limit of  
525 quantification, 20 cells/ $\mu$ L) within 2 weeks after receiving the first dose of Rituxan. The majority of  
526 patients showed peripheral B-cell depletion for at least 6 months. A small proportion of patients  
527 (~4%) had prolonged peripheral B-cell depletion lasting more than 3 years after a single course of  
528 treatment.

529 Total serum immunoglobulin levels, IgM, IgG, and IgA were reduced at 6 months with the  
530 greatest change observed in IgM. At Week 24 of the first course of Rituxan treatment, small  
531 proportions of patients experienced decreases in IgM (10%), IgG (2.8%), and IgA (0.8%) levels  
532 below the lower limit of normal. In the experience with Rituxan in RA patients during repeated  
533 rituximab treatment, 23.3%, 5.5%, and 0.5% of the patients experienced decreases in IgM, IgG, and  
534 IgA concentrations below the LLN at any time after receiving rituximab, respectively. The clinical  
535 consequences of decreases in immunoglobulin levels in RA patients treated with Rituxan are  
536 unclear.

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

### 541 **12.3 Pharmacokinetics**

542 Pharmacokinetics were characterized in 203 NHL patients receiving 375 mg/m<sup>2</sup> rituximab weekly  
543 by IV infusion for 4 doses. The mean C<sub>max</sub> increased with each successive infusion and was  
544 486 mcg/mL (range, 78–997 mcg/mL) following the fourth infusion. Peak and trough serum levels  
545 of rituximab were inversely correlated with pretreatment circulating CD19-positive B cells and  
546 tumor burden. Rituximab was detectable in the serum of patients 3 to 6 months after completion of  
547 treatment.

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

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

556 Following administration of 2 doses of rituximab in patients with RA, the mean ( $\pm$  S.D.; % CV)  
557 concentrations after the first infusion (C<sub>max first</sub>) and second infusion (C<sub>max second</sub>) were 157 ( $\pm$  46;  
558 29%) and 183 ( $\pm$  55; 30%) mcg/mL, and 318 ( $\pm$  86; 27%) and 381 ( $\pm$  98; 26%) mcg/mL for the  
559 2  $\times$  500 mg and 2  $\times$  1000 mg doses, respectively.

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

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

## 568 13 NONCLINICAL TOXICOLOGY

### 569 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

### 572 13.2 Animal Toxicology and/or Pharmacology

#### 573 *Reproductive Toxicology Studies*

574 An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys.  
575 Pregnant animals received rituximab via the intravenous route during early gestation (organogenesis  
576 period; post-coitum days 20 through 50). Rituximab was administered as loading doses on  
577 postcoitum (PC) Days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on PC Days 29,  
578 36, 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the  
579 exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Rituximab  
580 crosses the monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have  
581 decreased lymphoid tissue B cells.

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

591

## 592 14 CLINICAL STUDIES

### 593 14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL

594 The safety and effectiveness of Rituxan in relapsed, refractory CD20+ NHL were demonstrated in  
595 3 single-arm studies enrolling 296 patients.

#### 596 *Study 1*

597 A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or  
598 refractory, low-grade or follicular, B-cell NHL who received 375 mg/m<sup>2</sup> of Rituxan given as an  
599 intravenous infusion weekly for 4 doses. Patients with tumor masses > 10 cm or with  
600 > 5000 lymphocytes/ $\mu$ L in the peripheral blood were excluded from the study.

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

#### 604 *Study 2*

605 In a multicenter, single-arm study, 37 patients with relapsed or refractory, low-grade NHL  
606 received 375 mg/m<sup>2</sup> of Rituxan weekly for 8 doses. Results are summarized in Table 3.

#### 607 *Study 3*

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



613 *Bulky Disease*

614 In pooled data from Studies 1 and 3, 39 patients with bulky (single lesion > 10 cm in diameter)  
 615 and relapsed or refractory, low-grade NHL received Rituxan 375 mg/m<sup>2</sup> weekly for 4 doses. Results  
 616 are summarized in Table 3.  
 617

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

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

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

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

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

618  
 619 **14.2 Previously Untreated, Follicular, CD20-Positive, B-Cell NHL**

620 *Study 4*

621 A total of 322 patients with previously untreated follicular NHL were randomized (1:1) to receive  
 622 up to eight 3-week cycles of CVP chemotherapy alone (CVP) or in combination with Rituxan  
 623 375 mg/m<sup>2</sup> on Day 1 of each cycle (R-CVP) in an open-label, multicenter study. The main outcome  
 624 measure of the study was progression-free survival (PFS) defined as the time from randomization to  
 625 the first of progression, relapse, or death.

