

1 **1.14.1.3** **Draft Labeling Text**

2 **1.14.1.3.1** **Draft Clean Package Insert**

3 **RITUXAN<sup>®</sup>**  
4 **(Rituximab)**

5 **WARNINGS**

6 **Fatal Infusion Reactions:** Deaths within 24 hours of RITUXAN infusion  
7 have been reported. These fatal reactions followed an infusion reaction  
8 complex which included hypoxia, pulmonary infiltrates, acute respiratory  
9 distress syndrome, myocardial infarction, ventricular fibrillation or  
10 cardiogenic shock. Approximately 80% of fatal infusion reactions  
11 occurred in association with the first infusion. (See **WARNINGS** and  
12 **ADVERSE REACTIONS**.)

13 Patients who develop severe infusion reactions should have RITUXAN  
14 infusion discontinued and receive medical treatment.

15 **Tumor Lysis Syndrome (TLS):** Acute renal failure requiring dialysis  
16 with instances of fatal outcome has been reported in the setting of TLS  
17 following treatment with RITUXAN. (See **WARNINGS**.)

18 **Severe Mucocutaneous Reactions:** Severe mucocutaneous reactions,  
19 some with fatal outcome, have been reported in association with  
20 RITUXAN treatment. (See **WARNINGS** and **ADVERSE REACTIONS**.)

21 **DESCRIPTION**

22 The RITUXAN<sup>®</sup> (Rituximab) antibody is a genetically engineered  
23 chimeric murine/human monoclonal antibody directed against the CD20  
24 antigen found on the surface of normal and malignant B lymphocytes.  
25 The antibody is an IgG<sub>1</sub> kappa immunoglobulin containing murine light-  
26 and heavy-chain variable region sequences and human constant region  
27 sequences. Rituximab is composed of two heavy chains of 451 amino  
28 acids and two light chains of 213 amino acids (based on cDNA analysis)

29 and has an approximate molecular weight of 145 kD. Rituximab has a  
30 binding affinity for the CD20 antigen of approximately 8.0 nM.

31 The chimeric anti-CD20 antibody is produced by mammalian cell  
32 (Chinese Hamster Ovary) suspension culture in a nutrient medium  
33 containing the antibiotic gentamicin. Gentamicin is not detectable in the  
34 final product. The anti-CD20 antibody is purified by affinity and ion  
35 exchange chromatography. The purification process includes specific  
36 viral inactivation and removal procedures. Rituximab drug product is  
37 manufactured from bulk drug substance manufactured by Genentech, Inc.  
38 (US License No. 1048).

39 RITUXAN is a sterile, clear, colorless, preservative-free liquid  
40 concentrate for intravenous (IV) administration. RITUXAN is supplied at  
41 a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL)  
42 single-use vials. The product is formulated for IV administration in  
43 9 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate,  
44 0.7 mg/mL polysorbate 80, and Water for Injection. The pH is adjusted  
45 to 6.5.

## 46 **CLINICAL PHARMACOLOGY**

### 47 **General**

48 Rituximab binds specifically to the antigen CD20 (human  
49 B-lymphocyte-restricted differentiation antigen, Bp35), a hydrophobic  
50 transmembrane protein with a molecular weight of approximately 35 kD  
51 located on pre-B and mature B lymphocytes (1,2). The antigen is also  
52 expressed on >90% of B-cell non-Hodgkin's lymphomas (NHL), (3) but  
53 is not found on hematopoietic stem cells, pro-B cells, normal plasma cells  
54 or other normal tissues (4). CD20 regulates an early step(s) in the  
55 activation process for cell cycle initiation and differentiation, (4) and  
56 possibly functions as a calcium ion channel (5). CD20 is not shed from  
57 the cell surface and does not internalize upon antibody binding (6). Free  
58 CD20 antigen is not found in the circulation (2).

59 **Preclinical Pharmacology and Toxicology**

60 Mechanism of Action: The Fab domain of Rituximab binds to the CD20  
61 antigen on B lymphocytes, and the Fc domain recruits immune effector  
62 functions to mediate B-cell lysis *in vitro*. Possible mechanisms of cell  
63 lysis include complement-dependent cytotoxicity (CDC) (7) and  
64 antibody-dependent cell mediated cytotoxicity (ADCC). The antibody has  
65 been shown to induce apoptosis in the DHL-4 human B-cell lymphoma  
66 line (8).

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

71 **Human Pharmacokinetics/Pharmacodynamics**

72 In patients given single doses at 10, 50, 100, 250 or 500 mg/m<sup>2</sup> as an  
73 IV infusion, serum levels and the half-life of Rituximab were proportional  
74 to dose (9). In 14 patients given 375 mg/m<sup>2</sup> as an IV infusion for 4 weekly  
75 doses, the mean serum half-life was 76.3 hours (range, 31.5 to  
76 152.6 hours) after the first infusion and 205.8 hours (range, 83.9 to  
77 407.0 hours); after the fourth infusion (10,11,12). The wide range of  
78 half-lives may reflect the variable tumor burden among patients and the  
79 changes in CD20-positive (normal and malignant) B-cell populations upon  
80 repeated administrations.

81 RITUXAN at a dose of 375 mg/m<sup>2</sup> was administered as an IV infusion at  
82 weekly intervals for 4 doses to 203 patients naive to RITUXAN (12,13).  
83 The mean C<sub>max</sub> following the fourth infusion was 486 µg/mL (range,  
84 77.5 to 996.6 µg/mL). The peak and trough serum levels of Rituximab  
85 were inversely correlated with baseline values for the number of  
86 circulating CD20-positive B cells and measures of disease burden.  
87 Median steady-state serum levels were higher for responders compared  
88 with nonresponders; however, no difference was found in the rate of  
89 elimination as measured by serum half-life. Serum levels were higher in

90 patients with International Working Formulation (IWF) subtypes B, C,  
91 and D as compared with those with subtype A (10,13). Rituximab was  
92 detectable in the serum of patients 3 to 6 months after completion of  
93 treatment.

