

1 RITUXAN®

2 Rituximab

3

4 **WARNINGS**

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

12

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

15

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

19

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

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24

25 **DESCRIPTION**

26 The RITUXAN<sup>®</sup> (Rituximab) antibody is a genetically engineered chimeric  
27 murine/human monoclonal antibody directed against the CD20 antigen  
28 found on the surface of normal and malignant B lymphocytes. The  
29 antibody is an IgG<sub>1</sub> kappa immunoglobulin containing murine light- and  
30 heavy-chain variable region sequences and human constant region  
31 sequences. Rituximab is composed of two heavy chains of 451 amino  
32 acids and two light chains of 213 amino acids (based on cDNA analysis)  
33 and has an approximate molecular weight of 145 kD. Rituximab has a  
34 binding affinity for the CD20 antigen of approximately 8.0 nM.

35

36 The chimeric anti-CD20 antibody is produced by mammalian cell  
37 (Chinese Hamster Ovary) suspension culture in a nutrient medium  
38 containing the antibiotic gentamicin. Gentamicin is not detectable in the  
39 final product. The anti-CD20 antibody is purified by affinity and ion  
40 exchange chromatography. The purification process includes specific  
41 viral inactivation and removal procedures. Rituximab drug product is  
42 manufactured from either bulk drug substance manufactured by  
43 Genentech, Inc. (US License No. 1048) or utilizing formulated bulk  
44 Rituximab supplied by IDEC Pharmaceuticals Corporation (US License  
45 No. 1235) under a shared manufacturing arrangement.

46

47 RITUXAN is a sterile, clear, colorless, preservative-free liquid concentrate  
48 for intravenous (IV) administration. RITUXAN is supplied at a  
49 concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL)  
50 single-use vials. The product is formulated for IV administration in  
51 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate,  
52 0.7 mg/mL polysorbate 80, and Sterile Water for Injection. The pH is  
53 adjusted to 6.5.

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## 55 **CLINICAL PHARMACOLOGY**

### 56 **General**

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

68

### 69 **Preclinical Pharmacology and Toxicology**

70 Mechanism of Action: The Fab domain of Rituximab binds to the CD20  
71 antigen on B lymphocytes, and the Fc domain recruits immune effector  
72 functions to mediate B-cell lysis *in vitro*. Possible mechanisms of cell lysis  
73 include complement-dependent cytotoxicity (CDC)<sup>7</sup> and  
74 antibody-dependent cell mediated cytotoxicity (ADCC). The antibody has  
75 been shown to induce apoptosis in the DHL-4 human B-cell lymphoma  
76 line.<sup>8</sup>

77

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

82

### 83 **Human Pharmacokinetics/Pharmacodynamics**

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

93

94 RITUXAN at a dose of  $375 \text{ mg/m}^2$  was administered as an IV infusion at  
95 weekly intervals for 4 doses to 203 patients naive to RITUXAN. The  
96 mean  $C_{\text{max}}$  following the fourth infusion was  $486 \text{ } \mu\text{g/mL}$  (range,  
97  $77.5$  to  $996.6 \text{ } \mu\text{g/mL}$ ). The peak and trough serum levels of Rituximab  
98 were inversely correlated with baseline values for the number of  
99 circulating CD20 positive B cells and measures of disease burden.

100 Median steady-state serum levels were higher for responders compared  
101 with nonresponders; however, no difference was found in the rate of  
102 elimination as measured by serum half-life. Serum levels were higher in  
103 patients with International Working Formulation (IWF) subtypes B, C, and  
104 D as compared with those with subtype A. Rituximab was detectable in  
105 the serum of patients 3 to 6 months after completion of treatment.

106

107 RITUXAN at a dose of  $375 \text{ mg/m}^2$  was administered as an IV infusion at  
108 weekly intervals for 8 doses to 37 patients. The mean  $C_{\text{max}}$  after 8  
109 infusions was  $550 \text{ } \mu\text{g/mL}$  (range,  $171$  to  $1177 \text{ } \mu\text{g/mL}$ ). The mean  $C_{\text{max}}$   
110 increased with each successive infusion through the eighth infusion  
111 (Table 1).

