

## 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)                       | 02/2010 |
| Indications and Usage, Limitations of Use (1.4)        | 02/2010 |
| Dosage and Administration, CLL (2.3)                   | 02/2010 |
| Warnings and Precautions, HBV Reactivation (5.5)       | 12/2010 |
| Warnings and Precautions, Infections (5.6)             | 02/2010 |
| Warnings and Precautions, Renal (5.8)                  | 02/2010 |
| Warnings and Precautions, Laboratory Monitoring (5.11) | 02/2010 |

### 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 (5.6).
- Cardiac arrhythmias and angina can occur and can be life threatening. Monitor patients with these conditions closely (5.7).
- Bowel obstruction and perforation - evaluate complaints of abdominal pain (5.9).
- Do not administer live virus vaccines prior to or during Rituxan (5.10).
- Monitor CBC at regular intervals for severe cytopenias (5.11, 6.1).

### ADVERSE REACTIONS

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

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: 12/2010

**FULL PRESCRIBING INFORMATION: CONTENTS\***

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

**1 INDICATIONS AND USAGE**

- 1.1 Non-Hodgkin's Lymphoma (NHL)
- 1.2 Chronic Lymphocytic Leukemia (CLL)
- 1.3 Rheumatoid Arthritis (RA)
- 1.4 Limitations of Use

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Administration
- 2.2 Recommended Dose for NHL
- 2.3 Recommended Dose for CLL
- 2.4 Recommended Dose as a Component of Zevalin®
- 2.5 Recommended Dose for RA
- 2.6 Recommended Concomitant Medications
- 2.7 Preparation for Administration

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

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

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

**6 ADVERSE REACTIONS**

- 6.1 Clinical Trials Experience in Lymphoid Malignancies
- 6.2 Clinical Trials Experience Rheumatoid Arthritis
- 6.3 Immunogenicity
- 6.4 Postmarketing Experience

**7 DRUG INTERACTIONS**

**8 USE IN SPECIFIC POPULATIONS**

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

**10 OVERDOSAGE**

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

**13 NONCLINICAL TOXICOLOGY**

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

**14 CLINICAL STUDIES**

- 14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20 Positive, B-Cell NHL
- 14.2 Previously Untreated, Follicular, CD20-Positive, B-Cell NHL
- 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 Chronic Lymphocytic Leukemia (CLL)
- 14.6 Rheumatoid Arthritis (RA)

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

\*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), SEVERE**  
3 **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 occurred**  
8 **in association with the first infusion. Carefully monitor patients during infusions. Discontinue**  
9 **Rituxan infusion and provide medical treatment for Grade 3 or 4 infusion reactions [see Warnings**  
10 **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) with Rituxan monotherapy [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 chemotherapy
- 27 • Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent,
- 28 after first-line CVP chemotherapy
- 29 • Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other
- 30 anthracycline-based chemotherapy regimens

31 **1.2 Chronic Lymphocytic Leukemia (CLL)**

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

34 **1.3 Rheumatoid Arthritis (RA)**

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

38 **1.4 Limitations of Use**

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

40 **2 DOSAGE AND ADMINISTRATION**

41 **2.1 Administration**

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

43 Premedicate before each infusion [see *Dosage and Administration (2.6)*]. Administer only as an  
44 intravenous (IV) infusion [see *Dosage and Administration (2.6)*].

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

## 52 2.2 Recommended Dose for Non-Hodgkin's Lymphoma (NHL)

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

- 54 • **Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**  
55 Administer once weekly for 4 or 8 doses.
- 56 • **Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**  
57 Administer once weekly for 4 doses.
- 58 • **Previously Untreated, Follicular, CD20-Positive, B-Cell NHL**  
59 Administer on Day 1 of each cycle of CVP chemotherapy, for up to 8 doses.
- 60 • **Non-progressing, Low-Grade, CD20-Positive, B-cell NHL, after first-line CVP chemotherapy**  
61 Following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-  
62 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 for Chronic Lymphocytic Leukemia (CLL)

66 The recommended dose is:

- 67 • 375 mg/m<sup>2</sup> the day prior to the initiation of FC chemotherapy, then 500 mg/m<sup>2</sup> on Day 1 of cycles 2-6  
68 (every 28 days).

## 69 2.4 Recommended Dose as a Component of Zevalin<sup>®</sup>

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

## 75 2.5 Recommended Dose for Rheumatoid Arthritis (RA)

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

## 82 2.6 Recommended Concomitant Medications

83 Premedicate before each infusion with acetaminophen and an antihistamine.

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

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

## 88 2.7 Preparation for Administration

89 Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate  
90 matter and discoloration prior to administration. Do not use vial if particulates or discoloration is present.  
91 Withdraw the necessary amount of Rituxan and dilute to a final concentration of 1 to 4 mg/mL in an  
92 infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. Gently invert

93 the bag to mix the solution. Do not mix or dilute with other drugs. Discard any unused portion left in the  
94 vial.

