

1 **1.14.1.3 Draft 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 **DESCRIPTION**

22 The Rituxan[®] (Rituximab) antibody is a genetically engineered chimeric
23 murine/human monoclonal antibody directed against the CD20 antigen
24 found on the surface of normal and malignant B lymphocytes. The
25 antibody is an IgG₁ kappa immunoglobulin containing murine light- and
26 heavy-chain variable region sequences and human constant region
27 sequences. Rituximab is composed of two heavy chains of 451 amino
28 acids and two light chains of 213 amino acids (based on cDNA analysis)

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

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

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

45 **CLINICAL PHARMACOLOGY**

46 **General**

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

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

64 **Preclinical Pharmacology and Toxicology**

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

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

76 **Pharmacokinetics**

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

86 Rituxan at a dose of 375 mg/m² was administered as an IV infusion at
87 weekly intervals for 4 doses to 203 patients with NHL naive to Rituxan.¹³

CombinedReference

88 ¹⁴ The mean C_{\max} following the fourth infusion was 486 $\mu\text{g/mL}$ (range,
89 77.5–996.6 $\mu\text{g/mL}$). The peak and trough serum levels of Rituximab were
90 inversely correlated with baseline values for the number of circulating
91 CD20-positive B-cells and measures of disease burden. Median
92 steady-state serum levels were higher for responders compared with
93 nonresponders; however, no difference was found in the rate of
94 elimination as measured by serum half-life. Serum levels were higher in
95 patients with International Working Formulation (IWF) subtypes B, C,
96 and D as compared with those with subtype A.^{11,14} Rituximab was
97 detectable in the serum of patients 3 to 6 months after completion of
98 treatment.

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

104

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

Combined

Reference

108 Following the administration of 2 doses of Rituximab in patients with
109 rheumatoid arthritis, the mean C_{max} values were 183 mcg/mL (CV=24%)
110 for the 2×500 mg dose and 370 mcg/mL (CV=25%) for the 2×1000 mg
111 dose, respectively. Following 2×1000 mg Rituximab dose, mean volume
112 of distribution at steady state was 4.3 L (CV=28%). Mean systemic
113 serum clearance of Rituximab was 0.01 L/h (CV=38%), and mean
114 terminal elimination half-life after the second dose was 19 days
115 (CV=32%).

116 Special Populations

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

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

124 Pharmacodynamics

125 Administration of Rituxan resulted in a rapid and sustained depletion of
126 circulating and tissue-based B-cells. Lymph node biopsies performed
127 14 days after therapy showed a decrease in the percentage of B-cells in
128 seven of eight patients with NHL who had received single doses of
129 Rituximab ≥ 100 mg/m².¹⁰ Among the 166 patients in the pivotal NHL
130 study, circulating B-cells (measured as CD19-positive cells) were depleted
131 within the first three doses with sustained depletion for up to 6 to 9 months
132 post-treatment in 83% of patients.¹⁴ Of the responding patients assessed
133 (n=80), 1% failed to show significant depletion of CD19-positive cells
134 after the third infusion of Rituximab as compared to 19% of the
135 nonresponding patients. B-cell recovery began at approximately 6 months
136 following completion of treatment. Median B-cell levels returned to
137 normal by 12 months following completion of treatment.¹⁴

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

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

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

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

162 **CLINICAL STUDIES**

163 **Relapsed or Refractory, Low-Grade or Follicular, CD-20** 164 **Positive, B-Cell NHL**

165 Rituxan regimens tested include treatment weekly for 4 doses and
166 treatment weekly for 8 doses. Results for studies with a collective
167 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.

168

169 **Weekly for 4 Doses**170 **Study 1**

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

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

Combined

Reference

186 duration of response <3 months) relapse (53% vs. 36%). ORR in patients
187 previously treated with autologous bone marrow transplant was 78%
188 (18/23). The following adverse prognostic factors were *not* associated
189 with a lower response rate: age \geq 60 years, extranodal disease, prior
190 anthracycline therapy, and bone marrow involvement.

