

AUG 22 2007

1 **1.14.2.3 Final Labeling Text**2 **Rituxan®**
3 **(Rituximab)**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 Patients who develop severe infusion reactions should have Rituxan
13 infusion discontinued and receive medical treatment.

14 **Tumor Lysis Syndrome (TLS):** Acute renal failure requiring dialysis
15 with instances of fatal outcome has been reported in the setting of TLS
16 following treatment of non-Hodgkin's lymphoma (NHL) patients with
17 Rituxan. (See **WARNINGS**.)

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

21 **Progressive Multifocal Leukoencephalopathy (PML):** JC virus
22 infection resulting in PML and death has been reported in patients treated
23 with Rituxan. (See **WARNINGS** and **ADVERSE REACTIONS**.)

24 **DESCRIPTION**

25 The Rituxan® (Rituximab) antibody is a genetically engineered chimeric
26 murine/human monoclonal antibody directed against the CD20 antigen
27 found on the surface of normal and malignant B lymphocytes. The
28 antibody is an IgG₁ kappa immunoglobulin containing murine light- and
29 heavy-chain variable region sequences and human constant region

30 sequences. Rituximab is composed of two heavy chains of 451 amino
31 acids and two light chains of 213 amino acids (based on cDNA analysis)
32 and has an approximate molecular weight of 145 kD. Rituximab has a
33 binding affinity for the CD20 antigen of approximately 8.0 nM.

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

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

48 **CLINICAL PHARMACOLOGY**

49 **General**

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

61 B-cells are believed to play a role in the pathogenesis of rheumatoid
62 arthritis (RA) and associated chronic synovitis. In this setting, B-cells
63 may be acting at multiple sites in the autoimmune/inflammatory process,
64 including through production of rheumatoid factor (RF) and other
65 autoantibodies, antigen presentation, T cell activation, and/or
66 pro-inflammatory cytokine production.⁷

67 **Preclinical Pharmacology and Toxicology**

68 Mechanism of Action: The Fab domain of Rituximab binds to the
69 CD20 antigen on B lymphocytes, and the Fc domain recruits immune
70 effector functions to mediate B-cell lysis *in vitro*. Possible mechanisms of
71 cell lysis include complement-dependent cytotoxicity (CDC)⁸ and
72 antibody-dependent cell mediated cytotoxicity (ADCC). The antibody has
73 been shown to induce apoptosis in the DHL-4 human B-cell lymphoma
74 line.⁹

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

79 **Pharmacokinetics**

80 In patients with NHL given single doses at 10, 50, 100, 250 or 500 mg/m²
81 as an IV infusion, serum levels and the half-life of Rituximab were
82 proportional to dose.¹⁰ In 14 patients given 375 mg/m² as an IV infusion
83 for 4 weekly doses, the mean serum half-life was 76.3 hours (range,
84 31.5 to 152.6 hours) after the first infusion and 205.8 hours (range, 83.9 to
85 407.0 hours); after the fourth infusion.^{11, 12, 13} The wide range of half-lives
86 may reflect the variable tumor burden among patients and the changes in
87 CD20-positive (normal and malignant) B-cell populations upon repeated
88 administrations.

89 Rituxan at a dose of 375 mg/m² was administered as an IV infusion at
90 weekly intervals for 4 doses to 203 patients with NHL naive to
91 Rituxan.^{13, 14} The mean C_{max} following the fourth infusion was 486 µg/mL

92 (range, 77.5–996.6 $\mu\text{g/mL}$). The peak and trough serum levels of
93 Rituximab were inversely correlated with baseline values for the number
94 of circulating CD20-positive B-cells and measures of disease burden.
95 Median steady-state serum levels were higher for responders compared
96 with nonresponders; however, no difference was found in the rate of
97 elimination as measured by serum half-life. Serum levels were higher in
98 patients with International Working Formulation (IWF) subtypes B, C,
99 and D as compared with those with subtype A.^{11,14} Rituximab was
100 detectable in the serum of patients 3 to 6 months after completion of
101 treatment.

102 Rituxan at a dose of 375 mg/m^2 was administered as an IV infusion at
103 weekly intervals for 8 doses to 37 patients with NHL.¹⁵ The mean C_{max}
104 after 8 infusions was $550 \mu\text{g/mL}$ (range, 171–1177 $\mu\text{g/mL}$). The mean
105 C_{max} increased with each successive infusion through the eighth infusion
106 (Table 1).

Table 1
Rituximab C_{max} Values

Infusion Number	Mean C_{max} $\mu\text{g/mL}$	Range $\mu\text{g/mL}$
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

107

108 The pharmacokinetic profile of Rituxan when administered as 6 infusions
109 of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was
110 similar to that seen with Rituxan alone.¹⁶

111 Following the administration of 2 doses of Rituximab in patients with
112 rheumatoid arthritis, the mean C_{max} values were 183 mcg/mL ($\text{CV} = 24\%$)

113 for the 2 × 500 mg dose and 370 mcg/mL (CV=25%) for the 2 × 1000 mg
114 dose, respectively. Following 2 × 1000 mg Rituximab dose, mean volume
115 of distribution at steady state was 4.3 L (CV=28%). Mean systemic
116 serum clearance of Rituximab was 0.01 L/h (CV=38%), and mean
117 terminal elimination half-life after the second dose was 19 days
118 (CV=32%).

119 **Special Populations**

120 Gender: The female patients with RA (n=86) had a 37% lower clearance
121 of Rituximab than male patients with RA (n=25). The gender difference
122 in Rituximab clearance does not necessitate any dose adjustment because
123 safety and efficacy of Rituximab do not appear to be influenced by gender.

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

127 **Pharmacodynamics**

128 Administration of Rituxan resulted in a rapid and sustained depletion of
129 circulating and tissue-based B-cells. Lymph node biopsies performed
130 14 days after therapy showed a decrease in the percentage of B-cells in
131 seven of eight patients with NHL who had received single doses of
132 Rituximab $\geq 100 \text{ mg/m}^2$.¹⁰ Among the 166 patients in the pivotal NHL
133 study, circulating B-cells (measured as CD19-positive cells) were depleted
134 within the first three doses with sustained depletion for up to 6 to 9 months
135 post-treatment in 83% of patients.¹⁴ Of the responding patients assessed
136 (n=80), 1% failed to show significant depletion of CD19-positive cells
137 after the third infusion of Rituximab as compared to 19% of the
138 nonresponding patients. B-cell recovery began at approximately 6 months
139 following completion of treatment. Median B-cell levels returned to
140 normal by 12 months following completion of treatment.¹⁴

141 There were sustained and statistically significant reductions in both IgM
142 and IgG serum levels observed from 5 through 11 months following

143 Rituximab administration. However, only 14% of patients had reductions
144 in IgM and/or IgG serum levels, resulting in values below the normal
145 range.¹⁴

146 In RA patients, treatment with Rituxan induced depletion of peripheral
147 B lymphocytes, with all patients demonstrating near complete depletion
148 within 2 weeks after receiving the first dose of Rituxan. The majority of
149 patients showed peripheral B-cell depletion for at least 6 months, followed
150 by subsequent gradual recovery after that timepoint. A small proportion
151 of patients (4%) had prolonged peripheral B-cell depletion lasting more
152 than 3 years after a single course of treatment.

153 In RA studies, total serum immunoglobulin levels, IgM, IgG, and IgA
154 were reduced at 6 months with the greatest change observed in IgM.
155 However, mean immunoglobulin levels remained within normal levels
156 over the 24-week period. Small proportions of patients experienced
157 decreases in IgM (7%), IgG (2%), and IgA (1%) levels below the lower
158 limit of normal. The clinical consequences of decreases in
159 immunoglobulin levels in RA patients treated with Rituxan are unclear.

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

165 **CLINICAL STUDIES**

166 **Relapsed or Refractory, Low-Grade or Follicular, CD-20** 167 **Positive, B-Cell NHL**

168 Rituxan regimens tested include treatment weekly for 4 doses and
169 treatment weekly for 8 doses. Results for studies with a collective
170 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)

	Study 1 Weekly × 4 N=166	Study 2 Weekly × 8 N=37	Study 1 and Study 3 Bulky disease, Weekly × 4 N=39 ^a	Study 3 Retreatment, Weekly × 4 N=60
Overall Response Rate	48%	57%	36%	38%
Complete Response Rate	6%	14%	3%	10%
Median Duration of Response ^{b, c, d} (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+]

^a Six of these patients are included in the first column. Thus, data from 296 intent to treat patients are provided in this table.