### 95 **3 DOSAGE FORMS AND STRENGTHS**

96 100 mg/10 mL single-use vial

97 500 mg/50 mL single-use vial

### 98 **4 CONTRAINDICATIONS**

99 None.

## 100 **5 WARNINGS AND PRECAUTIONS**

### 101 **5.1 Infusion Reactions**

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

107 Premedicate patients with an antihistamine and acetaminophen prior to dosing. For RA patients,  
108 methylprednisolone 100 mg IV or its equivalent is recommended 30 minutes prior to each infusion.  
109 Institute medical management (e.g. glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion  
110 reactions as needed. Depending on the severity of the infusion reaction and the required interventions,  
111 temporarily or permanently discontinue Rituxan. Resume infusion at a minimum 50% reduction in rate after  
112 symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or  
113 pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high  
114 numbers of circulating malignant cells ( $\geq 25,000/\text{mm}^3$ ). [*See Boxed Warning, Warnings and Precautions*  
115 *(5.7), Adverse Reactions (6.1).*]

### 116 **5.2 Tumor Lysis Syndrome (TLS)**

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

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

### 123 **5.3 Severe Mucocutaneous Reactions**

124 Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with Rituxan. These  
125 reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis,  
126 vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has varied from  
127 1–13 weeks following Rituxan exposure. Discontinue Rituxan in patients who experience a severe  
128 mucocutaneous reaction. The safety of readministration of Rituxan to patients with severe mucocutaneous  
129 reactions has not been determined. [*See Boxed Warning, Adverse Reactions (6.1, 6.4).*]

### 130 **5.4 Progressive Multifocal Leukoencephalopathy (PML)**

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

136 Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations.  
137 Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar  
138 puncture. Discontinue Rituxan and consider discontinuation or reduction of any concomitant chemotherapy  
139 or immunosuppressive therapy in patients who develop PML. [*See Boxed Warning, Adverse Reactions*  
140 *(6.4).*]

## 141 **5.5 Hepatitis B Virus (HBV) Reactivation**

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

146 Screen patients at high risk of HBV infection before initiation of Rituxan. Closely monitor carriers of  
147 hepatitis B for clinical and laboratory signs of active HBV infection for several months following Rituxan  
148 therapy. Discontinue Rituxan and any concomitant chemotherapy in patients who develop viral hepatitis,  
149 and institute appropriate treatment including antiviral therapy. Insufficient data exist regarding the safety of  
150 resuming Rituxan in patients who develop hepatitis subsequent to HBV reactivation. [See *Adverse Reactions*  
151 (6.4).]

## 152 **5.6 Infections**

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

## 158 **5.7 Cardiovascular**

159 Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring  
160 during and after all infusions of Rituxan for patients who develop clinically significant arrhythmias, or who  
161 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 NHL. Renal  
164 toxicity has occurred in patients who experience tumor lysis syndrome and in patients with NHL  
165 administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and Rituxan  
166 is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue Rituxan in  
167 patients with a rising serum creatinine or oliguria. [See *Warnings and Precautions* (5.2).]

## 168 **5.9 Bowel Obstruction and Perforation**

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

## 174 **5.10 Immunization**

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

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

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

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

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

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

### 192 **5.11 Laboratory Monitoring**

193 In patients with lymphoid malignancies, during treatment with Rituxan monotherapy, obtain complete  
194 blood counts (CBC) and platelet counts prior to each Rituxan course. During treatment with Rituxan and  
195 chemotherapy, obtain CBC and platelet counts at weekly to monthly intervals and more frequently in  
196 patients who develop cytopenias [see *Adverse Reactions (6.1)*]. In patients with RA obtain CBC and  
197 platelet counts at two to four month intervals during Rituxan therapy. The duration of cytopenias caused by  
198 Rituxan can extend months beyond the treatment period.

### 199 **5.12 Concomitant Use with Biologic Agents and DMARDs other than Methotrexate in RA**

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

### 203 **5.13 Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis Factor 204 (TNF) Antagonists**

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

## 210 **6 ADVERSE REACTIONS**

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

- 212 • Infusion reactions [see *Warnings and Precautions (5.1)*]
- 213 • Tumor lysis syndrome [see *Warnings and Precautions (5.2)*]
- 214 • Mucocutaneous reactions [see *Warnings and Precautions (5.3)*]
- 215 • Progressive multifocal leukoencephalopathy [see *Warnings and Precautions (5.4)*]
- 216 • Hepatitis B reactivation with fulminant hepatitis [see *Warnings and Precautions (5.5)*]
- 217 • Infections [see *Warnings and Precautions (5.6)*]
- 218 • Cardiac arrhythmias [see *Warnings and Precautions (5.7)*]
- 219 • Renal toxicity [see *Warnings and Precautions (5.8)*]
- 220 • Bowel obstruction and perforation [see *Warnings and Precautions (5.9)*]

221  
222 The most common adverse reactions of Rituxan (incidence  $\geq 25\%$ ) observed in clinical trials of patients  
223 with NHL were infusion reactions, fever, lymphopenia, chills, infection, and asthenia.