191 Weekly for 8 Doses

192 *Study 2*

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

197 Bulky Disease, Weekly for 4 Doses

198 In pooled data (Study 1 and 3) from multiple studies of Rituxan,
199 39 patients with relapsed or refractory, bulky disease (single lesion
200 > 10 cm in diameter), low-grade NHL received 375 mg/m² of Rituxan
201 weekly for 4 doses. Results are summarized in [Table 2](#).^{16, 17} (For
202 information on the higher incidence of Grade 3 and 4 adverse events, see
203 **ADVERSE REACTIONS: Risk Factors Associated with Increased**
204 **Rates of Adverse Events.**)

205 Retreatment Weekly for 4 Doses

206 *Study 3*

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

215 **Previously Untreated, Follicular, CD-20 Positive, B-Cell NHL**
 216 **Study 4**

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

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

234
 235 **Previously Untreated, Low-Grade, CD-20 Positive, B-Cell NHL**
 236 **Study 5**

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

Combined

Reference

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

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

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

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

259 **Study 6**

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

Combined

Reference

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

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

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

284 Study 7

285 A total of 399 patients with DLBCL, aged ≥ 60 years, were randomized in
286 a 1:1 ratio to receive CHOP or R-CHOP induction. All patients received
287 up to 8, 3-week cycles of CHOP induction; patients in the R-CHOP arm
288 received Rituxan 375 mg/m² on Day 1 of each cycle. The main outcome
289 measure of the study was event free survival, defined as the time from
290 randomization to relapse, progression, change in therapy or death from
291 any cause. Among all enrolled patients, 80% had stage III or IV disease,
292 60% of patients had an age-adjusted IPI ≥ 2 , 80% had ECOG performance
293 status scores < 2 , 66% had elevated LDH levels, and 52% had extranodal
294 involvement in at least two sites. Efficacy results are presented in [Table 4](#).

295 Study 8

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

CombinedReference

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

306

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

309 Rheumatoid Arthritis (RA)

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

Combined

Reference

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

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

321 The proportions of Rituxan (1000 mg) treated patients achieving ACR 20,
322 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

323
324 Improvement was also noted for all components of ACR response
325 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.

326

327 The time course of ACR 20 response for this study is shown in [Figure 1](#).

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

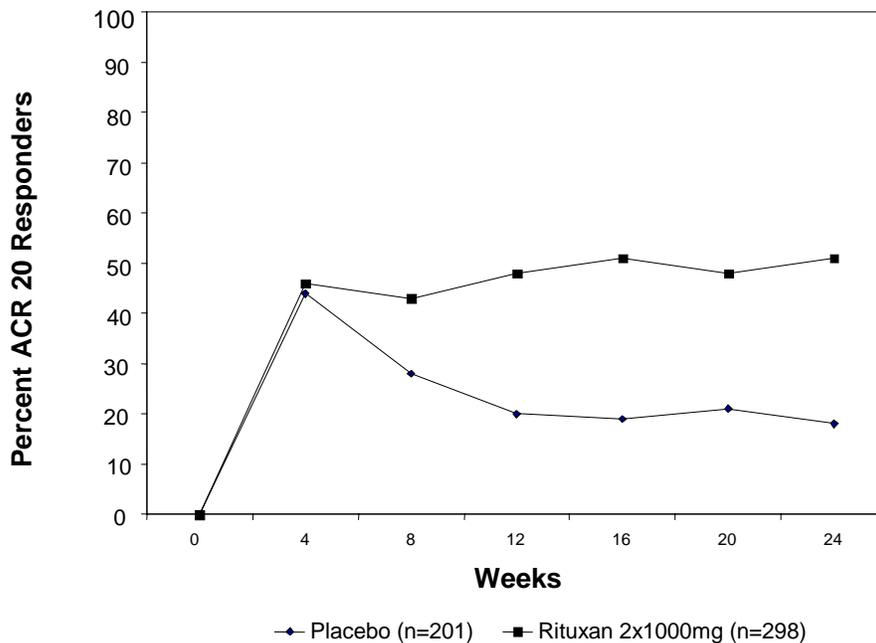
330 responses were observed for the Rituxan group by week 8 and were
 331 maintained through week 24 after a single course of treatment

332 (2 infusions) with Rituxan. Similar patterns were demonstrated for

333 ACR 50 and 70 responses.

334
335

Figure 1
ACR 20 Responses Over 24 Weeks



336
337

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

343 **INDICATIONS AND USAGE**

344 **Non-Hodgkin’s Lymphoma**

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

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

Combined

Reference

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

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

358 Rheumatoid Arthritis

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

363 CONTRAINDICATIONS

364 None.

365 WARNINGS (See **BOXED WARNINGS**)

366 Severe Infusion Reactions (see **BOXED WARNINGS** and 367 **ADVERSE REACTIONS**)

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

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

395 **Tumor Lysis Syndrome [TLS] (See **BOXED WARNINGS** and**
396 **ADVERSE REACTIONS)**

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

410 **Hepatitis B Reactivation with Related Fulminant Hepatitis and**
411 **Other Viral Infections**

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

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

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

436 **Cardiovascular**

437 Infusions should be discontinued in the event of serious or life-threatening
438 cardiac arrhythmias. Patients who develop clinically significant
439 arrhythmias should undergo cardiac monitoring during and after
440 subsequent infusions of Rituxan Patients with pre-existing cardiac

441 conditions including arrhythmias and angina have had recurrences of these
442 events during Rituxan therapy and should be monitored throughout the
443 infusion and immediate post-infusion period.