^b Kaplan-Meier projected with observed range.

^c "+" indicates an ongoing response.

^d Duration of response: interval from the onset of response to disease progression.

171

172 **Weekly for 4 Doses**

173 *Study 1*

174 A multicenter, open-label, single-arm study was conducted in 166 patients
175 with relapsed or refractory, low-grade or follicular B-cell NHL who
176 received 375 mg/m² of Rituxan given as an IV infusion weekly for
177 4 doses.¹⁴ Patients with tumor masses > 10 cm or with
178 > 5000 lymphocytes/μL in the peripheral blood were excluded from the
179 study. Results are summarized in Table 2. The median time to onset of
180 response was 50 days and the median duration of response was
181 11.2 months (range, 1.9–42.1+). Disease-related signs and symptoms
182 (including B-symptoms) were present in 23% (39/166) of patients at study
183 entry and resolved in 64% (25/39) of those patients.

184 In a multivariate analysis, the ORR was higher in patients with IWF B, C,
185 and D histologic subtypes as compared to IWF subtype A (58% vs. 12%),
186 higher in patients whose largest lesion was < 5 cm vs. > 7 cm (maximum,
187 21 cm) in greatest diameter (53% vs. 38%), and higher in patients with
188 chemosensitive relapse as compared with chemoresistant (defined as

189 duration of response <3 months) relapse (53% vs. 36%). ORR in patients
190 previously treated with autologous bone marrow transplant was 78%
191 (18/23). The following adverse prognostic factors were *not* associated
192 with a lower response rate: age \geq 60 years, extranodal disease, prior
193 anthracycline therapy, and bone marrow involvement.

194 Weekly for 8 Doses

195 *Study 2*

196 In a multicenter, single-arm study, 37 patients with relapsed or refractory,
197 low-grade NHL received 375 mg/m² of Rituxan weekly for 8 doses.
198 Results are summarized in Table 2. (See **ADVERSE REACTIONS:**
199 **Risk Factors Associated with Increased Rates of Adverse Events.**)

200 Bulky Disease, Weekly for 4 Doses

201 In pooled data (Study 1 and 3) from multiple studies of Rituxan,
202 39 patients with relapsed or refractory, bulky disease (single lesion
203 > 10 cm in diameter), low-grade NHL received 375 mg/m² of Rituxan
204 weekly for 4 doses. Results are summarized in Table 2.^{16,17} (For
205 information on the higher incidence of Grade 3 and 4 adverse events, see
206 **ADVERSE REACTIONS: Risk Factors Associated with Increased**
207 **Rates of Adverse Events.**)

208 Retreatment Weekly for 4 Doses

209 *Study 3*

210 In a multicenter, single-arm study, 60 patients received 375 mg/m² of
211 Rituxan weekly for 4 doses.¹⁸ All patients had relapsed or refractory,
212 low-grade or follicular B-cell NHL and had achieved an objective clinical
213 response to Rituxan administered 3.8–35.6 months (median 14.5 months)
214 prior to retreatment with Rituxan. Of these 60 patients, 55 received their
215 second course of Rituxan, 3 patients received their third course and
216 2 patients received their second and third courses of Rituxan in this study.
217 Results are summarized in Table 2.

218 **Previously Untreated, Follicular, CD-20 Positive, B-Cell NHL**

219 **Study 4**

220 A total of 322 patients with previously untreated follicular NHL were
221 randomized (1:1) to receive up to eight 3-week cycles of CVP
222 chemotherapy alone (CVP) or in combination with Rituxan 375 mg/m² on
223 Day 1 of each cycle (R-CVP) in an open-label, multicenter study. The
224 main outcome measure of the study was progression-free survival (PFS)
225 defined as the time from randomization to the first of progression, relapse
226 or death.

227 Twenty-six percent of the study population was >60 years of age, 99%
228 had Stage III or IV disease, and 50% had an International Prognostic
229 Index (IPI) score ≥ 2 . Of the 289 patients with available histologic
230 material for review, 95% had a centrally-confirmed diagnosis of follicular
231 (REAL follicular grade 1, 2 and 3) NHL. The results for PFS as
232 determined by a blinded, independent assessment of progression are
233 presented in Table 3. The point estimates may be influenced by the
234 presence of informative censoring. The PFS results based on investigator
235 assessment of progression were similar to those obtained by the
236 independent review assessment.

Table 3
Efficacy Results in Study 4

	Study Arm	
	CVP	R-CVP
Median PFS (years) ^a	1.4	2.4
Hazard ratio (95% CI) ^b	0.44 (0.29, 0.65)	

^a $p < 0.0001$, two-sided stratified log-rank test.

^b Estimates of Cox regression stratified by center.

237

238 **Previously Untreated, Low-Grade, CD-20 Positive, B-Cell NHL**

239 **Study 5**

240 A total of 322 patients with previously untreated low-grade, B-cell NHL
241 (IWF Grades A, B or C) who did not progress after 6 or 8 cycles of CVP

242 chemotherapy were enrolled in an open-label, multicenter, randomized
243 trial. Patients were randomized (1:1) to receive Rituxan, 375 mg/m² IV
244 infusion, once weekly for 4 doses every 6 months for up to 16 doses or no
245 further therapeutic intervention. The main outcome measure of the study
246 was progression-free survival defined as the time from randomization to
247 progression, relapse or death. Thirty-seven percent of the study
248 population was >60 years of age, 99% had Stage III or IV disease, and
249 63% had an IPI score ≥2. Among the 237 patients for whom histologic
250 material was available for review, 201 patients (85%) had centrally
251 confirmed IWF Grade A, B or C NHL.

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

255 **Diffuse Large B-Cell NHL (DLBCL)**

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

262 **Study 6**

263 A total of 632 patients aged ≥60 years with B-cell NHL Grade F, G, or H
264 by the International Working Formulation classification or DLBCL
265 (including primary mediastinal B-cell lymphoma) in the REAL
266 classification were randomized in a 1:1 ratio to treatment with CHOP or
267 R-CHOP. Patients were given 6 or 8, 21 day cycles of CHOP. Patients in
268 the R-CHOP arm also received 4 or 5 doses of Rituxan 375 mg/m² on
269 Days -7 and -3 (prior to Cycle 1), and 48–72 hours pre-Cycle 3,
270 pre-Cycle 5, and pre-Cycle 7 for patients receiving 8 cycles of CHOP
271 induction. The main outcome measure of the study was progression-free
272 survival, defined as the time from randomization to the first of

273 progression, relapse or death. Responding patients underwent a second
274 randomization to receive Rituxan or no further therapy.

275 Among all enrolled patients, 62% had centrally confirmed DLBCL
276 histology, 73% had Stage III–IV disease, 56% had IPI scores ≥ 2 , 86%
277 had ECOG performance status of < 2 , 57% had elevated LDH levels, and
278 30% had two or more extranodal disease sites involved. Efficacy results
279 are presented in Table 4. These results reflect a statistical approach which
280 allows for an evaluation of Rituxan administered in the induction setting
281 that excludes any potential impact of Rituxan given after the second
282 randomization.

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

287 Study 7

288 A total of 399 patients with DLBCL, aged ≥ 60 years, were randomized in
289 a 1:1 ratio to receive CHOP or R-CHOP induction. All patients received
290 up to 8, 3-week cycles of CHOP induction; patients in the R-CHOP arm
291 received Rituxan 375 mg/m^2 on Day 1 of each cycle. The main outcome
292 measure of the study was event free survival, defined as the time from
293 randomization to relapse, progression, change in therapy or death from
294 any cause. Among all enrolled patients, 80% had stage III or IV disease,
295 60% of patients had an age-adjusted IPI ≥ 2 , 80% had ECOG performance
296 status scores < 2 , 66% had elevated LDH levels, and 52% had extranodal
297 involvement in at least two sites. Efficacy results are presented in Table 4.

298 Study 8

299 A total of 823 patients with DLBCL, aged 18–60 years, were randomized
300 in a 1:1 ratio to receive an anthracycline-containing chemotherapy
301 regimen alone or in combination with Rituxan. The main outcome
302 measure of the study was time to treatment failure, defined as time from

303 randomization to the earliest of progressive disease, failure to achieve a
 304 complete response, relapse or death. Among all enrolled patients, 28%
 305 had Stage III–IV disease, 100% had IPI scores of ≤ 1 , 99% had ECOG
 306 performance status of < 2 , 29% had elevated LDH levels, 49% had bulky
 307 disease and 34% had extranodal involvement. Efficacy results are
 308 presented in Table 4.