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

### 226 **6.1 Clinical Trials Experience in Lymphoid Malignancies**

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

230 The data described below reflect exposure to Rituxan in 2282 patients, with exposures ranging from a  
231 single infusion up to 6–8 months. Rituxan was studied in both single-agent and active-controlled trials  
232 ( $n = 356$  and  $n = 1926$ ). The population included 679 patients with low-grade follicular lymphoma,  
233 927 patients with DLBCL, and 676 patients with CLL. Most NHL patients received Rituxan as an infusion  
234 of  $375 \text{ mg/m}^2$  per infusion, given as a single agent weekly for up to 8 doses, in combination with  
235 chemotherapy for up to 8 doses, or following chemotherapy for up to 16 doses. CLL patients received  
236 Rituxan  $375 \text{ mg/m}^2$  as an initial infusion followed by  $500 \text{ mg/m}^2$  for up to 5 doses, in combination with

237 fludarabine and cyclophosphamide. Seventy-one percent of CLL patients received 6 cycles and 90%  
238 received at least 3 cycles of Rituxan-based therapy.

#### 239 *Infusion Reactions*

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

#### 247 *Infections*

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

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

#### 255 *Cytopenias and hypogammaglobulinemia*

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

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

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

265 Adverse reactions in Table 1 occurred in 356 patients with relapsed or refractory, low-grade or follicular,  
266 CD20-positive, B-cell NHL treated in single-arm studies of Rituxan administered as a single agent [see  
267 *Clinical Studies (14.1)*]. Most patients 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<br>(%) | Grade 3 and 4<br>(%) |
|--|-------------------|----------------------|
| 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<br>(%) | Grade 3 and 4<br>(%) |
|-------------------------------|-------------------|----------------------|
| <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.

269

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

272 *Previously Untreated Low-Grade NHL*

273 In Study 4, patients in the R-CVP arm experienced a higher incidence of infusional toxicity and  
 274 neutropenia compared to patients in the CVP arm. The following adverse reactions occurred more  
 275 frequently ( $\geq 5\%$ ) in patients receiving R-CVP compared to CVP alone: rash (17% vs. 5%), cough (15% vs.  
 276 6%), flushing (14% vs. 3%), rigors (10% vs. 2%), pruritus (10% vs. 1%), neutropenia (8% vs. 3%), and  
 277 chest tightness (7% vs. 1%). [See *Clinical Studies (14.2)*.]

278 In Study 5, the following adverse reactions were reported more frequently ( $\geq 5\%$ ) in patients receiving  
 279 Rituxan following CVP compared to patients who received no further therapy: fatigue (39% vs. 14%),  
 280 anemia (35% vs. 20%), peripheral sensory neuropathy (30% vs. 18%), infections (19% vs. 9%), pulmonary  
 281 toxicity (18% vs. 10%), hepato-biliary toxicity (17% vs. 7%), rash and/or pruritus (17% vs. 5%), arthralgia  
 282 (12% vs. 3%), and weight gain (11% vs. 4%). Neutropenia was the only Grade 3 or 4 adverse reaction that  
 283 occurred more frequently ( $\geq 2\%$ ) in the Rituxan arm compared with those who received no further therapy  
 284 (4% vs. 1%). [See *Clinical Studies (14.3)*.]

285 *DLBCL*

286 In Studies 6 and 7, [see *Clinical Studies (14.4)*], the following adverse reactions, regardless of severity,  
 287 were reported more frequently ( $\geq 5\%$ ) in patients age  $\geq 60$  years receiving R-CHOP as compared to CHOP  
 288 alone: pyrexia (56% vs. 46%), lung disorder (31% vs. 24%), cardiac disorder (29% vs. 21%), and chills  
 289 (13% vs. 4%). Detailed safety data collection in these studies was primarily limited to Grade 3 and 4  
 290 adverse reactions and serious adverse reactions.

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

293 The following Grade 3 or 4 adverse reactions occurred more frequently among patients in the R-CHOP  
 294 arm compared with those in the CHOP arm: thrombocytopenia (9% vs. 7%) and lung disorder (6% vs. 3%).

295 Other Grade 3 or 4 adverse reactions occurring more frequently among patients receiving R-CHOP were  
296 viral infection (Study 7), neutropenia (Studies 7 and 8), and anemia (Study 8).

### 297 *CLL*

298 The data below reflect exposure to Rituxan in combination with fludarabine and cyclophosphamide in  
299 676 patients with CLL in Study 9 or Study 10 [see *Clinical Studies (14.5)*]. The age range was 30–83 years  
300 and 71% were men. Detailed safety data collection in Study 9 was limited to Grade 3 and 4 adverse  
301 reactions and serious adverse reactions.

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

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

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

### 312 **6.2 Clinical Trials Experience in Rheumatoid Arthritis**

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

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

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

320 In placebo-controlled studies, patients received 2 × 500 mg or 2 × 1000 mg intravenous infusions of  
321 Rituxan or placebo, in combination with methotrexate, during a 24-week period. From these studies, 938  
322 patients treated with Rituxan (2 × 1000 mg) or placebo have been pooled (see Table 2). Adverse reactions  
323 reported in ≥ 5% of patients were hypertension, nausea, upper respiratory tract infection, arthralgia, pyrexia  
324 and pruritus (see Table 2). The rates and types of adverse reactions in patients who received Rituxan 2 × 500  
325 mg were similar to those observed in patients who received Rituxan 2 × 1000 mg.

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

| Preferred Term                    | Placebo + MTX    | Rituxan + MTX    |
|-----------------------------------|------------------|------------------|
|                                   | N = 398<br>n (%) | N = 540<br>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.