94 RITUXAN at a dose of 375 mg/m<sup>2</sup> was administered as an IV infusion at  
95 weekly intervals for 8 doses to 37 patients (14). The mean C<sub>max</sub> after  
96 8 infusions was 550 µg/mL (range, 171 to 1177 µg/mL). The mean C<sub>max</sub>  
97 increased with each successive infusion through the eighth infusion  
98 (Table 1).

**Table 1**  
Rituximab C<sub>max</sub> Values

| Infusion Number | Mean C <sub>max</sub><br>µg/mL | Range<br>µg/mL |
|-----------------|--------------------------------|----------------|
| 1               | 242.6                          | 16.1–581.9     |
| 2               | 357.5                          | 106.8–948.6    |
| 3               | 381.3                          | 110.5–731.2    |
| 4               | 460.0                          | 138.0–835.8    |
| 5               | 475.3                          | 156.0–929.1    |
| 6               | 515.4                          | 152.7–865.2    |
| 7               | 544.6                          | 187.0–936.8    |
| 8               | 550.0                          | 170.6–1177.0   |

99  
100 The pharmacokinetic profile of RITUXAN when administered as  
101 6 infusions of 375 mg/m<sup>2</sup> in combination with 6 cycles of CHOP  
102 chemotherapy was similar to that seen with RITUXAN alone (15).

103 Administration of RITUXAN resulted in a rapid and sustained depletion  
104 of circulating and tissue-based B cells. Lymph node biopsies performed  
105 14 days after therapy showed a decrease in the percentage of B cells in  
106 seven of eight patients who had received single doses of Rituximab  
107 ≥ 100 mg/m<sup>2</sup> (9). Among the 166 patients in the pivotal study, circulating  
108 B cells (measured as CD19-positive cells) were depleted within the first  
109 three doses with sustained depletion for up to 6 to 9 months post-treatment

110 in 83% of patients (13). Of the responding patients assessed (n=80),  
 111 1% failed to show significant depletion of CD19-positive cells after the  
 112 third infusion of Rituximab as compared to 19% of the nonresponding  
 113 patients. B-cell recovery began at approximately 6 months following  
 114 completion of treatment. Median B-cell levels returned to normal by  
 115 12 months following completion of treatment (13).

116 There were sustained and statistically significant reductions in both IgM  
 117 and IgG serum levels observed from 5 through 11 months following  
 118 Rituximab administration. However, only 14% of patients had reductions  
 119 in IgM and/or IgG serum levels, resulting in values below the normal  
 120 range (13).

121 **CLINICAL STUDIES**

122 **Relapsed or Refractory, Low-Grade or Follicular,**  
 123 **CD20-Positive, B-Cell, NHL**

124 RITUXAN regimens tested include treatment weekly for 4 doses and  
 125 treatment weekly for 8 doses. Results for studies with a collective  
 126 enrollment of 296 patients are summarized below (Table 2):

**Table 2**  
 Summary of RITUXAN Efficacy Data by Schedule and Clinical Setting  
 (See [ADVERSE REACTIONS](#) for [Risk Factors Associated with Increased Rates of Adverse Events](#))

|   | Weekly × 4<br>N=166       | Weekly × 8<br>N=37        | Bulky disease,<br>Weekly × 4<br>N=39 <sup>a</sup> | Retreatment,<br>Weekly × 4<br>N=60 |
|---|---------------------------|---------------------------|---|------------------------------------|
| Overall Response Rate   | 48%                       | 57%                       | 36%   | 38%                                |
| Complete Response Rate  | 6%                        | 14%                       | 3%  | 10%                                |
| Median Duration of<br>Response <sup>b, c, d</sup><br>(Months) [Range] | 11.2<br>[1.9 to<br>42.1+] | 13.4<br>[2.5 to<br>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.

## 128 Weekly for 4 Doses

129 A multicenter, open-label, single-arm study was conducted in 166 patients  
130 with relapsed or refractory low-grade or follicular B-cell NHL who  
131 received 375 mg/m<sup>2</sup> of RITUXAN given as an IV infusion weekly for  
132 4 doses (13). Patients with tumor masses > 10 cm or with  
133 >5,000 lymphocytes/μL in the peripheral blood were excluded from the  
134 study. Results are summarized in Table 2. The median time to onset of  
135 response was 50 days and the median duration of response was  
136 11.2 months (range, 1.9 to 42.1+). Disease-related signs and symptoms  
137 (including B-symptoms) were present in 23% (39/166) of patients at study  
138 entry and resolved in 64% (25/39) of those patients.

139 In a multivariate analysis, the ORR was higher in patients with IWF B, C,  
140 and D histologic subtypes as compared to IWF subtype A (58% vs. 12%),  
141 higher in patients whose largest lesion was <5 cm vs. >7 cm (maximum,  
142 21 cm) in greatest diameter (53% vs. 38%), and higher in patients with  
143 chemosensitive relapse as compared with chemoresistant (defined as  
144 duration of response < 3 months) relapse (53% vs. 36%). ORR in patients  
145 previously treated with autologous bone marrow transplant was 78%  
146 (18/23). The following adverse prognostic factors were *not* associated  
147 with a lower response rate: age ≥ 60 years, extranodal disease, prior  
148 anthracycline therapy, and bone marrow involvement.

## 149 Weekly for 8 Doses

150 In a multicenter, single-arm study, 37 patients with relapsed or refractory,  
151 low-grade NHL received 375 mg/m<sup>2</sup> of RITUXAN weekly for 8 doses.  
152 Results are summarized in Table 2. (see ADVERSE REACTIONS, Risk  
153 Factors Associated with Increased Rates of Adverse Events.)