Table 4
 Efficacy Results in Studies 6, 7, and 8

	Study 6 (n=632)		Study 7 (n=399)		Study 8 (n=823)	
	CHOP	R-CHOP	CHOP	R-CHOP	Chemo	R-Chemo
Main outcome	Progression-free survival (years)		Event-free survival (years)		Time to treatment failure (years)	
Median of main outcome measure	1.6	3.1	1.1	2.9	NE ^b	NE ^b
Hazard ratio ^d	0.69 ^a		0.60 ^a		0.45 ^a	
Overall survival at 2 years ^c	63%	74%	58%	69%	86%	95%
Hazard ratio ^d	0.72 ^a		0.68 ^a		0.40 ^a	

^a Significant at $p < 0.05$, 2-sided.

^b NE = Not reliably estimable.

^c Kaplan-Meier estimates.

^d R-CHOP vs. CHOP.

309
 310 In Study 7, overall survival estimates at 5 years were 58% vs. 46% for
 311 R-CHOP and CHOP, respectively.

312 **Rheumatoid Arthritis (RA)**

313 The efficacy and safety of Rituxan were evaluated in 517 patients with
 314 active disease who were receiving methotrexate and had a prior inadequate
 315 response to at least one TNF inhibitor. Patients were ≥ 18 years,
 316 diagnosed with RA according to American College of Rheumatology
 317 (ACR) criteria and had at least 8 swollen and 8 tender joints. Patients
 318 received 2 doses of either Rituxan 1000 mg or placebo as an IV infusion

319 on days 1 and 15, in combination with continued methotrexate 10–25 mg
320 weekly.

321 Efficacy was assessed at 24 weeks. Glucocorticoids were given IV as
322 premedication prior to each Rituxan infusion and orally on a tapering
323 schedule from baseline through Day 16.

324 The proportions of Rituxan (1000 mg) treated patients achieving ACR 20,
325 50, and 70 responses in this study is shown in Table 5.

Table 5
ACR Responses at Week 24 in Placebo-Controlled Study
(Percent of Patients) (Modified Intent-to-Treat Population)

Response	Placebo+MTX n=201	Rituxan+MTX n=298
ACR 20	18%	51%
		p<0.0001
ACR 50	5%	27%
		p<0.0001
ACR 70	1%	12%
		p<0.0001

326
327 Improvement was also noted for all components of ACR response
328 following treatment with Rituxan, as shown in Table 6.

Table 6
Components of ACR Response
(Modified Intent-to-Treat Population)

Parameter (median)	Placebo + MTX (n=201)		Rituxan + MTX (n=298)	
	Baseline	Wk 24	Baseline	Wk 24
Tender Joint Count	31.0	27.0	33.0	13.0*
Swollen Joint Count	20.0	19.0	21.0	9.5*
Physician Global Assessment ^a	71.0	69.0	71.0	36.0*
Patient Global Assessment ^a	73.0	68.0	71.0	41.0*
Pain ^a	68.0	68.0	67.0	38.5*
Disability Index (HAQ) ^b	2.0	1.9	1.9	1.5*
CRP (mg/dL)	2.4	2.5	2.6	0.9*

^a Visual Analogue Scale: 0=best, 100=worst.

^b Disability Index of the Health Assessment Questionnaire: 0=best, 3=worst.

* p<0.001, Rituxan + MTX vs. Placebo + MTX.

329

330 The time course of ACR 20 response for this study is shown in Figure 1.

331 Although both treatment groups received a brief course of IV and oral
 332 glucocorticoids, resulting in similar benefits at week 4, higher ACR 20

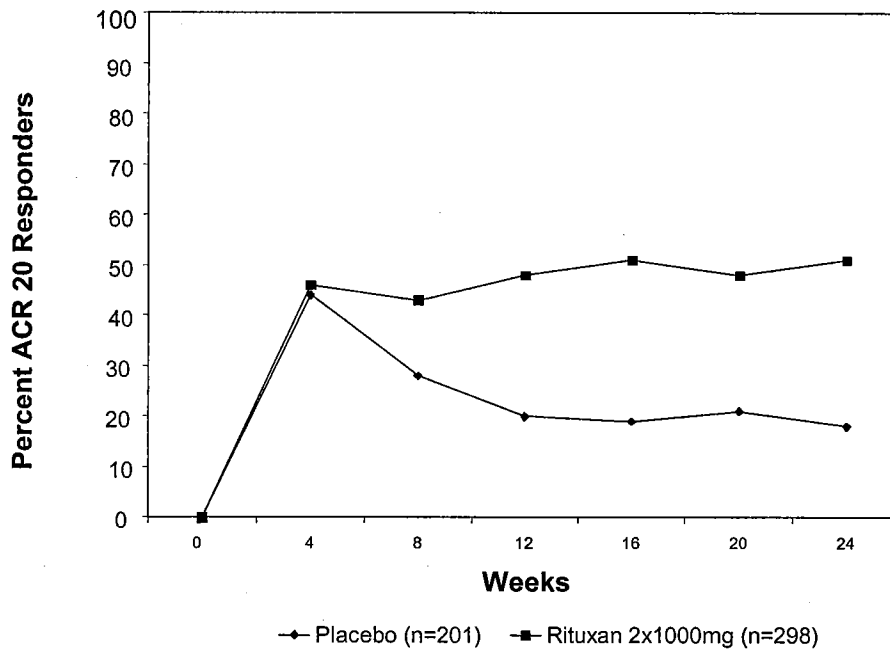
333 responses were observed for the Rituxan group by week 8 and were
 334 maintained through week 24 after a single course of treatment

335 (2 infusions) with Rituxan. Similar patterns were demonstrated for

336 ACR 50 and 70 responses.

337
338

Figure 1
ACR 20 Responses Over 24 Weeks



339
340

341 While the efficacy of Rituxan was supported by two well-controlled trials
342 in RA patients who had inadequate responses to non-biologic DMARDs,
343 but who had not failed TNF antagonist therapy, a favorable risk benefit
344 relationship has not been established in this population (See
345 **PRECAUTIONS.**)

346 **INDICATIONS AND USAGE**

347 **Non-Hodgkin's Lymphoma**

348 Rituxan[®] (Rituximab) is indicated for the treatment of patients with
349 relapsed or refractory, low-grade or follicular, CD20-positive, B-cell,
350 non-Hodgkin's lymphoma.

351 Rituxan[®] (Rituximab) is indicated for the first-line treatment of follicular,
352 CD20-positive, B-cell non-Hodgkin's lymphoma in combination with
353 CVP chemotherapy.

354 Rituxan[®] (Rituximab) is indicated for the treatment of low-grade,
355 CD20-positive, B-cell non-Hodgkin's lymphoma in patients with stable
356 disease or who achieve a partial or complete response following first-line
357 treatment with CVP chemotherapy.

358 Rituxan[®] (Rituximab) is indicated for the first-line treatment of diffuse
359 large B-cell, CD20-positive, non-Hodgkin's lymphoma in combination
360 with CHOP or other anthracycline-based chemotherapy regimens.

361 **Rheumatoid Arthritis**

362 Rituxan[®] (Rituximab) in combination with methotrexate is indicated to
363 reduce signs and symptoms in adult patients with moderately- to severely-
364 active rheumatoid arthritis who have had an inadequate response to one or
365 more TNF antagonist therapies.

366 **CONTRAINDICATIONS**

367 None.

368 **WARNINGS (See BOXED WARNINGS)**

369 **Severe Infusion Reactions (see BOXED WARNINGS and** 370 **ADVERSE REACTIONS)**

371 Rituxan has caused severe infusion reactions. In some cases, these
372 reactions were fatal. These severe reactions typically occurred during the
373 first infusion with time to onset of 30–120 minutes. Signs and symptoms
374 of severe infusion reactions may include urticaria, hypotension,
375 angioedema, hypoxia, or bronchospasm, and may require interruption of
376 Rituxan administration. The most severe manifestations and sequelae
377 include pulmonary infiltrates, acute respiratory distress syndrome,
378 myocardial infarction, ventricular fibrillation, cardiogenic shock, and
379 anaphylactic and anaphylactoid events. In the reported cases, the
380 following factors were more frequently associated with fatal outcomes:
381 female gender, pulmonary infiltrates, and chronic lymphocytic leukemia
382 or mantle cell lymphoma.