626 Twenty-six percent of the study population was > 60 years of age, 99% had Stage III or IV  
 627 disease, and 50% had an International Prognostic Index (IPI) score ≥ 2. The results for PFS as  
 628 determined by a blinded, independent assessment of progression are presented in Table 4. The point  
 629 estimates may be influenced by the presence of informative censoring. The PFS results based on  
 630 investigator assessment of progression were similar to those obtained by the independent review  
 631 assessment.  
 632

**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.

633

634 **14.3 Non-Progressing Low-Grade, CD20-Positive, B-Cell NHL Following First-Line CVP**  
635 **Chemotherapy**

636 *Study 5*

637 A total of 322 patients with previously untreated low-grade, B-cell NHL who did not progress  
638 after 6 or 8 cycles of CVP chemotherapy were enrolled in an open-label, multicenter, randomized  
639 trial. Patients were randomized (1:1) to receive Rituxan 375 mg/m<sup>2</sup> intravenous infusion, once  
640 weekly for 4 doses every 6 months for up to 16 doses or no further therapeutic intervention. The  
641 main outcome measure of the study was progression-free survival defined as the time from  
642 randomization to progression, relapse, or death. Thirty-seven percent of the study population was  
643 > 60 years of age, 99% had Stage III or IV disease, and 63% had an IPI score ≥ 2.

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

647 **14.4 Diffuse Large B-Cell NHL (DLBCL)**

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

653 *Study 6*

654 A total of 632 patients age ≥ 60 years with DLBCL (including primary mediastinal B-cell  
655 lymphoma) were randomized in a 1:1 ratio to treatment with CHOP or R-CHOP. Patients received  
656 6 or 8 cycles of CHOP, each cycle lasting 21 days. All patients in the R-CHOP arm received 4 doses  
657 of Rituxan 375 mg/m<sup>2</sup> on Days 7 and 3 (prior to Cycle 1) and 48–72 hours prior to Cycles 3 and 5.  
658 Patients who received 8 cycles of CHOP also received Rituxan prior to Cycle 7. The main outcome  
659 measure of the study was progression-free survival, defined as the time from randomization to the  
660 first of progression, relapse, or death. Responding patients underwent a second randomization to  
661 receive Rituxan or no further therapy.

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

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

671 *Study 7*

672 A total of 399 patients with DLBCL, age  $\geq 60$  years, were randomized in a 1:1 ratio to receive  
 673 CHOP or R-CHOP. All patients received up to eight 3-week cycles of CHOP induction; patients in  
 674 the R-CHOP arm received Rituxan 375 mg/m<sup>2</sup> on Day 1 of each cycle. The main outcome measure  
 675 of the study was event-free survival, defined as the time from randomization to relapse, progression,  
 676 change in therapy, or death from any cause. Among all enrolled patients, 80% had Stage III or IV  
 677 disease, 60% of patients had an age-adjusted IPI  $\geq 2$ , 80% had ECOG performance status scores  
 678  $< 2$ , 66% had elevated LDH levels, and 52% had extranodal involvement in at least two sites.  
 679 Efficacy results are presented in Table 5.

680 *Study 8*

681 A total of 823 patients with DLBCL, aged 18–60 years, were randomized in a 1:1 ratio to receive  
 682 an anthracycline-containing chemotherapy regimen alone or in combination with Rituxan. The main  
 683 outcome measure of the study was time to treatment failure, defined as time from randomization to  
 684 the earliest of progressive disease, failure to achieve a complete response, relapse, or death. Among  
 685 all enrolled patients, 28% had Stage III–IV disease, 100% had IPI scores of  $\leq 1$ , 99% had ECOG  
 686 performance status of  $< 2$ , 29% had elevated LDH levels, 49% had bulky disease, and 34% had  
 687 extranodal involvement. Efficacy results are presented in Table 5.  
 688

**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.

689  
 690 In Study 7, overall survival estimates at 5 years were 58% vs. 46% for R-CHOP and CHOP,  
 691 respectively.