## 154 Bulky Disease, Weekly for 4 Doses

155 In pooled data from multiple studies of RITUXAN, 39 patients with  
156 relapsed or refractory, bulky disease (single lesion > 10 cm in diameter),  
157 low-grade NHL received 375 mg/m<sup>2</sup> of RITUXAN weekly for 4 doses.  
158 Results are summarized in Table 2 (15, 16). (For information on the

159 higher incidence of Grade 3 and 4 adverse events, see [ADVERSE](#)  
160 [REACTIONS, Risk Factors Associated with Increased Rates of Adverse](#)  
161 [Events.](#))

#### 162 **Retreatment Weekly for 4 Doses**

163 In a multi-center, single-arm study, 60 patients received 375 mg/m<sup>2</sup> of  
164 RITUXAN weekly for 4 doses (17). All patients had relapsed or  
165 refractory, low-grade or follicular B-cell NHL and had achieved an  
166 objective clinical response to RITUXAN administered 3.8–35.6 months  
167 (median 14.5 months) prior to retreatment with RITUXAN. Of these  
168 60 patients, 55 received their second course of RITUXAN, 3 patients  
169 received their third course and 2 patients received their second and third  
170 courses of RITUXAN in this study. Results are summarized in [Table 2](#).

#### 171 **Diffuse, Large B-Cell, NHL**

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

#### 178 **Study 1**

179 A total of 632 patients aged ≥60 years with either B-cell NHL Grade F,  
180 G, or H by the International Working Formulation classification or  
181 DLBCL (including primary mediastinal B-cell lymphoma) in the REAL  
182 classification were randomized in a 1:1 ratio to treatment with CHOP or  
183 R-CHOP. Patients were given 6 or 8, 21 day cycles of CHOP. Patients in  
184 the R-CHOP arm also received 4 or 5 doses of RITUXAN 375 mg/m<sup>2</sup> on  
185 Days –7 and –3 (prior to Cycle 1), and 48 to 72 hours pre-Cycle 3,  
186 pre-Cycle 5, and pre-Cycle 7 for patients receiving 8 cycles of CHOP  
187 induction. The main outcome measure of the study was progression-free  
188 survival (PFS), defined as the time from randomization to the first of

189 progression, relapse or death. Responding patients underwent a second  
190 randomization to receive RITUXAN or no further therapy.

191 Among all enrolled patients, 62% had centrally confirmed DLBCL  
192 histology, 73% had Stage III–IV disease, 56% had IPI scores  $\geq 2$ , 86%  
193 had ECOG performance status of  $< 2$ , 57% had elevated LDH levels, and  
194 30% had two or more extranodal disease sites involved. Efficacy results  
195 are presented in [Table 3](#). These results reflect a statistical approach which  
196 allows for an evaluation of RITUXAN administered in the induction  
197 setting that excludes any potential impact of RITUXAN given after the  
198 second randomization.

199 Analysis of results after the second randomization in Study 1 demonstrates  
200 that for patients randomized to R-CHOP, additional RITUXAN exposure  
201 beyond induction was not associated with further improvements in  
202 progression free survival or overall survival.

### 203 Study 2

204 A total of 399 patients with DLBCL, aged  $\geq 60$  years, were randomized in  
205 a 1:1 ratio to receive CHOP or R-CHOP induction. All patients received  
206 up to 8, 3-week cycles of CHOP induction; patients in the R-CHOP arm  
207 received RITUXAN 375 mg/m<sup>2</sup> on Day 1 of each cycle. The main  
208 outcome measure of the study was event free survival (EFS), defined as  
209 the time from randomization to relapse, progression, change in therapy or  
210 death from any cause. Among all enrolled patients, 80% had stage III or  
211 IV disease, 60% of patients had an age-adjusted IPI  $\geq 2$ , 80% had ECOG  
212 performance status scores  $< 2$ , 66% had elevated LDH levels, and 52%  
213 had extranodal involvement in at least two sites. Efficacy results are  
214 presented in [Table 3](#).

### 215 Study 3

216 A total of 823 patients with DLBCL, aged 18–60 years, were randomized  
217 in a 1:1 ratio to receive an anthracycline-containing chemotherapy alone  
218 or in combination with RITUXAN. The main outcome measure of the

219 study was time to treatment failure (TTF), defined as time from  
 220 randomization to the earliest of progressive disease, failure to achieve a  
 221 complete response, relapse or death. Among all enrolled patients, 28%  
 222 had Stage III–IV disease, 100% had IPI scores of  $\leq 1$ , 99% had ECOG  
 223 performance status of  $< 2$ , 29% had elevated LDH levels, 49% had bulky  
 224 disease and 34% had extranodal involvement. Efficacy results are  
 225 presented in Table 3.

**Table 3**  
 Efficacy Results in Studies 1, 2, and 3

|   | Study 1<br>(n=632)                   |        | Study 2<br>(n=399)             |        | Study 3<br>(n=823)                   |                 |
|---|--------------------------------------|--------|--------------------------------|--------|--------------------------------------|-----------------|
|   | CHOP                                 | R-CHOP | CHOP                           | R-CHOP | Chemo                                | R-Chemo         |
| Main outcome                                | Progression-free survival<br>(years) |        | Event-free survival<br>(years) |        | Time to treatment failure<br>(years) |                 |
| Median of main<br>outcome measure           | 1.6                                  | 3.1    | 1.1                            | 2.9    | 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<br>years <sup>c</sup> | 63%                                  | 74%    | 58%                            | 69%    | 86%                                  | 95%             |
| 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.

226

227 In Study 2, overall survival estimates at 5 years were 58% vs. 46% for  
 228 R-CHOP and CHOP, respectively.

### 229 INDICATIONS AND USAGE

230 RITUXAN<sup>®</sup> (Rituximab) is indicated for the treatment of patients with  
 231 relapsed or refractory, low-grade or follicular, CD20-positive, B-cell,  
 232 non-Hodgkin's lymphoma.