383 *Management of severe infusion reactions:* The Rituxan infusion should be
384 interrupted for severe reactions. Medications and supportive care
385 measures including, but not limited to, epinephrine, antihistamines,
386 glucocorticoids, intravenous fluids, vasopressors, oxygen, bronchodilators,
387 and acetaminophen, should be available for immediate use and instituted
388 as medically indicated for use in the event of a reaction during
389 administration. In most cases, the infusion can be resumed at a 50%
390 reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have
391 completely resolved. Patients requiring close monitoring during first and
392 all subsequent infusions include those with pre-existing cardiac and
393 pulmonary conditions, those with prior clinically significant
394 cardiopulmonary adverse events and those with high numbers of
395 circulating malignant cells ($\geq 25,000/\text{mm}^3$) with or without evidence of
396 high tumor burden. (See **WARNINGS: Cardiovascular and**
397 **ADVERSE REACTIONS.**)

398 **Tumor Lysis Syndrome [TLS] (See BOXED WARNINGS and**
399 **ADVERSE REACTIONS)**

400 Rapid reduction in tumor volume followed by acute renal failure,
401 hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia, have
402 been reported within 12–24 hours after the first Rituxan infusion. Rare
403 instances of fatal outcome have been reported in the setting of TLS
404 following treatment with Rituxan in patients with NHL. The risks of TLS
405 appear to be greater in patients with high numbers of circulating malignant
406 cells ($\geq 25,000/\text{mm}^3$) or high tumor burden. Prophylaxis for TLS should
407 be considered for patients at high risk. Correction of electrolyte
408 abnormalities, monitoring of renal function and fluid balance, and
409 administration of supportive care, including dialysis, should be initiated as
410 indicated. Following complete resolution of the complications of TLS,
411 Rituxan has been tolerated when re-administered in conjunction with
412 prophylactic therapy for TLS in a limited number of cases.

413 **Hepatitis B Reactivation with Related Fulminant Hepatitis and**
414 **Other Viral Infections**

415 Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic
416 failure, and death has been reported in patients with hematologic
417 malignancies treated with Rituxan. The majority of patients received
418 Rituxan in combination with chemotherapy. The median time to the
419 diagnosis of hepatitis was approximately 4 months after the initiation of
420 Rituxan and approximately one month after the last dose.

421 Persons at high risk of HBV infection should be screened before initiation
422 of Rituxan. Carriers of hepatitis B should be closely monitored for
423 clinical and laboratory signs of active HBV infection and for signs of
424 hepatitis during and for up to several months following Rituxan therapy.
425 In patients who develop viral hepatitis, Rituxan and any concomitant
426 chemotherapy should be discontinued and appropriate treatment including
427 antiviral therapy initiated. There are insufficient data regarding the safety
428 of resuming Rituxan therapy in patients who develop hepatitis subsequent
429 to HBV reactivation.

430 The following additional serious viral infections, either new, reactivated or
431 exacerbated, have been identified in clinical studies or postmarketing
432 reports. The majority of patients received Rituxan in combination with
433 chemotherapy or as part of a hematopoietic stem cell transplant. These
434 viral infections included cytomegalovirus, herpes simplex virus,
435 parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C.
436 In some cases, the viral infections occurred up to one year following
437 discontinuation of Rituxan and have resulted in death.

438 **Progressive Multifocal Leukoencephalopathy (PML) (See**
439 **BOXED WARNINGS and ADVERSE REACTIONS)**

440 JC virus infection resulting in PML and death has been reported in
441 Rituxan-treated patients with hematologic malignancies or with
442 autoimmune diseases for which Rituxan has not been approved. The
443 majority of patients with hematologic malignancies diagnosed with PML
444 received Rituxan in combination with chemotherapy or as part of a

445 hematopoietic stem cell transplant. The patients with autoimmune
446 diseases had a history of prior, and may also have had concurrent,
447 immunosuppressive therapy and were diagnosed with PML within
448 12 months of their last infusion of Rituxan.

449 Physicians treating patients with Rituxan should consider PML in any
450 patient presenting with new onset neurologic manifestations. Consultation
451 with a neurologist, brain MRI, and lumbar puncture should be considered
452 as clinically indicated. In patients who develop PML, Rituxan should be
453 discontinued and reductions or discontinuation of any concomitant
454 chemotherapy or immunosuppressive therapy should be considered.

455 **Cardiovascular**

456 Infusions should be discontinued in the event of serious or life-threatening
457 cardiac arrhythmias. Patients who develop clinically significant
458 arrhythmias should undergo cardiac monitoring during and after
459 subsequent infusions of Rituxan. Patients with pre-existing cardiac
460 conditions including arrhythmias and angina have had recurrences of these
461 events during Rituxan therapy and should be monitored throughout the
462 infusion and immediate post-infusion period.

463 **Renal (See BOXED WARNINGS: 464 Tumor Lysis Syndrome [TLS] and ADVERSE REACTIONS)**

465 Rituxan administration has been associated with severe renal toxicity
466 including acute renal failure requiring dialysis and in some cases, has led
467 to a fatal outcome in hematologic malignancy patients. Renal toxicity has
468 occurred in patients with high numbers of circulating malignant cells
469 ($>25,000/\text{mm}^3$) or high tumor burden who experience tumor lysis
470 syndrome and in patients with NHL administered concomitant cisplatin
471 therapy during clinical trials. The combination of cisplatin and Rituxan is
472 not an approved treatment regimen. If this combination is used in clinical
473 trials *extreme caution* should be exercised; patients should be monitored
474 closely for signs of renal failure. Discontinuation of Rituxan should be
475 considered for those with rising serum creatinine or oliguria.

476 **Severe Mucocutaneous Reactions (See BOXED WARNINGS)**

477 Mucocutaneous reactions, some with fatal outcome, have been reported in
478 patients treated with Rituxan. These reports include paraneoplastic
479 pemphigus (an uncommon disorder which is a manifestation of the
480 patient's underlying malignancy),¹⁹ Stevens-Johnson syndrome, lichenoid
481 dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis.
482 The onset of the reaction in the reported cases has varied from 1–13 weeks
483 following Rituxan exposure. Patients experiencing a severe
484 mucocutaneous reaction should not receive any further infusions and seek
485 prompt medical evaluation. Skin biopsy may help to distinguish among
486 different mucocutaneous reactions and guide subsequent treatment.
487 The safety of readministration of Rituxan to patients with any of these
488 mucocutaneous reactions has not been determined.

489 **Concomitant use with biologic agents and DMARDs other than**
490 **methotrexate in RA:** Limited data are available on the safety of the use
491 of biologic agents or DMARDs other than methotrexate in patients
492 exhibiting peripheral B cell depletion following treatment with Rituximab.
493 Patients should be closely observed for signs of infection if biologic
494 agents and/or DMARDs are used concomitantly.

495 **Bowel Obstruction and Perforation**

496 Abdominal pain, bowel obstruction and perforation, in some cases leading
497 to death, were observed in patients receiving Rituxan in combination with
498 chemotherapy for DLBCL. In post-marketing reports, which include both
499 patients with low-grade or follicular NHL and DLBCL, the mean time to
500 onset of symptoms was 6 days (range 1–77) in patients with documented
501 gastro-intestinal perforation. Complaints of abdominal pain, especially
502 early in the course of treatment, should prompt a thorough diagnostic
503 evaluation and appropriate treatment.

504 **PRECAUTIONS**

505 **Information for Patients**

506 Patients should be provided the Rituxan Patient Information leaflet and
507 provided an opportunity to read it prior to each treatment session.

508 Because caution should be exercised in administering Rituxan to patients
509 with active infections, it is important that the patient's overall health be
510 assessed at each visit and any questions resulting from the patient's
511 reading of the Patient Information be discussed.

512 **Laboratory Monitoring**

513 Because Rituxan targets all CD20-positive B lymphocytes (malignant and
514 nonmalignant), complete blood counts (CBC) and platelet counts should
515 be obtained at regular intervals during Rituxan therapy and more
516 frequently in patients who develop cytopenias (see
517 **ADVERSE REACTIONS**). The duration of cytopenias caused by
518 Rituxan can extend well beyond the treatment period.

519 **Drug/Laboratory Interactions**

520 There have been no formal drug interaction studies performed with
521 Rituxan. However, renal toxicity was seen with this drug in combination
522 with cisplatin in clinical trials. (See **WARNINGS: Renal**.) In clinical
523 trials of patients with RA, concomitant administration of methotrexate or
524 cyclophosphamide did not alter the pharmacokinetics of Rituximab.