692 **14.5 Rheumatoid Arthritis (RA)**

693 **Reducing Signs and Symptoms: Initial and Re-Treatment Courses**

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

699 In RA Study 1, patients were randomized to receive either Rituxan 2 x 1000 mg + MTX or  
700 placebo + MTX for 24 weeks. Further courses of Rituxan 2 x 1000 mg + MTX were administered in  
701 an open label extension study at a frequency determined by clinical evaluation, but no sooner than  
702 16 weeks after the preceding course of Rituxan. In addition to the IV premedication, glucocorticoids  
703 were administered orally on a tapering schedule from baseline through Day 14. The proportions of  
704 patients achieving ACR 20, 50, and 70 responses at Week 24 of the placebo-controlled period are  
705 shown in [Table 6](#).

706 In RA Study 2, all patients received the first course of Rituxan 2 x 1000 mg + MTX. Patients who  
707 experienced ongoing disease activity were randomized to receive a second course of either  
708 Rituxan 2 x 1000 mg + MTX or placebo + MTX, the majority between Weeks 24–28. The  
709 proportions of patients achieving ACR 20, 50, and 70 responses at Week 24, before the re-treatment  
710 course, and at Week 48, after retreatment, are shown in [Table 6](#).

711

**Table 6**  
ACR Responses in Study 1 and Study 2 (Percent of Patients)  
(Modified Intent-to-Treat Population)

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

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

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

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

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Improvement was also noted for all components of ACR response following treatment with Rituxan, as shown in Table 7.



**Table 7**  
**Components of ACR Response at Week 24 in Study 1**  
**(Modified Intent-to-Treat Population)**

<b>Inadequate Response to TNF Antagonists</b>				
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.

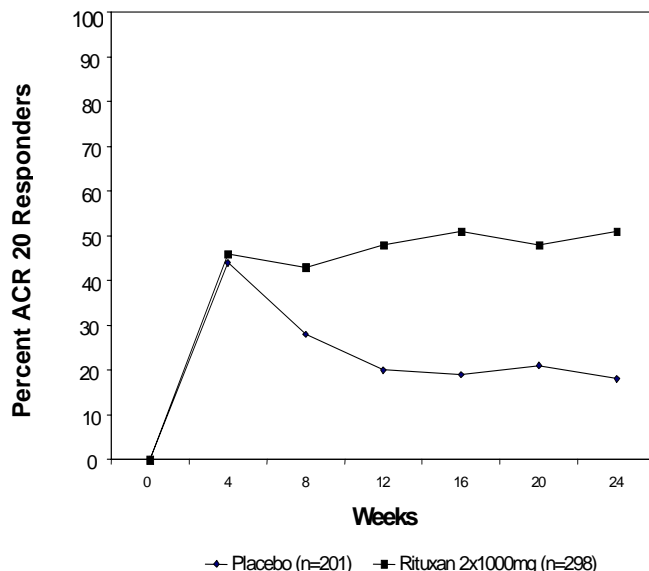
<sup>b</sup> Disability Index of the Health Assessment Questionnaire: 0 = best, 3 = worst.

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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.

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



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

729 **Radiographic Response**

730 In RA Study 1, structural joint damage was assessed radiographically and expressed as changes in  
731 Genant-modified Total Sharp Score (TSS) and its components, the erosion score (ES) and the joint  
732 space narrowing (JSN) score. Rituxan + MTX slowed the progression of structural damage  
733 compared to placebo + MTX after 1 year as shown in Table 8.  
734

**Table 8**  
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.

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736 In RA Study 1 and its open-label extension, 70% of patients initially randomized to Rituxan +  
737 MTX and 72% of patients initially randomized to placebo + MTX were evaluated radiographically at  
738 Year 2. As shown in Table 8, progression of structural damage in Rituxan + MTX patients was  
739 further reduced in the second year of treatment.

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

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

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

#### 758 **Physical Function Response**

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

763 Physical function was assessed at Weeks 24 and 48 using the Health Assessment Questionnaire  
764 Disability Index (HAQ-DI). From baseline to Week 24, a greater proportion of Rituxan-treated  
765 patients had an improvement in HAQ-DI of at least 0.22 (a minimal clinically important difference)  
766 and a greater mean HAQ-DI improvement compared to placebo, as shown in Table 10. HAQ-DI  
767 results for the Rituxan 500 mg treatment group were similar to the Rituxan 1000 mg treatment  
768 group; however radiographic responses were not assessed (see Dosing Precaution in the  
769 Radiographic Responses section above). These improvements were maintained at 48 weeks.  
770

**Table 9**  
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

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772 **16 HOW SUPPLIED/STORAGE AND HANDLING**

773 Rituxan vials [100 mg (NDC 50242-051-21) and 500 mg (NDC 50242-053-06)] are stable at  
774 2°C–8°C (36°F–46°F). Do not use beyond expiration date stamped on carton. Rituxan vials should  
775 be protected from direct sunlight. Do not freeze or shake.