233 RITUXAN<sup>®</sup> (Rituximab) is indicated for the first-line treatment of diffuse  
 234 large B-cell, CD20-positive, non-Hodgkin's lymphoma in combination  
 235 with CHOP or other anthracycline-based chemotherapy regimens.

236 **CONTRAINDICATIONS**

237 RITUXAN is contraindicated in patients with known anaphylaxis or  
238 IgE-mediated hypersensitivity to murine proteins or to any component of  
239 this product. (See WARNINGS.)

240 **WARNINGS (See BOXED WARNINGS.)**

241 **Severe Infusion Reactions (see BOXED WARNINGS, ADVERSE**  
242 **REACTIONS, and Hypersensitivity Reactions)**

243 RITUXAN has caused severe infusion reactions. In some cases, these  
244 reactions were fatal. These severe reactions typically occurred during the  
245 first infusion with time to onset of 30 to 120 minutes. Signs and  
246 symptoms of severe infusion reactions may include hypotension,  
247 angioedema, hypoxia or bronchospasm, and may require interruption of  
248 RITUXAN administration. The most severe manifestations and sequelae  
249 include pulmonary infiltrates, acute respiratory distress syndrome,  
250 myocardial infarction, ventricular fibrillation, and cardiogenic shock. In  
251 the reported cases, the following factors were more frequently associated  
252 with fatal outcomes: female gender, pulmonary infiltrates, and chronic  
253 lymphocytic leukemia or mantle cell lymphoma.

254 *Management of severe infusion reactions:* The RITUXAN infusion  
255 should be interrupted for severe reactions and supportive care measures  
256 instituted as medically indicated (e.g., intravenous fluids, vasopressors,  
257 oxygen, bronchodilators, diphenhydramine, and acetaminophen). In most  
258 cases, the infusion can be resumed at a 50% reduction in rate (e.g., from  
259 100 mg/hr to 50 mg/hr) when symptoms have completely resolved.  
260 Patients requiring close monitoring during first and all subsequent  
261 infusions include those with pre-existing cardiac and pulmonary  
262 conditions, those with prior clinically significant cardiopulmonary adverse  
263 events and those with high numbers of circulating malignant cells  
264 ( $\geq 25,000/\text{mm}^3$ ) with or without evidence of high tumor burden.

265 **Tumor Lysis Syndrome [TLS] (See **BOXED WARNINGS** and**  
266 **ADVERSE REACTIONS)**  
267 Rapid reduction in tumor volume followed by acute renal failure,  
268 hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatasemia,  
269 have been reported within 12 to 24 hours after the first RITUXAN  
270 infusion. Rare instances of fatal outcome have been reported in the setting  
271 of TLS following treatment with RITUXAN. The risks of TLS appear to  
272 be greater in patients with high numbers of circulating malignant cells  
273 ( $\geq 25,000/\text{mm}^3$ ) or high tumor burden. Prophylaxis for TLS should be  
274 considered for patients at high risk. Correction of electrolyte  
275 abnormalities, monitoring of renal function and fluid balance, and  
276 administration of supportive care, including dialysis, should be initiated as  
277 indicated. Following complete resolution of the complications of TLS,  
278 RITUXAN has been tolerated when re-administered in conjunction with  
279 prophylactic therapy for TLS in a limited number of cases.

280 **Hepatitis B Reactivation with Related Fulminant Hepatitis and**  
281 **Other Viral Infections**

282 Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic  
283 failure, and death has been reported in some patients with hematologic  
284 malignancies treated with RITUXAN. The majority of patients received  
285 RITUXAN in combination with chemotherapy. The median time to the  
286 diagnosis of hepatitis was approximately 4 months after the initiation of  
287 RITUXAN and approximately one month after the last dose.

288 Persons at high risk of HBV infection should be screened before initiation  
289 of RITUXAN. Carriers of hepatitis B should be closely monitored for  
290 clinical and laboratory signs of active HBV infection and for signs of  
291 hepatitis during and for up to several months following RITUXAN  
292 therapy. In patients who develop viral hepatitis, RITUXAN and any  
293 concomitant chemotherapy should be discontinued and appropriate  
294 treatment including antiviral therapy initiated. There are insufficient data  
295 regarding the safety of resuming RITUXAN therapy in patients who  
296 develop hepatitis subsequent to HBV reactivation.

297 **The following additional serious viral infections, either new, reactivated or**  
298 exacerbated, have been identified in clinical studies or postmarketing  
299 reports. The majority of patients received RITUXAN in combination with  
300 chemotherapy or as part of a hematopoietic stem cell transplant. These  
301 viral infections included JC virus [progressive multifocal  
302 leukoencephalopathy (PML)], cytomegalovirus, herpes simplex virus,  
303 parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In  
304 some cases, the viral infections occurred up to one year following  
305 discontinuation of RITUXAN and have resulted in death.

### 306 **Hypersensitivity Reactions**

307 RITUXAN has been associated with hypersensitivity reactions  
308 (non-IgE-mediated reactions) which may respond to adjustments in the  
309 infusion rate and in medical management. Hypotension, bronchospasm,  
310 and angioedema have occurred in association with RITUXAN infusion  
311 (see [Severe Infusion Reactions](#)). RITUXAN infusion should be  
312 interrupted for severe hypersensitivity reactions and can be resumed at a  
313 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms  
314 have completely resolved. Treatment of these symptoms with  
315 diphenhydramine and acetaminophen is recommended; additional  
316 treatment with bronchodilators or IV saline may be indicated. In most  
317 cases, patients who have experienced non-life-threatening hypersensitivity  
318 reactions have been able to complete the full course of therapy.  
319 (See [DOSAGE AND ADMINISTRATION](#).) Medications for the  
320 treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines  
321 and corticosteroids, should be available for immediate use in the event of a  
322 reaction during administration.