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

446 Rituxan administration has been associated with severe renal toxicity
447 including acute renal failure requiring dialysis and in some cases, has led
448 to a fatal outcome in hematologic malignancy patients. Renal toxicity has
449 occurred in patients with high numbers of circulating malignant cells
450 ($>25,000/\text{mm}^3$) or high tumor burden who experience tumor lysis
451 syndrome and in patients with NHL administered concomitant cisplatin
452 therapy during clinical trials. The combination of cisplatin and Rituxan is
453 not an approved treatment regimen. If this combination is used in clinical
454 trials *extreme caution* should be exercised; patients should be monitored
455 closely for signs of renal failure. Discontinuation of Rituxan should be
456 considered for those with rising serum creatinine or oliguria.

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

458 Mucocutaneous reactions, some with fatal outcome, have been reported in
459 patients treated with Rituxan. These reports include paraneoplastic
460 pemphigus (an uncommon disorder which is a manifestation of the
461 patient's underlying malignancy),¹⁹ Stevens-Johnson syndrome, lichenoid
462 dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis.
463 The onset of the reaction in the reported cases has varied from 1–13 weeks
464 following Rituxan exposure. Patients experiencing a severe
465 mucocutaneous reaction should not receive any further infusions and seek
466 prompt medical evaluation. Skin biopsy may help to distinguish among
467 different mucocutaneous reactions and guide subsequent treatment.
468 The safety of readministration of Rituxan to patients with any of these
469 mucocutaneous reactions has not been determined.

470 **Concomitant use with biologic agents and DMARDs other than**
471 **methotrexate in RA:** Limited data are available on the safety of the use

Combined

Reference

472 of biologic agents or DMARDs other than methotrexate in patients
473 exhibiting peripheral B cell depletion following treatment with Rituximab.
474 Patients should be closely observed for signs of infection if biologic
475 agents and/or DMARDs are used concomitantly.

476 **Bowel Obstruction and Perforation**

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

485 **PRECAUTIONS**

486 **Information for Patients**

487 Patients should be provided the Rituxan Patient Information leaflet and
488 provided an opportunity to read it prior to each treatment session.
489 Because caution should be exercised in administering Rituxan to patients
490 with active infections, it is important that the patient's overall health be
491 assessed at each visit and any questions resulting from the patient's
492 reading of the Patient Information be discussed.

493 **Laboratory Monitoring**

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

500 Drug/Laboratory Interactions

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

506 Immunization

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

511 Physicians should review the vaccination status of patients with RA being
512 considered for Rituxan treatment and follow the Centers for Disease
513 Control and Prevention (CDC) guidelines for adult vaccination with
514 non-live vaccines intended to prevent infectious disease, prior to therapy.
515 For patients with NHL, the benefits of primary and/or booster vaccinations
516 should be weighted against the risks of delay in initiation of Rituxan
517 therapy.

518 **Use in patients with RA who had no prior inadequate response to**
519 **TNF antagonists:** While efficacy of Rituxan was supported in two
520 well-controlled trials in patients with RA with prior inadequate responses
521 to non-biologic DMARDs, a favorable risk benefit relationship has not
522 been established in this population. The use of Rituxan in patients with
523 RA who have no prior inadequate response to one or more TNF
524 antagonists is not recommended (see **CLINICAL STUDIES:**
525 **Rheumatoid Arthritis**).

526 **Retreatment in patients with RA:** Safety and efficacy of retreatment
527 have not been established in controlled trials. A limited number of
528 patients have received two to five courses (two infusions per course) of
529 treatment in an uncontrolled setting. In clinical trials in patients with RA,

530 most of the patients who received additional courses did so 24 weeks after
531 the previous course and none were retreated sooner than 16 weeks.