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

Infusion Number	Mean C <sub>max</sub> µg/mL	Range 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

115

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

119

120 Administration of RITUXAN resulted in a rapid and sustained depletion of  
121 circulating and tissue-based B cells. Lymph node biopsies performed  
122 14 days after therapy showed a decrease in the percentage of B cells in  
123 seven of eight patients who had received single doses of Rituximab  
124  $\geq 100$  mg/m<sup>2</sup>.<sup>9</sup> Among the 166 patients in the pivotal study, circulating  
125 B cells (measured as CD19-positive cells) were depleted within the first  
126 three doses with sustained depletion for up to 6 to 9 months post-  
127 treatment in 83% of patients. Of the responding patients assessed  
128 (n = 80), 1% failed to show significant depletion of CD19-positive cells  
129 after the third infusion of Rituximab as compared to 19% of the  
130 nonresponding patients. B-cell recovery began at approximately 6 months

131 following completion of treatment. Median B-cell levels returned to normal  
132 by 12 months following completion of treatment.

133

134 There were sustained and statistically significant reductions in both IgM  
135 and IgG serum levels observed from 5 through 11 months following  
136 Rituximab administration. However, only 14% of patients had reductions  
137 in IgM and/or IgG serum levels, resulting in values below the normal  
138 range.

139

#### 140 **CLINICAL STUDIES**

141 Studies with a collective enrollment of 296 patients having relapsed or  
142 refractory low-grade or follicular B-cell NHL are described below (Table 2).  
143 RITUXAN regimens tested include treatment weekly for 4 doses and  
144 treatment weekly for 8 doses. Clinical settings studied were initial  
145 treatment, initial treatment of bulky disease, and retreatment.

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**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.)**

	<b>Initial, Weekly x 4 N = 166</b>	<b>Initial, Weekly x 8 N = 37</b>	<b>Initial, Bulky, Weekly x 4 N = 39<sup>1</sup></b>	<b>Retreatment, Weekly x 4 N = 60</b>
Overall Response Rate	48%	57%	36%	38%
Complete Response Rate	6%	14%	3%	10%
Median Duration Of Response <sup>2,3,4</sup> (Months) [Range]	11.2 [1.9 to 42.1+]	13.4 [2.5 to 36.5+]	6.9 [2.8 to 25.0+]	15.0 [3.0 to 25.1+]

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<sup>1</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>2</sup> Kaplan-Meier projected with observed range.

<sup>3</sup> "+" indicates an ongoing response.

<sup>4</sup> Duration of response: interval from the onset of response to disease progression.

**158 Initial Treatment, Weekly for 4 doses**

159 A multicenter, open-label, single-arm study was conducted in 166 patients  
160 with relapsed or refractory low-grade or follicular B-cell NHL who received  
161 375 mg/m<sup>2</sup> of RITUXAN given as an IV infusion weekly for 4 doses.<sup>13</sup>

162 Patients with tumor masses >10 cm or with >5,000 lymphocytes/ $\mu$ L in the  
163 peripheral blood were excluded from the study. The overall response rate  
164 (ORR) was 48% with 6% complete response (CR) and 42% partial  
165 response (PR) rates. The median time to onset of response was 50 days  
166 and the median duration of response was 11.2 months (range,

167 1.9 to 42.1+). Disease-related signs and symptoms (including  
168 B-symptoms) were present in 23% (39/166) of patients at study entry and  
169 resolved in 64% (25/39) of those patients.

170

171 In a multivariate analysis, the ORR was higher in patients with IWF B, C,  
172 and D histologic subtypes as compared to IWF subtype A (58% vs. 12%),  
173 higher in patients whose largest lesion was <5 cm vs. >7 cm (maximum,  
174 21 cm) in greatest diameter (53% vs. 38%), and higher in patients with  
175 chemosensitive relapse as compared with chemoresistant (defined as  
176 duration of response <3 months) relapse (53% vs. 36%). ORR in patients  
177 previously treated with autologous bone marrow transplant was 78%  
178 (18/23). The following adverse prognostic factors were *not* associated  
179 with a lower response rate: age  $\geq$ 60 years, extranodal disease, prior  
180 anthracycline therapy, and bone marrow involvement.

181

#### 182 **Initial Treatment, Weekly for 8 Doses**

183 In a multicenter, single-arm study, 37 patients with relapsed or refractory,  
184 low-grade NHL received 375 mg/m<sup>2</sup> of RITUXAN weekly for 8 doses. The  
185 ORR was 57% (CR 14%, PR 43%) with a projected median duration of  
186 response of 13.4 months (range, 2.5 to 36.5+).<sup>14</sup> (For information on the  
187 higher incidence of Grade 3 and 4 adverse events, see ADVERSE  
188 REACTIONS, Risk Factors Associated with Increased Rates of Adverse  
189 Events.)