### 323 **Cardiovascular**

324 Infusions should be discontinued in the event of serious or life-threatening  
325 cardiac arrhythmias. Patients who develop clinically significant  
326 arrhythmias should undergo cardiac monitoring during and after  
327 subsequent infusions of RITUXAN. Patients with pre-existing cardiac  
328 conditions including arrhythmias and angina have had recurrences of these

329 events during RITUXAN therapy and should be monitored throughout the  
330 infusion and immediate post-infusion period.

331 **Renal (See [BOXED WARNINGS: Tumor Lysis Syndrome \[TLS\]](#)**  
332 **and [ADVERSE REACTIONS](#))**

333 RITUXAN administration has been associated with severe renal toxicity  
334 including acute renal failure requiring dialysis and in some cases, has led  
335 to a fatal outcome. Renal toxicity has occurred in patients with high  
336 numbers of circulating malignant cells ( $>25,000/\text{mm}^3$ ) or high tumor  
337 burden who experience tumor lysis syndrome and in patients administered  
338 concomitant cisplatin therapy during clinical trials. The combination of  
339 cisplatin and RITUXAN is not an approved treatment regimen. If this  
340 combination is used in clinical trials *extreme caution* should be exercised;  
341 patients should be monitored closely for signs of renal failure.  
342 Discontinuation of RITUXAN should be considered for those with rising  
343 serum creatinine or oliguria.

344 **Severe Mucocutaneous Reactions (See [BOXED WARNINGS](#))**

345 Mucocutaneous reactions, some with fatal outcome, have been reported in  
346 patients treated with RITUXAN. These reports include paraneoplastic  
347 pemphigus (an uncommon disorder which is a manifestation of the  
348 patient's underlying malignancy) (18), Stevens-Johnson syndrome,  
349 lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal  
350 necrolysis. The onset of the reaction in the reported cases has varied from  
351 1 to 13 weeks following RITUXAN exposure. Patients experiencing a  
352 severe mucocutaneous reaction should not receive any further infusions  
353 and seek prompt medical evaluation. Skin biopsy may help to distinguish  
354 among different mucocutaneous reactions and guide subsequent treatment.  
355 The safety of readministration of RITUXAN to patients with any of these  
356 mucocutaneous reactions has not been determined.

357 **Bowel Obstruction and Perforation**

358 Abdominal pain, bowel obstruction and perforation, in some cases leading  
359 to death, were observed in patients receiving RITUXAN in combination

360 with chemotherapy for DLBCL. In post-marketing reports, which include  
361 both patients with low-grade or follicular NHL and DLBCL, the mean  
362 time to onset of symptoms was 6 days (range 1–77) in patients with  
363 documented gastro-intestinal perforation. Complaints of abdominal pain,  
364 especially early in the course of treatment, should prompt a thorough  
365 diagnostic evaluation and appropriate treatment.

## 366 **PRECAUTIONS**

### 367 **Laboratory Monitoring**

368 Because RITUXAN targets all CD20 positive B lymphocytes, malignant  
369 and nonmalignant, complete blood counts (CBC) and platelet counts  
370 should be obtained at regular intervals during RITUXAN therapy and  
371 more frequently in patients who develop cytopenias (see [ADVERSE](#)  
372 [REACTIONS](#)). The duration of cytopenias caused by RITUXAN can  
373 extend well beyond the treatment period.

### 374 **Drug/Laboratory Interactions**

375 There have been no formal drug interaction studies performed with  
376 RITUXAN. However, renal toxicity was seen with this drug in  
377 combination with cisplatin in clinical trials. (See [WARNINGS, Renal](#).)

### 378 **Immunization**

379 The safety of immunization with live viral vaccines following RITUXAN  
380 therapy has not been studied. The ability to generate a primary or  
381 anamnestic humoral response to vaccination is currently being studied.

### 382 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

383 No long-term animal studies have been performed to establish the  
384 carcinogenic or mutagenic potential of RITUXAN, or to determine its  
385 effects on fertility in males or females. Individuals of childbearing  
386 potential should use effective contraceptive methods during treatment and  
387 for up to 12 months following RITUXAN therapy.

388 **Pregnancy Category C**

389 Animal reproduction studies have not been conducted with RITUXAN. It  
390 is not known whether RITUXAN can cause fetal harm when administered  
391 to a pregnant woman or whether it can affect reproductive capacity.

392 Human IgG is known to pass the placental barrier, and thus may  
393 potentially cause fetal B-cell depletion; therefore, RITUXAN should be  
394 given to a pregnant woman only if clearly needed.

395 **Nursing Mothers**

396 It is not known whether RITUXAN is excreted in human milk. Because  
397 human IgG is excreted in human milk and the potential for absorption and  
398 immunosuppression in the infant is unknown, women should be advised to  
399 discontinue nursing until circulating drug levels are no longer detectable.

400 (See [CLINICAL PHARMACOLOGY](#).)

401 **Pediatric Use**

402 The safety and effectiveness of RITUXAN in pediatric patients have not  
403 been established.

404 **Geriatric Use**

405 Among patients with DLBCL in three randomized, active-controlled trials,  
406 927 patients received RITUXAN in combination with chemotherapy. Of  
407 these, 396 (43%) were age 65 or greater and 123 (13%) were age 75 or  
408 greater. No overall differences in effectiveness were observed between  
409 these subjects and younger subjects. However, elderly patients were more  
410 likely to experience cardiac adverse events, mostly supraventricular  
411 arrhythmias. Serious pulmonary adverse events were also more common  
412 among the elderly, including pneumonia and pneumonitis.

413 Among the 331 patients with low-grade or follicular lymphoma enrolled in  
414 clinical studies of single agent RITUXAN, 24% were 65 to 75 years old  
415 and 5% were 75 years old and older. No overall differences in safety or  
416 effectiveness were observed between these subjects and younger subjects.