525 **Immunization**

526 The safety of immunization with live viral vaccines following Rituxan
527 therapy has not been studied and vaccination with live virus vaccines is
528 not recommended. The ability to generate a primary or anamnestic
529 humoral response to vaccination is currently being studied.

530 Physicians should review the vaccination status of patients with RA being
531 considered for Rituxan treatment and follow the Centers for Disease
532 Control and Prevention (CDC) guidelines for adult vaccination with
533 non-live vaccines intended to prevent infectious disease, prior to therapy.

534 For patients with NHL, the benefits of primary and/or booster vaccinations
535 should be weighted against the risks of delay in initiation of Rituxan
536 therapy.

537 **Use in patients with RA who had no prior inadequate response to**
538 **TNF antagonists:** While efficacy of Rituxan was supported in two
539 well-controlled trials in patients with RA with prior inadequate responses
540 to non-biologic DMARDs, a favorable risk benefit relationship has not
541 been established in this population. The use of Rituxan in patients with
542 RA who have no prior inadequate response to one or more TNF
543 antagonists is not recommended (see **CLINICAL STUDIES:**
544 **Rheumatoid Arthritis**).

545 **Retreatment in patients with RA:** Safety and efficacy of retreatment
546 have not been established in controlled trials. A limited number of
547 patients have received two to five courses (two infusions per course) of
548 treatment in an uncontrolled setting. In clinical trials in patients with RA,
549 most of the patients who received additional courses did so 24 weeks after
550 the previous course and none were retreated sooner than 16 weeks.

551 **Carcinogenesis, Mutagenesis, and Impairment of Fertility**
552 No long-term animal studies have been performed to establish the
553 carcinogenic potential of Rituxan. Studies also have not been completed
554 to assess mutagenic potential of Rituxan, or to determine potential effects
555 on fertility in males or females. Individuals of childbearing potential
556 should use effective contraceptive methods during treatment and for up to
557 12 months following Rituxan therapy.

558 **Pregnancy Category C**

559 An embryo-fetal developmental toxicity study was performed on pregnant
560 cynomolgus monkeys. Animals were administered Rituximab via the
561 intravenous route during early gestation (organogenesis period;
562 post-coitum days 20 through 50). Rituximab was administered as loading
563 doses on post-coitum days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and

564 then weekly on post-coitum days 29, 36, 43 and 50, at 20, 50 or
565 100 mg/kg/week. The 100 mg/kg/week dose resulted in exposures of
566 0.8-fold a human 2 g dose based on AUC. Although Rituximab has been
567 shown to cross the monkey placenta, there was no evidence of
568 teratogenicity under the conditions of the experiment.

569 Nonteratogenic effects: Results from the embryo-fetal developmental
570 toxicology study described above showed that Rituximab treatment
571 produced a decrease in lymphoid tissue B cells in the offspring of treated
572 dams.

573 A subsequent pre- and postnatal developmental toxicity study in
574 cynomolgus monkeys was completed to assess developmental toxicity and
575 the recovery of B-cells and immune function in infants exposed to
576 Rituximab in utero. Due to the possibility of anti-drug antibody
577 development with a long dosing period, the animals were divided into
578 3 sets of dosing periods: one set received a loading dose of Rituximab (0,
579 15, or 75 mg/kg) every day for 3 days starting on post-coitum day 20
580 followed by weekly administration of Rituximab (0, 20 or 100 mg/kg)
581 through delivery and post-partum day 28 (~25 weeks); a second set
582 received a loading dose of Rituximab (15 or 75 mg/kg) every day for
583 3 days starting on post-coitum day 76 followed by weekly administration
584 of Rituximab (20 or 100 mg/kg) through post-coitum day 134 (~8 weeks);
585 a third set received a loading dose of Rituximab (15 or 75 mg/kg) every
586 day for 3 days starting on post-coitum day 132 followed by weekly
587 administration of Rituximab (20 or 100 mg/kg) through delivery and
588 post-partum day 28 (~8 weeks). The decreased B cells and
589 immunosuppression noted in the offspring of pregnant animals treated
590 with either 20 or 100 mg/kg/week Rituximab showed a return to normal
591 levels and function within 6 months post-birth. However, there are no
592 adequate and well-controlled studies in pregnant women. Because animal
593 reproductive studies are not always predictive of human response, this
594 drug should be used during pregnancy only if the potential benefit justifies
595 the potential risk to the fetus.

596 **Nursing Mothers**

597 Rituximab was excreted in the milk of lactating cynomolgus monkeys.
598 It is not known whether Rituxan is excreted in human milk. Because
599 human IgG is excreted in human milk and the potential for absorption and
600 immunosuppression in the infant is unknown, women should be advised to
601 discontinue nursing until circulating drug levels are no longer detectable.
602 (See **CLINICAL PHARMACOLOGY**.)

603 **Pediatric Use**

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

606 **Geriatric Use**

607 Among patients with DLBCL in three randomized, active-controlled trials,
608 927 patients received Rituxan in combination with chemotherapy.
609 Of these, 396 (43%) were age 65 or greater and 123 (13%) were age 75 or
610 greater. No overall differences in effectiveness were observed between
611 these subjects and younger subjects. However, elderly patients were more
612 likely to experience cardiac adverse events, mostly supraventricular
613 arrhythmias. Serious pulmonary adverse events were also more common
614 among the elderly, including pneumonia and pneumonitis.

615 Clinical studies of Rituxan in previously untreated, low-grade or follicular,
616 CD 20-positive, B-cell NHL and in relapsed or refractory, low-grade or
617 follicular lymphoma did not include sufficient numbers of subjects
618 aged 65 and over to determine whether they respond differently from
619 younger subjects.

620 Among the 517 patients in the phase 3 RA study, 16% were 65–75 years
621 old and 2% were 75 years old and older. The Rituxan ACR 20 response
622 rates in the older (age \geq 65 years) vs. younger (age $<$ 65 years) patients
623 were similar (53% vs. 51%, respectively). Adverse reactions, including
624 incidence, severity, and type of adverse reaction were similar between
625 older and younger patients.

626 **ADVERSE REACTIONS**

627 Because clinical trials are conducted under widely varying conditions,
628 adverse reaction rates observed in the clinical trials of a drug cannot be
629 directly compared to rates in the clinical trials of another drug and may not
630 reflect the rates observed in practice. The adverse reaction information
631 from clinical trials does, however, provide a basis for identifying the
632 adverse events that appear to be related to drug use and for approximating
633 rates.

634 The following serious adverse reactions, some with fatal outcomes, have
635 been reported in patients treated with Rituxan (see **BOXED WARNINGS**
636 and **WARNINGS**): severe or fatal infusion reactions, tumor lysis
637 syndrome, severe mucocutaneous reactions, hepatitis B reactivation with
638 fulminant hepatitis, progressive multifocal leukoencephalopathy (PML),
639 other viral infections, cardiac arrhythmias, renal toxicity, bowel
640 obstruction and perforation.

641 **Adverse Reactions in Patients with Non-Hodgkin's Lymphoma**

642 The overall safety database for Rituxan is based on clinical trial data from
643 1606 patients with NHL, who received Rituxan either as a single agent or
644 in combination with chemotherapy. Additional safety information was
645 obtained from post-marketing safety surveillance. The most common
646 adverse reactions were infusion reactions (see **INFUSION REACTIONS**
647 below).

648 Except as noted, adverse events described below occurred in the setting of
649 relapsed or refractory, low-grade or follicular, CD20-positive, B-cell,
650 NHL and are based on 356 patients treated in single-arm studies of
651 Rituxan administered as a single agent. Most patients received Rituxan
652 375 mg/m² weekly for 4 doses.

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

654 Mild to moderate infusion reactions consisting of fever and chills/rigors
655 occurred in the majority of patients during the first Rituxan infusion.

656 Other frequent infusion reaction symptoms included nausea, pruritus,
657 angioedema, asthenia, hypotension, headache, bronchospasm, throat
658 irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and
659 hypertension. These reactions generally occurred within 30 to
660 120 minutes of beginning the first infusion, and resolved with slowing or
661 interruption of the Rituxan infusion and with supportive care
662 (diphenhydramine, acetaminophen, IV saline, and vasopressors).
663 The incidence of infusion reactions was highest during the first infusion
664 (77%) and decreased with each subsequent infusion (30% with fourth
665 infusion and 14% with eighth infusion). Injection site pain was reported
666 in less than 5% of patients.