327

328 *Infusion Reactions*

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

346 *Infections*

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

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

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

359 *Cardiac Adverse Reactions*

360 In the pooled, placebo-controlled studies, the proportion of patients with serious cardiovascular reactions  
361 was 1.7% and 1.3% in the Rituxan and placebo treatment groups, respectively. Three cardiovascular deaths  
362 occurred during the double-blind period of the RA studies including all rituximab regimens ( $3/769 = 0.4\%$ )  
363 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 per 100  
365 patient years. The rate of myocardial infarction (MI) was 0.56 per 100 patient years (28 events in 26  
366 patients), which is consistent with MI rates in the general RA population. These rates did not increase over  
367 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 observed  
373 in 12% (67/540) of patients on Rituxan versus 10% (39/398) of patients on placebo. Hypophosphatemia  
374 was more common in patients who received corticosteroids. Newly-occurring hyperuricemia ( $> 10$  mg/dl)  
375 was observed in 1.5% (8/540) of patients on Rituxan versus 0.3% (1/398) of patients on placebo.

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

379 *Retreatment in Patients with RA*

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

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

389 **6.3 Immunogenicity**

390 As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of  
391 antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors  
392 including assay sensitivity and specificity, assay methodology, sample handling, timing of sample

393 collection, concomitant medications, and underlying disease. For these reasons, comparison of the  
394 incidence of antibodies to Rituxan with the incidence of antibodies to other products may be misleading.

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

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

#### 404 **6.4 Postmarketing Experience**

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

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

### 422 **7 DRUG INTERACTIONS**

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

### 427 **8 USE IN SPECIFIC POPULATIONS**

#### 428 **8.1 Pregnancy**

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

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

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

440 **8.3 Nursing Mothers**

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

445 **8.4 Pediatric Use**

446 FDA has not required pediatric studies in polyarticular juvenile idiopathic arthritis (PJIA) patients ages  
447 0 to 16 due to concerns regarding the potential for prolonged immunosuppression as a result of B cell  
448 depletion in the developing juvenile immune system.

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

450 **8.5 Geriatric Use**

451 *Diffuse Large B-Cell NHL*

452 Among patients with DLBCL evaluated in three randomized, active-controlled trials, 927 patients  
453 received Rituxan in combination with chemotherapy. Of these, 396 (43%) were age 65 or greater and 123  
454 (13%) were age 75 or greater. No overall differences in effectiveness were observed between these patients  
455 and younger patients. Cardiac adverse reactions, mostly supraventricular arrhythmias, occurred more  
456 frequently among elderly patients. Serious pulmonary adverse reactions were also more common among  
457 the elderly, including pneumonia and pneumonitis.

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

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

462 *Chronic Lymphocytic Leukemia*

463 Among patients with CLL evaluated in two randomized active-controlled trials, 243 of  
464 676 Rituxan-treated patients (36%) were 65 years of age or older; of these, 100 Rituxan-treated patients  
465 (15%) were 70 years of age or older.

466 In exploratory analyses defined by age, there was no observed benefit from the addition of Rituxan to  
467 fludarabine and cyclophosphamide among patients 70 years of age or older in Study 9 or in Study 10; there  
468 was also no observed benefit from the addition of Rituxan to fludarabine and cyclophosphamide among  
469 patients 65 years of age or older in Study 10 [see *Clinical Studies (14.5)*]. Patients 70 years or older  
470 received lower dose intensity of fludarabine and cyclophosphamide compared to younger patients,  
471 regardless of the addition of Rituxan. In Study 9, the dose intensity of Rituxan was similar in older and  
472 younger patients, however in Study 10 older patients received a lower dose intensity of Rituxan.

473 The incidence of Grade 3 and 4 adverse reactions was higher among patients receiving R-FC who were  
474 70 years or older compared to younger patients for neutropenia [44% vs. 31% (Study 9); 56% vs. 39%  
475 (Study 10)], febrile neutropenia [16% vs. 6% (Study 9)], anemia [5% vs. 2% (Study 9); 21% vs. 10% (Study  
476 10)], thrombocytopenia [19% vs. 8% (Study 10)], pancytopenia [7% vs. 2% (Study 9); 7% vs. 2% (Study  
477 10)] and infections [30% vs. 14% (Study 10)].

478 *Rheumatoid Arthritis*

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

483 **10 OVERDOSAGE**

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

486 **11 DESCRIPTION**

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

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

496 **12 CLINICAL PHARMACOLOGY**

497 **12.1 Mechanism of Action**

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

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

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

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

518 **12.2 Pharmacodynamics**

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

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

527 In RA patients, treatment with Rituxan induced depletion of peripheral B lymphocytes, with the majority  
528 of patients demonstrating near complete depletion (CD19 counts below the lower limit of quantification,  
529 20 cells/ $\mu$ l) within 2 weeks after receiving the first dose of Rituxan. The majority of patients showed  
530 peripheral B-cell depletion for at least 6 months. A small proportion of patients (~4%) had prolonged  
531 peripheral B-cell depletion lasting more than 3 years after a single course of treatment.

532 Total serum immunoglobulin levels, IgM, IgG, and IgA were reduced at 6 months with the greatest  
533 change observed in IgM. At Week 24 of the first course of Rituxan treatment, small proportions of patients  
534 experienced decreases in IgM (10%), IgG (2.8%), and IgA (0.8%) levels below the lower limit of normal

(LLN). In the experience with Rituxan in RA patients during repeated Rituxan treatment, 23.3%, 5.5%, and 0.5% of patients experienced decreases in IgM, IgG, and IgA concentrations below LLN at any time after receiving Rituxan, respectively. The clinical consequences of decreases in immunoglobulin levels in RA patients treated with Rituxan are unclear.