417 **ADVERSE REACTIONS**

418 Because clinical trials are conducted under widely varying conditions,  
419 adverse reaction rates observed in the clinical trials of a drug cannot be  
420 directly compared to rates in the clinical trials of another drug and may not  
421 reflect the rates observed in practice. The adverse reaction information  
422 from clinical trials does, however, provide a basis for identifying the  
423 adverse events that appear to be related to drug use and for approximating  
424 rates.

425 **The overall safety database for RITUXAN is based on clinical trial data**  
426 from 1283 patients with NHL, who received RITUXAN either as a single  
427 agent or in combination with chemotherapy. Additional safety  
428 information was obtained from post-marketing safety surveillance. The  
429 most common adverse reactions were infusion reactions (see INFUSION  
430 REACTIONS below).

431 **The following serious adverse reactions, some with fatal outcomes, have**  
432 been reported in patients treated with RITUXAN (see **BOXED**  
433 **WARNINGS** and **WARNINGS**): severe or fatal infusion reactions, tumor  
434 lysis syndrome, severe mucocutaneous reactions, hepatitis B reactivation  
435 with fulminant hepatitis, other viral infections, hypersensitivity reactions,  
436 cardiac arrhythmias, renal toxicity, bowel obstruction and perforation.

437 **Except as noted, adverse events described below occurred in the setting of**  
438 relapsed or refractory, low-grade or follicular, CD20-positive, B-cell,  
439 NHL and are based on 356 patients treated in nonrandomized, single-arm  
440 studies of RITUXAN administered as a single agent. Most patients  
441 received RITUXAN 375 mg/m<sup>2</sup> weekly for 4 doses.

442 **Infusion Reactions (See **BOXED WARNINGS** and **WARNINGS**)**

443 Mild to moderate infusion reactions consisting of fever and chills/rigors  
444 occurred in the majority of patients during the first RITUXAN infusion.  
445 Other frequent infusion reaction symptoms included nausea, pruritus,  
446 angioedema, asthenia, hypotension, headache, bronchospasm, throat

447 irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and  
448 hypertension. These reactions generally occurred within 30 to  
449 120 minutes of beginning the first infusion, and resolved with slowing or  
450 interruption of the RITUXAN infusion and with supportive care  
451 (diphenhydramine, acetaminophen, IV saline, and vasopressors. The  
452 incidence of infusion reactions was highest during the first infusion (77%)  
453 and decreased with each subsequent infusion (30% with fourth infusion  
454 and 14% with eighth infusion). Injection site pain was reported in less  
455 than 5% of patients.

456 **Infectious Events (See WARNINGS: Hepatitis B Reactivation**  
457 **with Related Fulminant Hepatitis and Other Viral Infections)**

458 RITUXAN induced B-cell depletion in 70% to 80% of patients and was  
459 associated with decreased serum immunoglobulins in a minority of  
460 patients; the lymphopenia lasted a median of 14 days (range, 1 to  
461 588 days). Infectious events occurred in 31% of patients: 19% of patients  
462 had bacterial infections, 10% had viral infections, 1% had fungal  
463 infections, and 6% were unknown infections. Incidence is not additive  
464 because a single patient may have had more than one type of infection.  
465 Serious infectious events (Grade 3 or 4), including sepsis, occurred in 2%  
466 of patients.

467 **Hematologic Events**

468 Grade 3 and 4 cytopenias were reported in 48% of patients treated with  
469 RITUXAN; these include: lymphopenia (40%), neutropenia (6%),  
470 leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median  
471 duration of lymphopenia was 14 days (range, 1 to 588 days) and of  
472 neutropenia was 13 days (range, 2 to 116 days). A single occurrence of  
473 transient aplastic anemia (pure red cell aplasia) and two occurrences of  
474 hemolytic anemia following RITUXAN therapy were reported.

475 **Pulmonary Events**

476 135 patients (38%) experienced pulmonary events in clinical trials. The  
477 most common respiratory system adverse events experienced were

478 increased cough, rhinitis, bronchospasm, dyspnea, and sinusitis. In both  
479 clinical studies and post-marketing surveillance, there have been a limited  
480 number of reports of bronchiolitis obliterans presenting up to 6 months  
481 post-RITUXAN infusion and a limited number of reports of pneumonitis  
482 (including interstitial pneumonitis) presenting up to 3 months post-  
483 RITUXAN infusion, some of which resulted in fatal outcomes. The safety  
484 of resumption or continued administration of RITUXAN in patients with  
485 pneumonitis or bronchiolitis obliterans is unknown.

#### 486 **Immunogenicity**

487 The observed incidence of antibody positivity in an assay is highly  
488 dependent on the sensitivity and specificity of the assay and may be  
489 influenced by several factors including sample handling, concomitant  
490 medications, and underlying disease. For these reasons, comparison of the  
491 incidence of antibodies to RITUXAN with the incidence of antibodies to  
492 other products may be misleading.

493 In clinical studies of patients with low-grade or follicular NHL receiving  
494 single-agent RITUXAN, human antichimeric antibody (HACA) was  
495 detected in 4 of 356 (1.1%) patients and 3 had an objective clinical  
496 response. These data reflect the percentage of patients whose test results  
497 were considered positive for antibodies to RITUXAN using an enzyme-  
498 linked immunosorbant assay (limit of detection = 7 ng/mL).

#### 499 **Single Agent RITUXAN for Relapsed or Refractory, Low-Grade 500 or Follicular, CD20-Positive, B-Cell, NHL**

501 Study subjects ranged from 22 to 81 years of age. Sixty percent were  
502 male; 93% were Caucasian, 1% were African American, 2% were  
503 Hispanic, 2% were Asian, and 2% were from other racial groups.

504 [Table 4](#) lists the most common, as well as Grade 3 and 4, adverse events  
505 observed.