667 **Infectious Events (See WARNINGS: Hepatitis B Reactivation**
668 **with Related Fulminant Hepatitis and Other Viral Infections;**
669 **Progressive Multifocal Leukoencephalopathy (PML))**

670 Rituxan induced B-cell depletion in 70% to 80% of patients with NHL and
671 was associated with decreased serum immunoglobulins in a minority of
672 patients; the lymphopenia lasted a median of 14 days (range, 1–588 days).
673 Infectious events occurred in 31% of patients: 19% of patients had
674 bacterial infections, 10% had viral infections, 1% had fungal infections,
675 and 6% were unknown infections. Incidence is not additive because a
676 single patient may have had more than one type of infection. Serious
677 infectious events (Grade 3 or 4), including sepsis, occurred in 2% of
678 patients.

679 **Hematologic Events**

680 Grade 3 and 4 cytopenias were reported in 48% of patients treated with
681 Rituxan; these include: lymphopenia (40%), neutropenia (6%),
682 leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median
683 duration of lymphopenia was 14 days (range, 1–588 days) and of
684 neutropenia was 13 days (range, 2–116 days). A single occurrence of
685 transient aplastic anemia (pure red cell aplasia) and two occurrences of
686 hemolytic anemia following Rituxan therapy were reported.

687 **Pulmonary Events**

688 135 patients (38%) experienced pulmonary events in clinical trials.
689 The most common respiratory system adverse events experienced were
690 increased cough, rhinitis, bronchospasm, dyspnea, and sinusitis. In both
691 clinical studies and post-marketing surveillance, there have been a limited
692 number of reports of bronchiolitis obliterans presenting up to 6 months
693 post-Rituxan infusion and a limited number of reports of pneumonitis
694 (including interstitial pneumonitis) presenting up to 3 months post-Rituxan
695 infusion, some of which resulted in fatal outcomes. The safety of
696 resumption or continued administration of Rituxan in patients with
697 pneumonitis or bronchiolitis obliterans is unknown.

698 **Immunogenicity**

699 The observed incidence of antibody positivity in an assay is highly
700 dependent on the sensitivity and specificity of the assay and may be
701 influenced by several factors including sample handling, concomitant
702 medications, and underlying disease. For these reasons, comparison of the
703 incidence of antibodies to Rituxan with the incidence of antibodies to
704 other products may be misleading.

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

711 **Single Agent Rituxan for Relapsed or Refractory, Low-Grade**
712 **or Follicular, CD20-Positive, B-Cell NHL**

713 The data below were obtained in 356 patients receiving single agent
714 Rituxan for treatment of relapsed, refractory, low grade or follicular NHL
715 (see **CLINICAL STUDIES**). The majority of patients received
716 375 mg/m² IV weekly × 4 doses. The median age was 57 (range
717 22–81 years). Sixty percent were male; 93% were Caucasian, 1% were

718 Black, 2% were Hispanic, 2% were Asian, and 2% were from other racial
719 groups.

720 Table 7 lists the most common, as well as Grade 3 and 4, adverse events
721 observed.

Table 7
 Incidence of Adverse Events in $\geq 5\%$ of Patients
 with Relapsed or Refractory, Low-Grade or Follicular
 NHL, Receiving Single-agent Rituxan (N=356)^{a,b}

	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 7 (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)^{a,b}

	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

^a Adverse Events observed up to 12 months following Rituxan.

^b Adverse Events graded for severity by NCI-CTC criteria²⁰.

723

724 Risk Factors Associated With Increased Rates of Adverse Events
 725 Administration of Rituxan weekly for 8 doses resulted in higher rates of
 726 Grade 3 and 4 adverse events¹⁵ overall (70%) compared with
 727 administration weekly for 4 doses (57%). The incidence of Grade 3 or 4
 728 adverse events was similar in patients retreated with Rituxan compared
 729 with initial treatment (58% and 57%, respectively). The incidence of the
 730 following clinically significant adverse events was higher in patients with
 731 bulky disease (lesions ≥ 10 cm) (N=39) versus patients with lesions
 732 < 10 cm (N=195): abdominal pain, anemia, dyspnea, hypotension, and
 733 neutropenia.

734 **Previously Untreated, Follicular, CD20-Positive, B-Cell NHL**

735 The safety data were obtained in a single, multi-center, randomized study
736 of 321 patients of whom 162 received Rituxan in combination with CVP
737 chemotherapy (R-CVP) and 159 received CVP chemotherapy alone
738 (CVP). Eighty-five percent of R-CVP patients received the maximum
739 number of doses (8) of Rituxan. The median age was 52 years, 54% were
740 male, and 96% were Caucasian.

741 Patients in the R-CVP arm had higher incidences of infusional toxicity and
742 of neutropenia as compared to those in the CVP arm. The following
743 adverse events occurred more frequently ($\geq 5\%$) in patients receiving
744 R-CVP compared to CVP alone: rash (17% vs. 5%), cough
745 (15% vs. 6%), flushing (14% vs. 3%), rigors (10% vs. 2%), pruritis
746 (10% vs. 1%), neutropenia (8% vs. 3%), and chest tightness (7% vs. 1%).

747 **Previously Untreated, Low-Grade, CD20-Positive, B-Cell NHL**

748 Safety data were obtained in a single, multi-center, randomized study of
749 322 patients of whom 161 received Rituxan and 161 received no treatment
750 following 6–8 cycles of CVP chemotherapy. Ninety-five patients (59%)
751 received the maximum number of doses (16) of Rituxan.

752 The median age for the Rituxan treated patients was 58 years. Fifty-five
753 percent were male, 93% were Caucasian, and 5% Black.

754 The following adverse events were reported more frequently ($\geq 5\%$) in
755 patients receiving Rituxan following CVP compared with those who
756 received no further therapy: fatigue (39% vs. 14%), anemia
757 (35% vs. 20%), peripheral sensory neuropathy (30% vs. 18%), infections
758 (19% vs. 9%), pulmonary toxicity (18% vs. 10%), hepato-biliary toxicity
759 (17% vs. 7%), rash and/or pruritis (17% vs. 5%), arthralgia (12% vs. 3%),
760 and weight gain (11% vs. 4%). Neutropenia was the only Grade 3 or
761 4 adverse event that occurred more frequently ($\geq 2\%$) in the Rituxan arm
762 compared with those who received no further therapy (4% vs. 1%).

763 **Rituxan in Combination with Chemotherapy for DLBCL**

764 Adverse events described in the setting of DLBCL are based on three
765 randomized, active-controlled clinical trials in which 927 patients received
766 Rituxan in combination with chemotherapy and 802 patients received
767 chemotherapy alone. Detailed safety data collection was primarily limited
768 to Grade 3 and 4 adverse events and serious adverse events.

769 The population varied from 18–92 years of age and 55% were male; racial
770 distribution was collected only for Study 6 (see **CLINICAL STUDIES**
771 section) where 90% of patients were Caucasian, 5% were Black, 3% were
772 Hispanic and 2% were from other racial groups. Patients received
773 4–8 doses of Rituxan at 375 mg/m².

774 The following adverse events, regardless of severity, were reported more
775 frequently (≥5%) in patients age ≥60 years receiving R-CHOP as
776 compared to CHOP alone: pyrexia (56% vs. 46%), lung disorder (31% vs.
777 24%), cardiac disorder (29% vs. 21%), and chills (13% vs. 4%). In one of
778 these studies (Study 7), more detailed assessment of cardiac toxicity
779 revealed that supraventricular arrhythmias or tachycardia accounted for
780 most of the difference in cardiac disorders, with 4.5% vs. 1.0% incidences
781 for R-CHOP and CHOP, respectively.

782 The following Grade 3 or 4 adverse events were reported more frequently
783 among patients in the R-CHOP arm compared with those in the CHOP
784 arm: thrombocytopenia (9% vs. 7%) and lung disorder (6% vs. 3%).
785 Other severe adverse events reported more commonly among patients
786 receiving R-CHOP in one or more studies were viral infection,
787 neutropenia and anemia.

788 **Adverse Reactions in Patients with Rheumatoid Arthritis**

789 In general, the adverse events observed in patients with RA were similar
790 in type to those seen in patients with non-Hodgkin's lymphoma (see
791 **WARNINGS, PRECAUTIONS** and other sections under

792 **ADVERSE REACTIONS**). Specific safety considerations in this
 793 indication are discussed below.

794 Where specific percentages are noted, these data are based on 938 patients
 795 treated in Phase 2 and 3 studies of Rituxan (2 × 1000 mg) or placebo
 796 administered in combination with methotrexate.