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

### 12.3 Pharmacokinetics

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

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

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

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

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

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

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

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

### 13.2 Animal Toxicology and/or Pharmacology

#### *Reproductive Toxicology Studies*

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

A subsequent pre- and postnatal reproductive toxicity study in cynomolgus monkeys was completed to assess developmental effects including the recovery of B cells and immune function in infants exposed to rituximab in utero. Animals were treated with a loading dose of 0, 15, or 75 mg/kg every day for 3 days,

583 followed by weekly dosing with 0, 20, or 100 mg/kg dose. Subsets of pregnant females were treated from  
 584 PC Day 20 through postpartum Day 78, PC Day 76 through PC Day 134, and from PC Day 132 through  
 585 delivery and postpartum Day 28. Regardless of the timing of treatment, decreased B cells and  
 586 immunosuppression were noted in the offspring of rituximab-treated pregnant animals. The B-cell counts  
 587 returned to normal levels, and immunologic function was restored within 6 months postpartum.

588 **14 CLINICAL STUDIES**

589 **14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**

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

592 *Study 1*

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

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

600 *Study 2*

601 In a multicenter, single-arm study, 37 patients with relapsed or refractory, low-grade NHL received  
 602 375 mg/m<sup>2</sup> of Rituxan weekly for 8 doses. Results are summarized in Table 3.

603 *Study 3*

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

609 *Bulky Disease*

610 In pooled data from studies 1 and 3, 39 patients with bulky (single lesion > 10 cm in diameter) and  
 611 relapsed or refractory, low-grade NHL received Rituxan 375 mg/m<sup>2</sup> weekly for 4 doses. Results are  
 612 summarized in Table 3.  
 613

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

|  | Study 1<br>Weekly $\times$ 4<br>N = 166 | Study 2<br>Weekly $\times$ 8<br>N = 37 | Study 1 and Study 3<br>Bulky disease,<br>Weekly $\times$ 4<br>N = 39 <sup>a</sup> | Study 3<br>Retreatment,<br>Weekly $\times$ 4<br>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><br>(Months) [Range] | 11.2<br>[1.9 to 42.1+]                  | 13.4<br>[2.5 to 36.5+]                 | 6.9<br>[2.8 to 25.0+]   | 15.0<br>[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.

615 **14.2 Previously Untreated, Follicular, CD20-Positive, B-Cell NHL**

616 *Study 4*

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

622 Twenty-six percent of the study population was > 60 years of age, 99% had Stage III or IV disease, and  
623 50% had an International Prognostic Index (IPI) score ≥ 2. The results for PFS as determined by a blinded,  
624 independent assessment of progression are presented in Table 4. The point estimates may be influenced by  
625 the presence of informative censoring. The PFS results based on investigator assessment of progression  
626 were similar to those obtained by the independent review assessment.

627

**Table 4**  
Efficacy Results in Study 4

|                                    | Study Arm         |              |
|------------------------------------|-------------------|--------------|
|                                    | R-CVP<br>N=162    | CVP<br>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.

628

629 **14.3 Non-Progressing Low-Grade, CD20-Positive, B-Cell NHL Following First-Line CVP**  
630 **Chemotherapy**

631 *Study 5*

632 A total of 322 patients with previously untreated low-grade, B-cell NHL who did not progress after 6 or  
633 8 cycles of CVP chemotherapy were enrolled in an open-label, multicenter, randomized trial. Patients were  
634 randomized (1:1) to receive Rituxan, 375 mg/m<sup>2</sup> intravenous infusion, once weekly for 4 doses every  
635 6 months for up to 16 doses or no further therapeutic intervention. The main outcome measure of the study  
636 was progression-free survival defined as the time from randomization to progression, relapse, or death.  
637 Thirty-seven percent of the study population was > 60 years of age, 99% had Stage III or IV disease, and  
638 63% had an IPI score ≥ 2.

639 There was a reduction in the risk of progression, relapse, or death (hazard ratio estimate in the range of  
640 0.36 to 0.49) for patients randomized to Rituxan as compared to those who received no additional treatment.

641 **14.4 Diffuse Large B-Cell NHL (DLBCL)**

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

646 *Study 6*

647 A total of 632 patients age ≥ 60 years with DLBCL (including primary mediastinal B-cell lymphoma)  
648 were randomized in a 1:1 ratio to treatment with CHOP or R-CHOP. Patients received 6 or 8 cycles of  
649 CHOP, each cycle lasting 21 days. All patients in the R-CHOP arm received 4 doses of Rituxan 375 mg/m<sup>2</sup>  
650 on Days -7 and -3 (prior to Cycle 1) and 48-72 hours prior to Cycles 3 and 5. Patients who received  
651 8 cycles of CHOP also received Rituxan prior to Cycle 7. The main outcome measure of the study was  
652 progression-free survival, defined as the time from randomization to the first of progression, relapse, or  
653 death. Responding patients underwent a second randomization to receive Rituxan or no further therapy.