190

191 **Initial Treatment, Bulky Disease, Weekly for 4 Doses**

192 In pooled data from multiple studies of RITUXAN, 39 patients with  
193 relapsed or refractory, bulky disease (single lesion >10 cm in diameter),  
194 low-grade NHL received 375 mg/m<sup>2</sup> of RITUXAN weekly for 4 doses. The  
195 ORR was 36% (CR 3%, PR 33%) with a median duration of response of  
196 6.9 months (range 2.8 to 25.0+). (For information on the higher incidence  
197 of Grade 3 and 4 adverse events, see ADVERSE REACTIONS, Risk  
198 Factors Associated with Increased Rates of Adverse Events.)

199

200 **Retreatment, Weekly for 4 Doses**

201 In a multi-center, single-arm study, 60 patients received 375 mg/m<sup>2</sup> of  
202 RITUXAN weekly for 4 doses.<sup>15</sup> All patients had relapsed or refractory,  
203 low-grade or follicular B-cell NHL and had achieved an objective clinical  
204 response to a prior course of RITUXAN. Of these 60 patients, 55  
205 received their second course of RITUXAN, 3 patients received their third  
206 course and 2 patients received their second and third courses of  
207 RITUXAN in this study. The ORR was 38% (10% CR and 28% PR) with a  
208 projected median duration of response of 15 months (range, 3.0 to 25.1+  
209 months).

210

211 **INDICATIONS AND USAGE**

212 RITUXAN is indicated for the treatment of patients with relapsed or  
213 refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's  
214 lymphoma.

215

216 **CONTRAINDICATIONS**

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

220

221 **WARNINGS (See BOXED WARNINGS.)**

222 **Severe Infusion Reactions (See BOXED WARNINGS, ADVERSE**

223 **REACTIONS and Hypersensitivity Reactions):** RITUXAN has caused

224 severe infusion reactions. In some cases, these reactions were fatal.

225 These severe reactions typically occurred during the first infusion with

226 time to onset of 30 to 120 minutes. Signs and symptoms of severe

227 infusion reactions may include hypotension, angioedema, hypoxia or

228 bronchospasm, and may require interruption of RITUXAN administration.

229 The most severe manifestations and sequelae include pulmonary

230 infiltrates, acute respiratory distress syndrome, myocardial infarction,

231 ventricular fibrillation, and cardiogenic shock. In the reported cases, the

232 following factors were more frequently associated with fatal outcomes:

233 female gender, pulmonary infiltrates, and chronic lymphocytic leukemia or  
234 mantle cell lymphoma.

235

236 *Management of severe infusion reactions:* The RITUXAN infusion should  
237 be interrupted for severe reactions and supportive care measures  
238 instituted as medically indicated (e.g., intravenous fluids, vasopressors,  
239 oxygen, bronchodilators, diphenhydramine, and acetaminophen). In most  
240 cases, the infusion can be resumed at a 50% reduction in rate (e.g., from  
241 100 mg/hr to 50 mg/hr) when symptoms have completely resolved.

242 Patients requiring close monitoring during first and all subsequent  
243 infusions include those with pre-existing cardiac and pulmonary  
244 conditions, those with prior clinically significant cardiopulmonary adverse  
245 events and those with high numbers of circulating malignant cells  
246 ( $\geq 25,000/\text{mm}^3$ ) with or without evidence of high tumor burden.

247

248 **Tumor Lysis Syndrome [TLS] (See BOXED WARNINGS and**  
249 **ADVERSE REACTIONS):** Rapid reduction in tumor volume followed by  
250 acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or  
251 hyperphosphatasemia, have been reported within 12 to 24 hours after the  
252 first RITUXAN infusion. Rare instances of fatal outcome have been  
253 reported in the setting of TLS following treatment with RITUXAN. The  
254 risks of TLS appear to be greater in patients with high numbers of  
255 circulating malignant cells ( $\geq 25,000/\text{mm}^3$ ) or high tumor burden.

256 Prophylaxis for TLS should be considered for patients at high risk.  
257 Correction of electrolyte abnormalities, monitoring of renal function and  
258 fluid balance, and administration of supportive care, including dialysis,  
259 should be initiated as indicated. Following complete resolution of the  
260 complications of TLS, RITUXAN has been tolerated when re-administered  
261 in conjunction with prophylactic therapy for TLS in a limited number of  
262 cases.