Table 8
 Incidence of All Adverse Events*
 Occurring in ≥2% and at least 1% Greater than Placebo Among
 Rheumatoid Arthritis Patients in Clinical Studies Up to Week 24
 (Pooled)

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

* Coded using MedDRA.

797

798 **Infusion Reactions**

799 In Rituxan RA placebo-controlled studies, 32% of Rituxan-treated patients
 800 experienced an adverse event during or within 24 hours following their

801 first infusion, compared to 23% of placebo-treated patients receiving their
802 first infusion. The incidence of adverse events during the 24-hour period
803 following the second infusion, Rituxan or placebo, decreased to 11% and
804 13%, respectively. Acute infusion reactions (manifested by fever, chills,
805 rigors, pruritus, urticaria/rash, angioedema, sneezing, throat irritation,
806 cough, and/or bronchospasm, with or without associated hypotension or
807 hypertension) were experienced by 27% of Rituxan-treated patients
808 following their first infusion, compared to 19% of placebo-treated patients
809 receiving their first placebo infusion. The incidence of these acute
810 infusion reactions following the second infusion of Rituxan or placebo
811 decreased to 9% and 11%, respectively. Serious acute infusion reactions
812 were experienced by <1% of patients in either treatment group. Acute
813 infusion reactions required dose modification (stopping, slowing or
814 interruption of the infusion) in 10% and 2% of patients receiving
815 Rituximab or placebo, respectively, after the first course. The proportion
816 of patients experiencing acute infusion reactions decreased with
817 subsequent courses of Rituxan. The administration of IV glucocorticoids
818 prior to Rituxan infusions reduced the incidence and severity of such
819 reactions, however, there was no clear benefit from the administration of
820 oral glucocorticoids for the prevention of acute infusion reactions.
821 Patients in clinical studies also received antihistamines and acetaminophen
822 prior to Rituxan infusions.

823 Infections

824 In RA clinical studies, 39% of patients in the Rituxan group experienced
825 an infection of any type compared to 34% of patients in the placebo group.
826 The most common infections were nasopharyngitis, upper respiratory tract
827 infections, urinary tract infections, bronchitis, and sinusitis. The only
828 infections to show an absolute increase over placebo of at least 1% were
829 upper respiratory tract infections, which affected 7% of Rituxan-treated
830 patients and 6% of placebo-treated patients and rhinitis, which affected
831 3% of Rituxan-treated patients and 2% of placebo-treated patients.

832 The incidence of serious infections was 2% in the Rituxan-treated patients
833 and 1% in the placebo group. One fatal infection (bronchopneumonia)
834 occurred with Rituximab monotherapy during the 24-weeks
835 placebo-controlled period in one of the Phase 2 RA studies.

836 **Cardiac Events**

837 The incidence of serious cardiovascular events in the double-blind part of
838 the clinical trials was 1.7% and 1.3% in Rituxan and placebo treatment
839 groups, respectively. Three cardiovascular deaths occurred during the
840 double-blind period of the RA studies including all Rituximab regimens
841 (3/769=0.4%) as compared to none in the placebo treatment group
842 (0/389).

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

847 **Immunogenicity**

848 A total of 54/990 patients (5%) with RA tested positive for HACA.
849 Of these, most became positive by week 24. Following the first course,
850 however, some became positive at week 16 or after 24 weeks. Some
851 patients tested positive after the second course of treatment. Limited data
852 are available on the safety or efficacy of Rituxan retreatment in patients
853 who develop HACA. One of 10 HACA-positive patients who received
854 retreatment with Rituxan experienced a serious acute infusion reaction
855 (bronchospasm). The clinical relevance of HACA formation in
856 Rituximab-treated patients is unclear.

857 **Post-Marketing Reports**

858 The following adverse reactions have been identified during post-approval
859 use of Rituxan in hematologic malignancies. Because these reactions are
860 reported voluntarily from a population of uncertain size, it is not always
861 possible to reliably estimate their frequency or establish a causal

862 relationship to drug exposure. Decisions to include these reactions in
863 labeling are typically based on one or more of the following factors:
864 (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength
865 of causal connection to Rituxan.

866 *Hematologic:* prolonged pancytopenia, marrow hypoplasia, and late onset
867 neutropenia, hyperviscosity syndrome in Waldenstrom's
868 macroglobulinemia.

869 *Cardiac:* fatal cardiac failure.

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

873 *Infection:* viral infections, including progressive multifocal
874 leukoencephalopathy (PML), increase in fatal infections in HIV-associated
875 lymphoma.

876 *Skin:* severe mucocutaneous reactions.

877 *Gastrointestinal:* bowel obstruction and perforation.

878 **OVERDOSAGE**

879 There has been no experience with overdosage in human clinical trials.
880 Single doses of up to 500 mg/m² have been given in dose-escalation
881 clinical trials.¹⁰

882 **DOSAGE AND ADMINISTRATION**

883 **Relapsed or Refractory, Low-Grade or Follicular,** 884 **CD20-Positive, B-Cell Non-Hodgkin's Lymphoma**

885 The recommended dose of Rituxan is 375 mg/m² IV infusion once weekly
886 for 4 or 8 doses.

887 **Retreatment Therapy**

888 The recommended dose of Rituxan is 375 mg/m² IV infusion once weekly
889 for 4 doses in responding patients who develop progressive disease after
890 previous Rituxan therapy. Currently there are limited data concerning
891 more than 2 courses.

892 **Previously Untreated, Follicular, CD20-Positive, B-Cell NHL**

893 The recommended dose of Rituxan is 375 mg/m² IV infusion, given on
894 Day 1 of each cycle of CVP chemotherapy, for up to 8 doses.

895 **Previously Untreated, Low-Grade, CD20-Positive, B-Cell NHL**

896 The recommended dose of Rituxan in patients who have not progressed
897 following 6–8 cycles of CVP chemotherapy is 375 mg/m² IV infusion,
898 once weekly for 4 doses every 6 months for up to 16 doses.

899 **Diffuse Large B-Cell NHL**

900 The recommended dose of Rituxan is 375 mg/m² IV per infusion given on
901 Day 1 of each cycle of chemotherapy for up to 8 infusions.

902 **Rheumatoid Arthritis**

903 Rituxan is given as two-1000 mg IV infusions separated by 2 weeks.
904 Glucocorticoids administered as methylprednisolone 100 mg IV or its
905 equivalent 30 minutes prior to each infusion are recommended to reduce
906 the incidence and severity of infusion reactions. Safety and efficacy of
907 retreatment have not been established in controlled trials (see
908 **PRECAUTIONS: Retreatment in patients with RA**).

909 Rituxan is given in combination with methotrexate.

910 **Rituxan as a Component of Zevalin[®] (Ibritumomab tiuxetan)**
911 **Therapeutic Regimen**

912 As a required component of the Zevalin therapeutic regimen, Rituxan
913 250 mg/m² should be infused within 4 hours prior to the administration of
914 Indium-111- (In-111-) Zevalin and within 4 hours prior to the
915 administration of Yttrium-90- (Y-90-) Zevalin. Administration of Rituxan

916 and In-111-Zevalin should precede Rituxan and Y-90-Zevalin by
917 7–9 days. Refer to the Zevalin package insert for full prescribing
918 information regarding the Zevalin therapeutic regimen.

919 Rituxan may be administered in an outpatient setting. **DO NOT**
920 **ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.** (See
921 **Administration**).

922 **Instructions for Administration**

923 Preparation for Administration

924 Use appropriate aseptic technique. Withdraw the necessary amount of
925 Rituxan and dilute to a final concentration of 1 to 4 mg/mL into an
926 infusion bag containing either 0.9% Sodium Chloride, USP, or
927 5% Dextrose in Water, USP. Gently invert the bag to mix the solution.
928 Discard any unused portion left in the vial. Parenteral drug products
929 should be inspected visually for particulate matter and discoloration prior
930 to administration.

931 Rituxan solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for
932 24 hours. Rituxan solutions for infusion have been shown to be stable for
933 an additional 24 hours at room temperature. However, since Rituxan
934 solutions do not contain a preservative, diluted solutions should be stored
935 refrigerated (2°C–8°C). No incompatibilities between Rituxan and
936 polyvinylchloride or polyethylene bags have been observed.

937 **Administration: DO NOT ADMINISTER AS AN INTRAVENOUS** 938 **PUSH OR BOLUS**

939 Infusion reactions may occur (see **BOXED WARNINGS, WARNINGS,**
940 **and ADVERSE REACTIONS**). Premedication consisting of
941 acetaminophen and an antihistamine should be considered before each
942 infusion of Rituxan. Premedication may attenuate infusion reactions.
943 Since transient hypotension may occur during Rituxan infusion,
944 consideration should be given to withholding antihypertensive
945 medications 12 hours prior to Rituxan infusion.