654 Among all enrolled patients, 62% had centrally confirmed DLBCL histology, 73% had Stage III–IV  
 655 disease, 56% had IPI scores  $\geq 2$ , 86% had ECOG performance status of  $< 2$ , 57% had elevated LDH levels,  
 656 and 30% had two or more extranodal disease sites involved. Efficacy results are presented in Table 5.  
 657 These results reflect a statistical approach which allows for an evaluation of Rituxan administered in the  
 658 induction setting that excludes any potential impact of Rituxan given after the second randomization.

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

#### 662 Study 7

663 A total of 399 patients with DLBCL, age  $\geq 60$  years, were randomized in a 1:1 ratio to receive CHOP or  
 664 R-CHOP. All patients received up to eight 3-week cycles of CHOP induction; patients in the R-CHOP arm  
 665 received Rituxan 375 mg/m<sup>2</sup> on Day 1 of each cycle. The main outcome measure of the study was  
 666 event-free survival, defined as the time from randomization to relapse, progression, change in therapy, or  
 667 death from any cause. Among all enrolled patients, 80% had Stage III or IV disease, 60% of patients had an  
 668 age-adjusted IPI  $\geq 2$ , 80% had ECOG performance status scores  $< 2$ , 66% had elevated LDH levels, and  
 669 52% had extranodal involvement in at least two sites. Efficacy results are presented in Table 5.

#### 670 Study 8

671 A total of 823 patients with DLBCL, aged 18–60 years, were randomized in a 1:1 ratio to receive an  
 672 anthracycline-containing chemotherapy regimen alone or in combination with Rituxan. The main outcome  
 673 measure of the study was time to treatment failure, defined as time from randomization to the earliest of  
 674 progressive disease, failure to achieve a complete response, relapse, or death. Among all enrolled patients,  
 675 28% had Stage III–IV disease, 100% had IPI scores of  $\leq 1$ , 99% had ECOG performance status of  $< 2$ ,  
 676 29% had elevated LDH levels, 49% had bulky disease, and 34% had extranodal involvement. Efficacy  
 677 results are presented in Table 5.  
 678

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

|  | Study 6<br>(n = 632)                 |                   | Study 7<br>(n = 399)           |                   | Study 8<br>(n = 823)                 |                   |
|--|--------------------------------------|-------------------|--------------------------------|-------------------|--------------------------------------|-------------------|
|  | R-CHOP                               | CHOP              | R-CHOP                         | CHOP              | R-Chemo                              | Chemo             |
| Main outcome                             | Progression-free survival<br>(years) |                   | Event-free survival<br>(years) |                   | Time to treatment failure<br>(years) |                   |
| Median of main outcome<br>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.

679 In Study 7, overall survival estimates at 5 years were 58% vs. 46% for R-CHOP and CHOP, respectively.  
 680 **14.5 Chronic Lymphocytic Leukemia (CLL)**

682 The safety and effectiveness of Rituxan were evaluated in two randomized (1:1) multicenter open-label  
 683 studies comparing FC alone or in combination with Rituxan for up to 6 cycles in patients with previously  
 684 untreated CLL [Study 9 (n = 817)] or previously treated CLL [Study 10 (n = 552)]. Patients received  
 685 fludarabine 25 mg/m<sup>2</sup>/day and cyclophosphamide 250 mg/m<sup>2</sup>/day on days 1, 2 and 3 of each cycle, with or

686 without Rituxan. In both studies, seventy-one percent of CLL patients received 6 cycles and 90% received  
687 at least 3 cycles of Rituxan-based therapy.

688 In Study 9, 30% of patients were 65 years or older, 31% were Binet stage C, 45% had B symptoms, more  
689 than 99% had ECOG performance status (PS) 0-1, 74% were male, and 100% were White. In Study 10,  
690 44% of patients were 65 years or older, 28% had B symptoms, 82% received a prior alkylating drug, 18%  
691 received prior fludarabine, 100% had ECOG PS 0-1, 67% were male and 98% were White.

692 The main outcome measure in both studies was progression-free survival (PFS), defined as the time from  
693 randomization to progression, relapse, or death, as determined by investigators (Study 9) or an independent  
694 review committee (Study 10). The investigator assessed results in Study 10 were supportive of those  
695 obtained by the independent review committee. Efficacy results are presented in Table 6.  
696

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

|                         | Study 9*               |             | Study 10*            |             |
|-------------------------|------------------------|-------------|----------------------|-------------|
|                         | (Previously untreated) |             | (Previously treated) |             |
|                         | R-FC<br>N=408          | FC<br>N=409 | R-FC<br>N=276        | FC<br>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           | 86%                    | 73%         | 54%                  | 45%         |
| (95% CI)                | (82, 89)               | (68, 77)    | (48, 60)             | (37, 51)    |

\* As defined in 1996 National Cancer Institute Working Group guidelines

697 Across both studies, 243 of 676 Rituxan-treated patients (36%) were 65 years of age or older and 100  
698 Rituxan-treated patients (15%) were 70 years of age or older. The results of exploratory subset analyses in  
699 elderly patients are presented in Table 7.  
700  
701

**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.

702

## 703 14.6 Rheumatoid Arthritis (RA)

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

705 The efficacy and safety of Rituxan were evaluated in two randomized, double-blind, placebo-controlled  
706 studies of adult patients with moderately to severely active RA who had a prior inadequate response to at

707 least one TNF inhibitor. Patients were 18 years of age or older, diagnosed with active RA according to  
 708 American College of Rheumatology (ACR) criteria, and had at least 8 swollen and 8 tender joints.