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

781

782 **17 PATIENT COUNSELING INFORMATION**

783 See Medication Guide (17.2).

784 **17.1 General Counseling Information**

785 Patients should be provided the Rituxan Medication Guide and provided an opportunity to read  
786 prior to each treatment session. Because caution should be exercised in administering Rituxan to  
787 patients with active infections, it is important that the patient’s overall health be assessed at each  
788 visit and the risks of Rituxan therapy and any questions resulting from the patient’s reading of the  
789 Medication Guide be discussed.

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

793 **Immunosuppression**

794 Inform patients that Rituxan may lower the ability of the immune system to fight infections.  
795 Instruct patients of the importance of contacting their doctor if they develop any symptoms of  
796 infection, including new-onset neurologic symptoms that may be suggestive of PML including new  
797 or worsening medical problems, such as a new or sudden change in thinking, walking, strength,  
798 vision, or other problems that have lasted over several days.

799 **Infusion Reactions**

800 Advise patients of the potential for serious, including fatal infusion reactions and ask them to  
801 report promptly any symptoms suggestive of infusion reactions including hives, swelling, dizziness,  
802 blurred vision, drowsiness, headache, cough, wheezing, or trouble breathing while receiving or after  
803 receiving Rituxan.

804 **Other Medical Conditions**

805 Counsel patients with NHL about the possible risk of tumor lysis syndrome while receiving  
806 Rituxan.

807 Advise patients to report promptly any symptoms suggestive of severe mucocutaneous reactions  
808 such as painful sores on skin or in mouth, ulcers, blisters, or peeling skin while receiving or after  
809 receiving Rituxan.

810 **17.2 Medication Guide**

811 **MEDICATION GUIDE**  
812 **RITUXAN<sup>®</sup> (ri-tuk'-san)**  
813 **(rituximab)**

814 Read the Medication Guide given to you before you start Rituxan and before each Rituxan infusion.  
815 The information may have changed. This Medication Guide does not take the place of talking to  
816 your doctor about your medical condition or your treatment. Talk with your doctor if you have any  
817 questions about your treatment with Rituxan.

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

819 Rituxan can cause serious side effects including:

- 820 • **Progressive Multifocal Leukoencephalopathy (PML)**
- 821 • PML is a rare brain infection. PML usually causes death or severe disability.
  - 822 • Call your doctor right away if you notice any new or worsening medical problems, such as a  
823 new or sudden change in thinking, walking, strength, vision, or other problems that have  
824 lasted over several days.
  - 825 • PML usually happens in patients with weakened immune systems.
  - 826 • PML can occur during treatment with Rituxan or after treatment has finished.
  - 827 • There is no known treatment, prevention, or cure for PML.
- 828 • **Infusion reactions.** Tell your doctor or get medical treatment right away if you get hives,  
829 swelling, dizziness, blurred vision, drowsiness, headache, cough, wheezing, or have trouble  
830 breathing while receiving or after receiving Rituxan.
- 831 • **Tumor Lysis Syndrome (TLS).** TLS is caused by the fast breakdown of certain types of cancer  
832 cells. TLS can cause kidney failure and the need for dialysis treatment. Patients receiving  
833 Rituxan for non-Hodgkin's lymphoma (NHL) may get TLS. Your doctor will check you for  
834 TLS.
- 835 • **Severe skin reactions.** Tell your doctor or get medical treatment right away if you get any of  
836 these symptoms: painful sores on your skin or in your mouth, ulcers, blisters, or peeling skin  
837 while receiving or after receiving Rituxan.

838 See **“What are possible side effects with Rituxan?”** for other serious side effects.

839 **What is Rituxan?**

840 Rituxan is a prescription medicine used in adults:

- 841 • alone or with other anti-cancer medicines to treat certain types of NHL.
- 842 • with another medicine called methotrexate to reduce the signs and symptoms of moderately to  
843 severely active Rheumatoid Arthritis (RA) after at least one other medicine called a Tumor  
844 Necrosis Factor (TNF) antagonist has been used and did not work well.