946 **First Infusion**

947 The Rituxan solution for infusion should be administered intravenously at
948 an initial rate of 50 mg/hr. Rituxan should not be mixed or diluted with
949 other drugs. If infusion reactions do not occur, escalate the infusion rate
950 in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
951 If an infusion reaction develops, the infusion should be temporarily
952 slowed or interrupted (see **BOXED WARNINGS** and **WARNINGS**).
953 The infusion can continue at one-half the previous rate upon improvement
954 of patient symptoms.

955 **Subsequent Infusions**

956 If the patient tolerated the first infusion well, subsequent Rituxan infusions
957 can be administered at an initial rate of 100 mg/hr, and increased by
958 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr
959 as tolerated. If the patient did not tolerate the first infusion well, follow
960 the guidelines under First Infusion.

961 **Stability and Storage**

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

967 **HOW SUPPLIED**

968 Rituxan[®] (Rituximab) is supplied as 100 mg and 500 mg of sterile,
969 preservative-free, single-use vials.

970 Single unit 100 mg carton: Contains one 10 mL vial of Rituxan
971 (10 mg/mL).

972 NDC 50242-051-21

973 Single unit 500 mg carton: Contains one 50 mL vial of Rituxan
974 (10 mg/mL).

975 NDC 50242-053-06

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Manufactured by: 4835502

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1 DNA Way

South San Francisco, CA 94080-4990

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1051

Patient Information

1052

Rituxan® (ri-tuk'-san)

1053

(Rituximab)

1054 Read this patient information leaflet when you have been prescribed

1055 Rituxan and each time you are scheduled to receive a Rituxan infusion.

1056 This information does not take the place of talking to your doctor about

1057 your medical condition or your treatment. Talk with your doctor if you

1058 have any questions about your treatment with Rituxan.

1059 **What is the most important safety information I should know about**

1060 **Rituxan?**

1061 **Rituxan can cause the following serious side effects, some of which**

1062 **could be life-threatening:**

1063 • **Infusion reactions.** Tell your doctor or get medical treatment right
1064 away if you get hives, swelling, dizziness, blurred vision, drowsiness,
1065 headache, cough, wheezing, or have trouble breathing while receiving
1066 or after receiving Rituxan.

1067 • **Tumor Lysis Syndrome (TLS).** TLS is caused by the fast
1068 breakdown of certain blood cancers. TLS can cause kidney failure
1069 and the need for dialysis treatment. Patients receiving Rituxan for
1070 non-Hodgkin's lymphoma may get TLS.

1071 • **Severe skin reactions.** Tell your doctor or get medical treatment
1072 right away if you get painful sores, ulcers, blisters, or peeling skin
1073 while receiving or after receiving Rituxan.

- 1074 • **Progressive Multifocal Leukoencephalopathy (PML).** PML is a
1075 rare brain infection that usually causes death or severe disability.
- 1076 • PML has been reported in patients during or after their treatment with
1077 Rituxan.
- 1078 • There is no known treatment, prevention, or cure for PML.
- 1079 • Call your doctor right away if you notice any new or worsening
1080 medical problems, such as a new or sudden change in thinking,
1081 walking, strength, vision, or other problems that have lasted over
1082 several days.
- 1083 Also, see “What are possible side-effects with Rituxan?” for other serious
1084 side effects, some of which could be life-threatening.

1085 **What is Rituxan?**

1086 Rituxan is a biologic medicine used in adults:

- 1087 • alone or with other anti-cancer medicines to treat certain types of
1088 non-Hodgkin’s lymphoma (NHL).
- 1089 • with another medicine called methotrexate to reduce the signs and
1090 symptoms of Rheumatoid Arthritis (RA) after at least one other
1091 medicine called a tumor necrosis factor (TNF) inhibitor has been used
1092 and did not work well.

1093 Rituxan has not been studied in children.

1094 **How does Rituxan work?**

1095 Rituxan works by getting rid of certain B-cells in the blood. B-cells are a
1096 type of white blood cell found in the blood. B-cells usually help the body
1097 fight infection. B-cells play an important role in diseases such as NHL
1098 and RA. Rituxan may also get rid of healthy B-cells and this can give you
1099 a higher chance for getting infections.

1100 **Who should not receive Rituxan?**

1101 Do not receive Rituxan if you ever had an allergic reaction to Rituxan.

1102 **What should I tell my doctor before treatment with Rituxan?**

1103 Tell your doctor about all of your medical conditions, including if you:

- 1104 • have an infection or have an infection that will not go away or that
1105 keeps coming back.
- 1106 • are scheduled to have surgery.
- 1107 • have had hepatitis B virus infection or are a carrier of hepatitis B
1108 virus. Your doctor should check you closely for signs of a hepatitis
1109 infection during treatment with Rituxan and for several months after
1110 treatment ends.
- 1111 • have any scheduled vaccinations. It is not known if Rituxan affects
1112 your ability to respond to vaccines.
- 1113 • have heart or lung problems.
- 1114 • are pregnant or planning to become pregnant. It is not known if
1115 Rituxan can harm your unborn baby.
- 1116 • are breastfeeding. It is not known if Rituxan passes into human breast
1117 milk. You should not breastfeed while being treated with Rituxan.

1118 Tell your doctor about all the other medicines you take, including
1119 prescription and nonprescription medicines, vitamins, or herbal
1120 supplements. If you have RA, tell your doctor if you are taking or took
1121 another biologic medicine called a TNF inhibitor or a DMARD (disease
1122 modifying anti-rheumatic drug).

1123 **How do I receive Rituxan?**

- 1124 • Rituxan is given through a needle placed in a vein (IV infusion), in
1125 your arm. Rituxan therapy is given in different ways for NHL and
1126 RA. Talk to your doctor about how you will receive Rituxan.
- 1127 • Your doctor may prescribe other medicines before each infusion of
1128 Rituxan to prevent or reduce pain, or to reduce fever and allergic
1129 reactions.
- 1130 • Your doctor should do regular blood tests to check for side effects or
1131 reactions to Rituxan.

1132 **What are possible side effects with Rituxan?**

1133 Rituxan can cause the following serious side effects, some of which could
1134 be life-threatening side effects, including (See “What is the most
1135 important safety information I should know about Rituxan?”)

- 1136 • Infusion reactions
- 1137 • Tumor Lysis Syndrome (TLS)
- 1138 • Severe skin reactions
- 1139 • Progressive Multifocal Leukoencephalopathy (PML)

1140 **Other serious side effects with Rituxan include:**

- 1141 • **Hepatitis B virus reactivation.** Tell your doctor if you had
1142 Hepatitis B virus or are a carrier of Hepatitis B virus. Rituxan may
1143 make you sick with Hepatitis B virus again and cause serious liver
1144 problems. People with active liver disease due to Hepatitis B should
1145 stop receiving Rituxan.
- 1146 • **Heart Problems.** Tell your doctor about any heart problems you
1147 have including chest pain (angina) and irregular heart beats. Rituxan
1148 can cause chest pain and irregular heart beats which may require
1149 treatment.
- 1150 • **Infections.** Rituxan can increase your chances for getting infections.
1151 Call your doctor right away if you have a persistent cough, fever,
1152 chills, congestion, or any flu-like symptoms while receiving Rituxan.
1153 These symptoms may be signs of a serious infection.
- 1154 • **Stomach and bowel problems.** Serious stomach and bowel
1155 problems have been seen when Rituxan has been used with
1156 anti-cancer medicines in some patients with non-Hodgkin’s
1157 lymphoma. Call your doctor right away if you have any stomach area
1158 pain during treatment with Rituxan.

1159 **Common side effects with Rituxan include:**

1160 Fever, chills, shakes, itching, hives, sneezing, swelling, throat irritation or
1161 tightness, and cough. These usually occur within 24 hours after the first
1162 infusion. Other common side effects include headache, nausea, upper

1163 respiratory tract infection, and aching joints. If you have any of these
1164 symptoms, tell your doctor or nurse.

1165 **What if I still have questions?**

1166 If you have any questions about Rituxan or your health, talk with your
1167 doctor. You can also visit the Rituxan internet sites at www.Rituxan.com
1168 or the companies' internet sites at www.Gene.com or
1169 www.Biogenidec.com or call 1-877-4-Rituxan (877-474-8892).

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