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

715 In RA Study 2, all patients received the first course of Rituxan 2 × 1000 mg + MTX. Patients who  
 716 experienced ongoing disease activity were randomized to receive a second course of either Rituxan  
 717 2 × 1000 mg MTX or placebo + MTX, the majority between Weeks 24–28. The proportions of patients  
 718 achieving ACR 20, 50, and 70 responses at Week 24, before the re-treatment course, and at Week 48, after  
 719 retreatment, are shown in Table 8.

720

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

<sup>a</sup> In Study 2, all patients received a first course of Rituxan 2 × 1000 mg. Patients who experienced ongoing disease activity were randomized to receive a second course of either Rituxan 2 × 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).

721

722 Improvement was also noted for all components of ACR response following treatment with Rituxan, as  
 723 shown in Table 9.  
 724

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

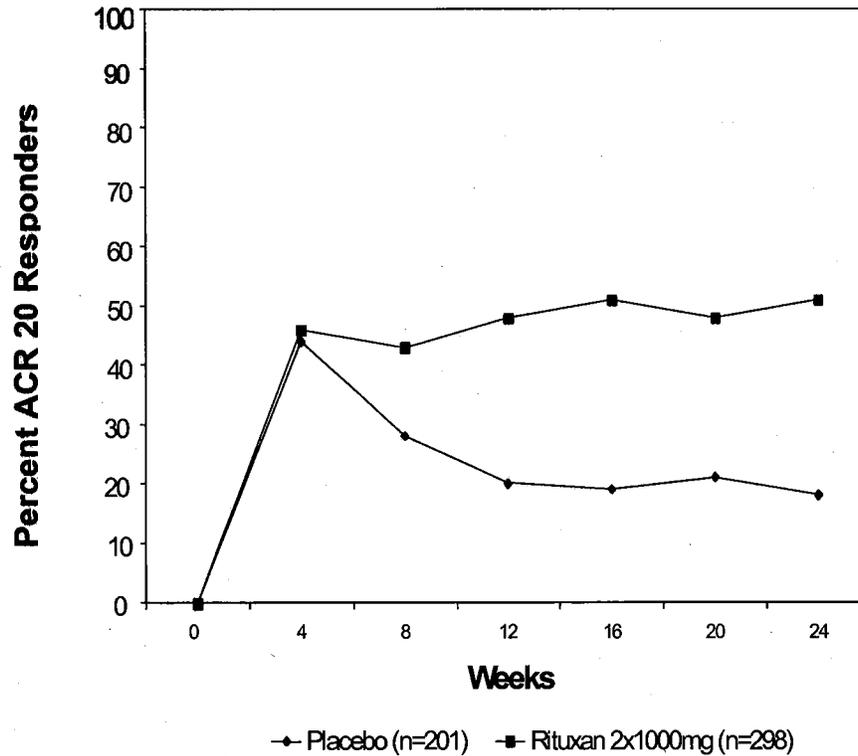
| Inadequate Response to TNF Antagonists   |                            |       |                            |       |
|--|----------------------------|-------|----------------------------|-------|
| Parameter<br>(median)                    | Placebo + MTX<br>(n = 201) |       | Rituxan + MTX<br>(n = 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.

725  
 726 The time course of ACR 20 response for Study 1 is shown in Figure 1. Although both treatment groups  
 727 received a brief course of intravenous and oral glucocorticoids, resulting in similar benefits at Week 4,  
 728 higher ACR 20 responses were observed for the Rituxan group by Week 8. A similar proportion of patients  
 729 achieved these responses through Week 24 after a single course of treatment (2 infusions) with Rituxan.  
 730 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)



731

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

733

734 *Radiographic Response*

735 In RA Study 1, structural joint damage was assessed radiographically and expressed as changes in  
 736 Genant-modified Total Sharp Score (TSS) and its components, the erosion score (ES) and the joint space  
 737 narrowing (JSN) score. Rituxan + MTX slowed the progression of structural damage compared to placebo  
 738 + 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.

739

740 In RA Study 1 and its open-label extension, 70% of patients initially randomized to Rituxan + MTX and  
741 72% of patients initially randomized to placebo + MTX were evaluated radiographically at Year 2. As  
742 shown in Table 10, progression of structural damage in Rituxan + MTX patients was further reduced in the  
743 second year of treatment.

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

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

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

761 *Physical Function Response*

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

765 Physical function was assessed at Weeks 24 and 48 using the Health Assessment Questionnaire Disability  
766 Index (HAQ-DI). From baseline to Week 24, a greater proportion of Rituxan-treated patients had an

767 improvement in HAQ-DI of at least 0.22 (a minimal clinically important difference) and a greater mean  
 768 HAQ-DI improvement compared to placebo, as shown in Table 11. HAQ-DI results for the Rituxan 500 mg  
 769 treatment group were similar to the Rituxan 1000 mg treatment group; however radiographic responses were  
 770 not assessed (see Dosing Precaution in the Radiographic Responses section above). These improvements  
 771 were maintained at 48 weeks.  
 772

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

|   | Placebo<br>+ MTX<br>n = 172 | Rituxan<br>2 x 1000 mg + MTX<br>n = 170 | Treatment Difference<br>(Rituxan – Placebo) <sup>b</sup><br>(95% CI) |
|---|-----------------------------|---|--|
| Mean Improvement from Baseline  | 0.19                        | 0.42                                    | 0.23 (0.11, 0.34)  |
| Percent of patients with “Improved” score (Change<br>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.