263

264 **Hypersensitivity Reactions:**

265 RITUXAN has been associated with hypersensitivity reactions (non-IgE-  
266 mediated reactions) which may respond to adjustments in the infusion  
267 rate and in medical management. Hypotension, bronchospasm, and  
268 angioedema have occurred in association with RITUXAN infusion (see  
269 Severe Infusion Reactions). RITUXAN infusion should be interrupted for  
270 severe hypersensitivity reactions and can be resumed at a 50% reduction  
271 in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have  
272 completely resolved. Treatment of these symptoms with  
273 diphenhydramine and acetaminophen is recommended; additional  
274 treatment with bronchodilators or IV saline may be indicated. In most  
275 cases, patients who have experienced non-life-threatening  
276 hypersensitivity reactions have been able to complete the full course of  
277 therapy. (See DOSAGE and ADMINISTRATION.) Medications for the  
278 treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines

279 and corticosteroids, should be available for immediate use in the event of  
280 a reaction during administration.

281

282 **Cardiovascular:**

283 Infusions should be discontinued in the event of serious or life-threatening  
284 cardiac arrhythmias. Patients who develop clinically significant  
285 arrhythmias should undergo cardiac monitoring during and after  
286 subsequent infusions of RITUXAN. Patients with pre-existing cardiac  
287 conditions including arrhythmias and angina have had recurrences of  
288 these events during RITUXAN therapy and should be monitored  
289 throughout the infusion and immediate post-infusion period.

290

291 **Renal:**

292 RITUXAN administration has been associated with severe renal toxicity  
293 including acute renal failure requiring dialysis and in some cases, has led  
294 to a fatal outcome. Renal toxicity has occurred in patients with high  
295 numbers of circulating malignant cells ( $>25,000/\text{mm}^3$ ) or high tumor  
296 burden who experience tumor lysis syndrome (see Tumor Lysis  
297 Syndrome) and in patients administered concomitant cisplatin therapy  
298 during clinical trials. The combination of cisplatin and RITUXAN is not an  
299 approved treatment regimen. If this combination is used in clinical trials  
300 *extreme caution* should be exercised; patients should be monitored

301 closely for signs of renal failure. Discontinuation of RITUXAN should be  
302 considered for those with rising serum creatinine or oliguria.

303

304 **Severe Mucocutaneous Reactions (See BOXED WARNINGS and**  
305 **ADVERSE REACTIONS):**

306 Mucocutaneous reactions, some with fatal outcome, have been reported  
307 in patients treated with RITUXAN. These reports include paraneoplastic  
308 pemphigus (an uncommon disorder which is a manifestation of the  
309 patient's underlying malignancy),<sup>16</sup> Stevens-Johnson syndrome, lichenoid  
310 dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The  
311 onset of the reaction in the reported cases has varied from 1 to 13 weeks  
312 following RITUXAN exposure. Patients experiencing a severe  
313 mucocutaneous reaction should not receive any further infusions and  
314 seek prompt medical evaluation. Skin biopsy may help to distinguish  
315 among different mucocutaneous reactions and guide subsequent  
316 treatment. The safety of readministration of RITUXAN to patients with  
317 any of these mucocutaneous reactions has not been determined.

318

319 **PRECAUTIONS**

320 **Laboratory Monitoring:** Because RITUXAN targets all CD20-positive B  
321 lymphocytes, malignant and nonmalignant, complete blood counts (CBC)  
322 and platelet counts should be obtained at regular intervals during  
323 RITUXAN therapy and more frequently in patients who develop

324 cytopenias (see ADVERSE REACTIONS). The duration of cytopenias  
325 caused by RITUXAN can extend well beyond the treatment period.

326

327 **Drug/Laboratory Interactions:** There have been no formal drug  
328 interaction studies performed with RITUXAN. However, renal toxicity was  
329 seen with this drug in combination with cisplatin in clinical trials. (See  
330 WARNINGS, Renal.)

331

332 **HACA Formation:** Human antichimeric antibody (HACA) was detected in  
333 4 of 356 patients and 3 had an objective clinical response. The data  
334 reflect the percentage of patients whose test results were considered  
335 positive for antibodies to RITUXAN using an enzyme-linked  
336 immunosorbant assay (limit of detection = 7 ng/mL). The observed  
337 incidence of antibody positivity in an assay is highly dependent on the  
338 sensitivity and specificity of the assay and may be influenced by several  
339 factors including sample handling, concomitant medications, and  
340 underlying disease. For these reasons, comparison of the incidence of  
341 antibodies to RITUXAN with the incidence of antibodies to other products  
342 may be misleading.