**Table 4**  
 Incidence of Adverse Events in  $\geq 5\%$  of Patients  
 with Relapsed or Refractory, Low-Grade or Follicular  
 NHL, Receiving Single-agent RITUXAN (N=356)<sup>a,b</sup>

|  | All Grades (%) | Grade 3 and 4 (%) |
|--|----------------|-------------------|
| Any Adverse Events                         | 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>Cardiovascular System</u>               | 25             | 3                 |
| Hypotension                                | 10             | 1                 |
| Hypertension                               | 6              | 1                 |
| <u>Digestive System</u>                    | 37             | 2                 |
| Nausea                                     | 23             | 1                 |
| Diarrhea                                   | 10             | 1                 |
| Vomiting                                   | 10             | 1                 |
| <u>Hemic and Lymphatic System</u>          | 67             | 48                |
| Lymphopenia                                | 48             | 40                |
| Leukopenia                                 | 14             | 4                 |
| Neutropenia                                | 14             | 6                 |
| Thrombocytopenia                           | 12             | 2                 |
| Anemia                                     | 8              | 3                 |
| <u>Metabolic and Nutritional Disorders</u> | 38             | 3                 |
| Angioedema                                 | 11             | 1                 |
| Hyperglycemia                              | 9              | 1                 |
| Peripheral Edema                           | 8              | 0                 |
| LDH Increase                               | 7              | 0                 |

**Table 4 (cont'd)**  
 Incidence of Adverse Events in  $\geq 5\%$  of Patients  
 with Relapsed or Refractory, Low-Grade or Follicular  
 NHL, Receiving Single-agent RITUXAN (N=356)<sup>a,b</sup>

|                               | All Grades (%) | Grade 3 and 4 (%) |
|-------------------------------|----------------|-------------------|
| <u>Musculoskeletal System</u> | 26             | 3                 |
| Myalgia                       | 10             | 1                 |
| Arthralgia                    | 10             | 1                 |
| <u>Nervous System</u>         | 32             | 1                 |
| Dizziness                     | 10             | 1                 |
| Anxiety                       | 5              | 1                 |
| <u>Respiratory System</u>     | 38             | 4                 |
| Increased Cough               | 13             | 1                 |
| Rhinitis                      | 12             | 1                 |
| Bronchospasm                  | 8              | 1                 |
| Dyspnea                       | 7              | 1                 |
| Sinusitis                     | 6              | 0                 |
| <u>Skin and Appendages</u>    | 44             | 2                 |
| Night Sweats                  | 15             | 1                 |
| Rash                          | 15             | 1                 |
| Pruritus                      | 14             | 1                 |
| Urticaria                     | 8              | 1                 |

<sup>a</sup> Adverse Events observed up to 12 months following RITUXAN.

<sup>b</sup> Adverse Events graded for severity by NCI-CTC criteria (19).

507

508 **Risk Factors Associated with Increased Rates of Adverse**  
 509 **Events**

510 Administration of RITUXAN weekly for 8 doses resulted in higher rates  
 511 of Grade 3 and 4 adverse events (14) overall (70%) compared with  
 512 administration weekly for 4 doses (57%). The incidence of Grade 3 or 4  
 513 adverse events was similar in patients retreated with RITUXAN compared  
 514 with initial treatment (58% and 57%, respectively). The incidence of the  
 515 following clinically significant adverse events was higher in patients with  
 516 bulky disease (lesions  $\geq 10$  cm) (N=39) versus patients with lesions  
 517  $< 10$  cm (N=195): abdominal pain, anemia, dyspnea, hypotension, and  
 518 neutropenia.

519 **RITUXAN in Combination with Chemotherapy for DLBCL**

520 Except as noted, adverse events described in the setting of DLBCL are  
521 based on three randomized, active-controlled clinical trials in which  
522 927 patients received RITUXAN in combination with chemotherapy and  
523 802 received chemotherapy alone. Detailed safety data collection was  
524 primarily limited to Grade 3 and 4 adverse events and serious adverse  
525 events.

526 The population varied from 18 to 92 years of age and 55% were male;  
527 racial distribution was collected only for Study 1 (see **CLINICAL**  
528 **STUDIES** section) where 90% of patients were Caucasian, 5% were  
529 African American, 3% were Hispanic and 2% were from other racial  
530 groups. Patients received 4–8 doses of RITUXAN at 375 mg/m<sup>2</sup>.

531 The following adverse events, regardless of severity, were reported more  
532 frequently (≥5%) in patients age ≥60 years receiving R-CHOP as  
533 compared to CHOP alone: cardiac disorder (29% vs. 21%), pyrexia  
534 (56% vs. 46%), chills (13% vs. 4%) and lung disorder (31% vs. 24%).  
535 In one of these studies (Study 2), more detailed assessment of cardiac  
536 toxicity revealed that supraventricular arrhythmias or tachycardia  
537 accounted for most of the difference in cardiac disorders, with  
538 4.5% vs. 1.0% incidences for R-CHOP and CHOP, respectively.

539 The following Grade 3 or 4 adverse events were reported more frequently  
540 among patients in the R-CHOP arm compared with those in the CHOP  
541 arm: thrombocytopenia (9% vs. 7%) and lung disorder (6% vs. 3%).  
542 Other severe adverse events reported more commonly among patients  
543 receiving R-CHOP in one or more studies were viral infection,  
544 neutropenia and anemia.

545 **Post-Marketing Reports**

546 The following adverse reactions have been identified during post-approval  
547 use of RITUXAN. Because these reactions are reported voluntarily from a  
548 population of uncertain size, it is not always possible to reliably estimate

549 their frequency or establish a causal relationship to drug exposure.  
550 Decisions to include these reactions in labeling are typically based on one  
551 or more of the following factors: (1) seriousness of the reaction,  
552 (2) frequency of reporting, or (3) strength of causal connection to  
553 RITUXAN.

554 *Hematologic:* prolonged pancytopenia, marrow hypoplasia, and late onset  
555 neutropenia, hyperviscosity syndrome in Waldenstrom's  
556 macroglobulinemia.