773

774 **16 HOW SUPPLIED/STORAGE AND HANDLING**

775 Rituxan vials [100 mg (NDC 50242-051-21) and 500 mg (NDC 50242-053-06)] are stable at 2°C–8°C  
 776 (36°F–46°F). Do not use beyond expiration date stamped on carton. Rituxan vials should be protected  
 777 from direct sunlight. Do not freeze or shake.

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

782 **17 PATIENT COUNSELING INFORMATION**

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

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

790 **MEDICATION GUIDE**  
791 **RITUXAN® (ri-tuk'-san)**  
792 **(rituximab)**  
793 **for injection**

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

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

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

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

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

- 805 • hives (red itchy welts) or rash
- 806 • itching
- 807 • swelling of your lips, tongue, throat or face
- 808 • sudden cough
- 809 • shortness of breath, difficulty breathing, or wheezing
- 810 • weakness
- 811 • dizziness or feel faint
- 812 • palpitations (feel like your heart is racing or fluttering)
- 813 • chest pain

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

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

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

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

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

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

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

- 833 • painful sores or ulcers on your skin, lips or in your mouth
- 834 • blisters
- 835 • peeling skin
- 836 • rash
- 837 • pustules

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

#### 839 **What is Rituxan?**

840 Rituxan is a prescription medicine used to treat:

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

848 People with serious infections should not receive Rituxan.  
849 It is not known if Rituxan is safe or effective in children.

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

852 Before receiving Rituxan, tell your doctor if you:

- 853 • have had a severe infusion reaction to Rituxan in the past
- 854 • have a history of heart problems, irregular heart beat or chest pain
- 855 • have lung or kidney problems
- 856 • have an infection or weakened immune system.
- 857 • have or have had any severe infections including:
  - 858 • Hepatitis B virus (HBV)
  - 859 • Hepatitis C virus (HCV)
  - 860 • Cytomegalovirus (CMV)
  - 861 • Herpes simplex virus (HSV)
  - 862 • Parvovirus B19
  - 863 • Varicella zoster virus (chickenpox or shingles)
  - 864 • West Nile Virus
- 865 • have had a recent vaccination or are scheduled to receive vaccinations. You should not receive certain  
866 vaccines before or after you receive Rituxan. Tell your doctor if anyone in your household is scheduled

867 to receive a vaccination. Some types of vaccines can spread to people with a weakened immune  
868 system, and cause serious problems.

869 • have any other medical conditions

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

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

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

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

878 • a Tumor Necrosis Factor (TNF) inhibitor medicine

879 • a Disease Modifying Anti-Rheumatic Drug (DMARD)

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

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

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

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

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

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

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

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

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

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

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

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

900 ○ fever

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

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

903 ○ earache or headache

904 ○ pain during urination

905 ○ white patches in the mouth or throat

- 906           ○ cuts, scrapes or incisions that are red, warm, swollen or painful
- 907 ● **Heart problems.** Rituxan may cause chest pain and irregular heart beats which may need treatment, or  
908 your doctor may decide to stop your treatment with Rituxan.
- 909 ● **Kidney problems,** especially if you are receiving Rituxan for NHL. Your doctor should do blood test to  
910 check how well your kidneys are working.
- 911 ● **Stomach and Serious bowel problems that can sometimes lead to death.** Bowel problems, including  
912 blockage or tears in the bowel can happen if you receive Rituxan with chemotherapy medicines to treat  
913 non-Hodgkin's lymphoma. Tell your doctor right away if you have any stomach area pain during  
914 treatment with Rituxan.
- 915 ● **Low blood cell counts.** Your doctor may do blood test during treatment with Rituxan to check you  
916 blood cell counts.
- 917           ○ **White blood cells.** White blood cells fight against bacterial infections. Low white blood  
918 cells can cause you to get infections, which may be serious. See "Increased risk of  
919 infections" above for a list of symptoms of infection.
- 920           ○ **Red blood cells.** Red blood cells carry oxygen to your body tissues and organs.
- 921           ○ **Platelets.** Platelets are blood cells that help your blood to clot.

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

- 923 ● infusion reactions (see What is the most important information I should know about Rituxan?)
- 924 ● chills
- 925 ● infections
- 926 ● body aches
- 927 ● tiredness
- 928 ● low white blood cells

929 Other side effects with Rituxan include:

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

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

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

935 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-  
936 1088.

937 **General information about Rituxan**

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

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

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

944 Active ingredient: rituximab

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

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

947

948 Manufactured by:

949 Genentech, Inc.

950 A Member of the Roche Group

951 1 DNA Way

952 South San Francisco, CA 94080-4990

953 ©2010 Biogen Idec Inc. and Genentech, Inc.

954 Revised 02XX/2010 (4851501)

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

956