845 Rituxan has not been studied in children.

846 **What should I tell my doctor before treatment with Rituxan?**

847 Tell your doctor about all of your medical conditions, including if you:

- 848 • had a severe infusion reaction to Rituxan in the past.
- 849 • have an infection or have an infection that will not go away or that keeps coming back.
- 850 • have or had hepatitis (liver) infection. See **“What are the possible side effects of Rituxan?”** If  
851 so, your doctor should check you closely for signs of hepatitis infection during treatment with  
852 Rituxan and for several months after treatment ends.

- 853 • are scheduled to receive any vaccinations. You should not receive live vaccines after you  
854 receive Rituxan.
- 855 • have heart or lung problems.
- 856 • are pregnant or planning to become pregnant. It is not known if Rituxan can harm your unborn  
857 baby.
- 858 • are breastfeeding. It is not known if Rituxan passes into human breast milk. You should not  
859 breastfeed while being treated with Rituxan and after finishing treatment, until blood tests show  
860 that there is no Rituxan in your blood.

861 Tell your doctor about all the medicines you take, including prescription and nonprescription  
862 medicines, vitamins, or herbal supplements. If you have RA, especially tell your doctor if you take  
863 or have taken another medicine called a TNF antagonist or a DMARD (disease-modifying  
864 anti-rheumatic drug).

### 865 **How do I receive Rituxan?**

- 866 • Rituxan is given through a needle placed in a vein (IV or intravenous infusion) in your arm.  
867 Talk to your doctor about how you will receive Rituxan.
- 868 • Your doctor may prescribe medicines before each infusion of Rituxan to reduce side effects of  
869 infusions (such as fever and chills).
- 870 • Your doctor should do regular blood tests to check for side effects to Rituxan.

871 Before each Rituxan treatment, your doctor or nurse will ask you questions about your general health  
872 to make sure that Rituxan is still right for you. Tell your doctor or nurse about any new symptoms  
873 and symptoms that get worse over a few days or that will not go away.

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

875 The “**What is the most important information I should know about Rituxan?**” section lists  
876 certain serious and life-threatening side effects with Rituxan. Rituxan can cause other serious and  
877 life-threatening side effects including:

- 878 • **Hepatitis B virus reactivation.** Tell your doctor if you had hepatitis B virus or are a carrier of  
879 hepatitis B virus. Receiving Rituxan could cause the hepatitis B virus to become an active  
880 infection again. This may cause serious liver problems and death. People with active liver  
881 disease due to hepatitis B should stop receiving Rituxan.
- 882 • **Heart problems.** Tell your doctor about any heart problems you have including chest pain  
883 (angina) and irregular heart beats. Rituxan can cause chest pain and irregular heart beats which  
884 may require treatment.
- 885 • **Infections.** Rituxan can increase your chances for getting infections. Call your doctor right  
886 away if you have a cough that will not go away, fever, chills, congestion, or any flu-like  
887 symptoms while receiving Rituxan. These symptoms may be signs of a serious infection.
- 888 • **Stomach and bowel problems.** Serious stomach and bowel problems have been seen when  
889 Rituxan has been used with anti-cancer medicines in some patients with non-Hodgkin’s  
890 lymphoma. Call your doctor right away if you have any stomach area pain during treatment with  
891 Rituxan.

### 892 **Common side effects during Rituxan infusions include:**

- 893 • fever • headache
- 894 • chills and shakes • nausea
- 895 • itching • hives
- 896 • cough • sneezing
- 897 • throat irritation or tightness

898 Other side effects with Rituxan include:

- 899 • aching joints
- 900 • upper respiratory tract infection
- 901 • decreased blood cell counts
- 902 • lung problems

903 Tell your doctor about any side effect that bothers you or that does not go away. These are not all of  
904 the possible side effects with Rituxan. Ask your doctor for more information.

905 **General Information about Rituxan**

906 This Medication Guide provides a summary of the most important information about Rituxan.  
907 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If  
908 you would like more information or have any questions, talk with your doctor. You can ask your  
909 doctor for information about Rituxan that is written for healthcare professionals. You can also visit  
910 [www.Rituxan.com](http://www.Rituxan.com) or call 1-877-474-8892.

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

912 Active ingredient: rituximab

913 Inactive ingredients: sodium chloride, sodium citrate dihydrate, polysorbate 80, and water for  
914 injection.

915  
916 Jointly Marketed by: Biogen Idec Inc. and Genentech USA, Inc.

917  
918 Manufactured by:

919 Genentech, Inc.  
920 1 DNA Way  
921 South San Francisco, CA 94080-4990

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