343

344 **Immunization:** The safety of immunization with live viral vaccines  
345 following RITUXAN therapy has not been studied. The ability to generate

346 a primary or anamnestic humoral response to vaccination is currently  
347 being studied.

348

349 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No long-term  
350 animal studies have been performed to establish the carcinogenic or  
351 mutagenic potential of RITUXAN, or to determine its effects on fertility in  
352 males or females. Individuals of childbearing potential should use  
353 effective contraceptive methods during treatment and for up to 12 months  
354 following RITUXAN therapy.

355

356 **Pregnancy Category C:** Animal reproduction studies have not been  
357 conducted with RITUXAN. It is not known whether RITUXAN can cause  
358 fetal harm when administered to a pregnant woman or whether it can  
359 affect reproductive capacity. Human IgG is known to pass the placental  
360 barrier, and thus may potentially cause fetal B-cell depletion; therefore,  
361 RITUXAN should be given to a pregnant woman only if clearly needed.

362

363 **Nursing Mothers:** It is not known whether RITUXAN is excreted in  
364 human milk. Because human IgG is excreted in human milk and the  
365 potential for absorption and immunosuppression in the infant is unknown,  
366 women should be advised to discontinue nursing until circulating drug  
367 levels are no longer detectable. (See CLINICAL PHARMACOLOGY.)

368

369 **Pediatric Use:** The safety and effectiveness of RITUXAN in pediatric  
370 patients have not been established.

371

372 **Geriatric Use:** Among the 331 patients enrolled in clinical studies of  
373 single agent RITUXAN, 24% were 65 to 75 years old and 5% were 75  
374 years old and older. The overall response rates were higher in older (age  
375  $\geq 65$  years) vs. younger (age  $< 65$  years) patients (52% vs. 44%,  
376 respectively). However, the median duration of response, based on  
377 Kaplan-Meier estimates, was shorter in older vs. younger patients:  
378 10.1 months (range, 1.9 to 36.5+) vs. 11.4 months (range, 2.1 to 42.1+),  
379 respectively. This shorter duration of response was not statistically  
380 significant. Adverse reactions, including incidence, severity and type of  
381 adverse reaction were similar between older and younger patients.

382

### 383 **ADVERSE REACTIONS**

384 The most serious adverse reactions caused by RITUXAN include infusion  
385 reactions, tumor lysis syndrome, mucocutaneous reactions,  
386 hypersensitivity reactions, cardiac arrhythmias and angina, and renal  
387 failure. Please refer to the BOXED WARNINGS and WARNINGS  
388 sections for detailed descriptions of these reactions. Infusion reactions  
389 and lymphopenia are the most commonly occurring adverse reactions.

390

391 Because clinical trials are conducted under widely varying conditions,  
392 adverse reaction rates observed in the clinical trials of a drug cannot be  
393 directly compared to rates in the clinical trials of another drug and may not  
394 reflect the rates observed in practice. The adverse reaction information  
395 from clinical trials does, however, provide a basis for identifying the  
396 adverse events that appear to be related to drug use and for  
397 approximating rates.

398

399 Additional adverse reactions have been identified during postmarketing  
400 use of RITUXAN. Because these reactions are reported voluntarily from a  
401 population of uncertain size, it is not always possible to reliably estimate  
402 their frequency or establish a causal relationship to RITUXAN exposure.  
403 Decisions to include these reactions in labeling are typically based on one  
404 or more of the following factors: (1) seriousness of the reaction, (2)  
405 frequency of reporting, or (3) strength of causal connection to RITUXAN.

406

407 Where specific percentages are noted, these data are based on 356  
408 patients treated in nonrandomized, single-arm studies of RITUXAN  
409 administered as a single agent. Most patients received RITUXAN  
410 375 mg/m<sup>2</sup> weekly for 4 doses. These include 39 patients with bulky  
411 disease (lesions  $\geq$  10 cm) and 60 patients who received more than 1  
412 course of RITUXAN. Thirty-seven patients received 375 mg/m<sup>2</sup> for 8  
413 doses and 25 patients received doses other than 375 mg/m<sup>2</sup> for 4 doses

414 and up to 500 mg/m<sup>2</sup> single dose in the Phase 1 setting. Adverse events  
415 of greater severity are referred to as "Grade 3 and 4 events" defined by  
416 the commonly used National Cancer Institute Common Toxicity Criteria.<sup>17</sup>