532 **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

533 No long-term animal studies have been performed to establish the
534 carcinogenic potential of Rituxan. Studies also have not been completed
535 to assess mutagenic potential of Rituxan, or to determine potential effects
536 on fertility in males or females. Individuals of childbearing potential
537 should use effective contraceptive methods during treatment and for up to
538 12 months following Rituxan therapy.

539 **Pregnancy Category C**

540 An embryo-fetal developmental toxicity study was performed on pregnant
541 cynomolgus monkeys. Animals were administered Rituximab via the
542 intravenous route during early gestation (organogenesis period;
543 post-coitum days 20 through 50). Rituximab was administered as loading
544 doses on post-coitum days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and
545 then weekly on post-coitum days 29, 36, 43 and 50, at 20, 50 or
546 100 mg/kg/week. The 100 mg/kg/week dose resulted in exposures of
547 0.8-fold a human 2 g dose based on AUC. Although Rituximab has been
548 shown to cross the monkey placenta, there was no evidence of
549 teratogenicity under the conditions of the experiment.

550 Nonteratogenic effects: Results from the embryo-fetal developmental
551 toxicology study described above showed that Rituximab treatment
552 produced a decrease in lymphoid tissue B cells in the offspring of treated
553 dams.

554 A subsequent pre- and postnatal developmental toxicity study in
555 cynomolgus monkeys was completed to assess developmental toxicity and
556 the recovery of B-cells and immune function in infants exposed to
557 Rituximab *in utero*. Rituximab was administered from early gestation
558 (post-coitum day 20) through lactation (post-partum day 28). Due to the
559 possibility of anti-drug antibody development with such a long dosing

Combined

Reference

560 period, the animals were divided into 3 sets of dosing periods: one set
561 received Rituximab (20 or 100 mg/kg weekly) from post-coitum day 20
562 through delivery and post-partum day 28 (~25 weeks); a second set
563 received Rituximab (20 or 100 mg/kg weekly) from post-coitum day 50
564 through post-coitum day 76 (8 weeks); a third set received Rituximab
565 (20 or 100 mg/kg weekly) from post-coitum day 76 through delivery and
566 post-partum day 28 (~8 weeks). For each of these dosing periods, a
567 loading dose was administered for the first 3 days of the period at doses of
568 15 or 75 mg/kg/day. The decreased B cells and immunosuppression noted
569 in the offspring of pregnant animals treated with either 20 or
570 100 mg/kg/week Rituximab showed a return to normal levels and function
571 within 6 months post-birth. However, there are no adequate and
572 well-controlled studies in pregnant women. Because animal reproductive
573 studies are not always predictive of human response, this drug should be
574 used during pregnancy only if the potential benefit justifies the potential
575 risk to the fetus.

576 Nursing Mothers

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

583 Pediatric Use

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

586 Geriatric Use

587 Among patients with DLBCL in three randomized, active-controlled trials,
588 927 patients received Rituxan in combination with chemotherapy.
589 Of these, 396 (43%) were age 65 or greater and 123 (13%) were age 75 or
590 greater. No overall differences in effectiveness were observed between

Combined

Reference

591 these subjects and younger subjects. However, elderly patients were more
592 likely to experience cardiac adverse events, mostly supraventricular
593 arrhythmias. Serious pulmonary adverse events were also more common
594 among the elderly, including pneumonia and pneumonitis.

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

600 Among the 517 patients in the phase 3 RA study, 16% were 65–75 years
601 old and 2% were 75 years old and older. The Rituxan ACR 20 response
602 rates in the older (age ≥ 65 years) vs. younger (age < 65 years) patients
603 were similar (53% vs. 51%, respectively). Adverse reactions, including
604 incidence, severity, and type of adverse reaction were similar between
605 older and younger patients.

606 **ADVERSE REACTIONS**

607 Because clinical trials are conducted under widely varying conditions,
608 adverse reaction rates observed in the clinical trials of a drug cannot be
609 directly compared to rates in the clinical trials of another drug and may not
610 reflect the rates observed in practice. The adverse reaction information
611 from clinical trials does, however, provide a basis for identifying the
612 adverse events that appear to be related to drug use and for approximating
613 rates.

614 The following serious adverse reactions, some with fatal outcomes, have
615 been reported in patients treated with Rituxan (see **BOXED WARNINGS**
616 and **WARNINGS**): severe or fatal infusion reactions, tumor lysis
617 syndrome, severe mucocutaneous reactions, hepatitis B reactivation with
618 fulminant hepatitis, other viral infections, cardiac arrhythmias, renal
619 toxicity, bowel obstruction and perforation.