557 *Cardiac:* fatal cardiac failure.

558 *Immune/Autoimmune Events:* uveitis, optic neuritis, systemic vasculitis,  
559 pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis and  
560 vasculitis with rash.

561 *Infection:* increased in fatal infections in HIV-associated lymphoma.

562 *Skin:* severe mucocutaneous reactions

563 *Gastrointestinal:* bowel obstruction and perforation

## 564 **OVERDOSAGE**

565 There has been no experience with overdosage in human clinical trials.  
566 Single doses of up to 500 mg/m<sup>2</sup> have been given in dose-escalating  
567 clinical trials (9).

## 568 **DOSAGE AND ADMINISTRATION**

### 569 **Relapsed or Refractory, Low-Grade or Follicular,** 570 **CD20-Positive, B-Cell, Non-Hodgkin's Lymphoma**

571 The recommended dose of RITUXAN is 375 mg/m<sup>2</sup> IV infusion once  
572 weekly for 4 or 8 doses.

### 573 **Retreatment Therapy**

574 The recommended dose of RITUXAN is 375 mg/m<sup>2</sup> IV infusion once  
575 weekly for 4 doses in responding patients who develop progressive disease

576 after previous RITUXAN therapy. Currently there are limited data  
577 concerning more than 2 courses.

### 578 **Diffuse Large B-Cell NHL**

579 The recommended dose of RITUXAN is 375 mg/m<sup>2</sup> IV per infusion given  
580 on Day 1 of each cycle of chemotherapy for up to 8 infusions.

### 581 **RITUXAN as a Component of Zevalin™ (Ibritumomab Tiuxetan)** 582 **Therapeutic Regimen**

583 As a required component of the Zevalin therapeutic regimen, RITUXAN  
584 250 mg/m<sup>2</sup> should be infused within 4 hours prior to the administration of  
585 Indium-111- (In-111-) Zevalin and within 4 hours prior to the  
586 administration of Yttrium90- (Y-90-) Zevalin. Administration of  
587 RITUXAN and In-111-Zevalin should precede RITUXAN and  
588 Y-90-Zevalin by 7–9 days. Refer to the Zevalin package insert for full  
589 prescribing information regarding the Zevalin therapeutic regimen.

590 RITUXAN may be administered in an outpatient setting. **DO NOT**  
591 **ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.**  
592 (See [Administration.](#))

### 593 **Instructions for Administration**

#### 594 Preparation for Administration

595 Use appropriate aseptic technique. Withdraw the necessary amount of  
596 RITUXAN and dilute to a final concentration of 1 to 4 mg/mL into an  
597 infusion bag containing either 0.9% Sodium Chloride, USP, or  
598 5% Dextrose in Water, USP. Gently invert the bag to mix the solution.  
599 Discard any unused portion left in the vial. Parenteral drug products  
600 should be inspected visually for particulate matter and discoloration prior  
601 to administration.

602 RITUXAN solutions for infusion may be stored at 2–8°C (36–46°F) for  
603 24 hours. RITUXAN solutions for infusion have been shown to be stable  
604 for an additional 24 hours at room temperature. However, since  
605 RITUXAN solutions do not contain a preservative, diluted solutions

606 should be stored refrigerated (2–8°C). No incompatibilities between  
607 RITUXAN and polyvinylchloride or polyethylene bags have been  
608 observed.

609 **Administration: DO NOT ADMINISTER AS AN INTRAVENOUS**  
610 **PUSH OR BOLUS**

611 Infusion and hypersensitivity reactions may occur (see [BOXED](#)  
612 [WARNINGS](#), [WARNINGS](#), and [ADVERSE REACTIONS](#)).

613 Premedication consisting of acetaminophen and diphenhydramine should  
614 be considered before each infusion of RITUXAN. Premedication may  
615 attenuate infusion reactions. Since transient hypotension may occur  
616 during RITUXAN infusion, consideration should be given to withholding  
617 antihypertensive medications 12 hours prior to RITUXAN infusion.

618 **First Infusion**

619 The RITUXAN solution for infusion should be administered intravenously  
620 at an initial rate of 50 mg/hr. RITUXAN should not be mixed or diluted  
621 with other drugs. If hypersensitivity or infusion reactions do not occur,  
622 escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a  
623 maximum of 400 mg/hr. If a hypersensitivity (non-IgE-mediated) or an  
624 infusion reaction develops, the infusion should be temporarily slowed or  
625 interrupted (see [BOXED WARNINGS](#) and [WARNINGS](#)). The infusion  
626 can continue at one-half the previous rate upon improvement of patient  
627 symptoms.

628 **Subsequent Infusions**

629 If the patient tolerated the first infusion well, subsequent RITUXAN  
630 infusions can be administered at an initial rate of 100 mg/hr, and increased  
631 by 100 mg/hr increments at 30-minute intervals, to a maximum of  
632 400 mg/hr as tolerated. If the patient did not tolerate the first infusion  
633 well, follow the guidelines under First Infusion.

634 **Stability and Storage**

635 RITUXAN vials are stable at 2–8°C (36–46°F). Do not use beyond  
636 expiration date stamped on carton. RITUXAN vials should be protected  
637 from direct sunlight. Do not freeze or shake. Refer to the “Preparation  
638 and Administration” section for information on the stability and storage of  
639 solutions of RITUXAN diluted for infusion.

640 **HOW SUPPLIED**

641 RITUXAN<sup>®</sup> (Rituximab) is supplied as 100 mg and 500 mg of sterile,  
642 preservative-free, single-use vials.

643 Single unit 100 mg carton: Contains one 10 mL vial of RITUXAN  
644 (10 mg/mL).

645 NDC 50242-051-21

646 Single unit 500 mg carton: Contains one 50 mL vial of RITUXAN  
647 (10 mg/mL).

648 NDC 50242-053-06

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**Genentech, Inc.**

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