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

621 The overall safety database for Rituxan is based on clinical trial data from
622 1606 patients with NHL, who received Rituxan either as a single agent or
623 in combination with chemotherapy. Additional safety information was
624 obtained from post-marketing safety surveillance. The most common
625 adverse reactions were infusion reactions (see **INFUSION REACTIONS**
626 below).

627 Except as noted, adverse events described below occurred in the setting of
628 relapsed or refractory, low-grade or follicular, CD20-positive, B-cell,
629 NHL and are based on 356 patients treated in single-arm studies of
630 Rituxan administered as a single agent. Most patients received Rituxan
631 375 mg/m² weekly for 4 doses.

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

633 Mild to moderate infusion reactions consisting of fever and chills/rigors
634 occurred in the majority of patients during the first Rituxan infusion.
635 Other frequent infusion reaction symptoms included nausea, pruritus,
636 angioedema, asthenia, hypotension, headache, bronchospasm, throat
637 irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and
638 hypertension. These reactions generally occurred within 30 to
639 120 minutes of beginning the first infusion, and resolved with slowing or
640 interruption of the Rituxan infusion and with supportive care
641 (diphenhydramine, acetaminophen, IV saline, and vasopressors).
642 The incidence of infusion reactions was highest during the first infusion
643 (77%) and decreased with each subsequent infusion (30% with fourth
644 infusion and 14% with eighth infusion). Injection site pain was reported
645 in less than 5% of patients.

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

648 Rituxan induced B-cell depletion in 70% to 80% of patients with NHL and
649 was associated with decreased serum immunoglobulins in a minority of
650 patients; the lymphopenia lasted a median of 14 days (range, 1–588 days).

Combined

Reference

651 Infectious events occurred in 31% of patients: 19% of patients had
652 bacterial infections, 10% had viral infections, 1% had fungal infections,
653 and 6% were unknown infections. Incidence is not additive because a
654 single patient may have had more than one type of infection. Serious
655 infectious events (Grade 3 or 4), including sepsis, occurred in 2% of
656 patients.

657 Hematologic Events

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

665 Pulmonary Events

666 135 patients (38%) experienced pulmonary events in clinical trials.
667 The most common respiratory system adverse events experienced were
668 increased cough, rhinitis, bronchospasm, dyspnea, and sinusitis. In both
669 clinical studies and post-marketing surveillance, there have been a limited
670 number of reports of bronchiolitis obliterans presenting up to 6 months
671 post-Rituxan infusion and a limited number of reports of pneumonitis
672 (including interstitial pneumonitis) presenting up to 3 months post-Rituxan
673 infusion, some of which resulted in fatal outcomes. The safety of
674 resumption or continued administration of Rituxan in patients with
675 pneumonitis or bronchiolitis obliterans is unknown.

676 Immunogenicity

677 The observed incidence of antibody positivity in an assay is highly
678 dependent on the sensitivity and specificity of the assay and may be
679 influenced by several factors including sample handling, concomitant
680 medications, and underlying disease. For these reasons, comparison of the

Combined

Reference

681 incidence of antibodies to Rituxan with the incidence of antibodies to
682 other products may be misleading.

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

689 **Single Agent Rituxan for Relapsed or Refractory, Low-Grade** 690 **or Follicular, CD20-Positive, B-Cell NHL**

691 The data below were obtained in 356 patients receiving single agent
692 Rituxan for treatment of relapsed, refractory, low grade or follicular NHL
693 (see **CLINICAL STUDIES**). The majority of patients received
694 375 mg/m² IV weekly × 4 doses. The median age was 57 (range
695 22–81 years). Sixty percent were male; 93% were Caucasian, 1% were
696 Black, 2% were Hispanic, 2% were Asian, and 2% were from other racial
697 groups.

698 [Table 7](#) lists the most common, as well as Grade 3 and 4, adverse events
699 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.

701

702 Risk Factors Associated With Increased Rates of Adverse Events

703 Administration of Rituxan weekly for 8 doses resulted in higher rates of

704 Grade 3 and 4 adverse events¹⁵ overall (70%) compared with

705 administration weekly for 4 doses (57%). The incidence of Grade 3 or 4

706 adverse events was similar in patients retreated with Rituxan compared

707 with initial treatment (58% and 57%, respectively). The incidence of the

708 following clinically significant adverse events was higher in patients with

709 bulky disease (lesions ≥ 10 cm) (N=39) versus patients with lesions

710 < 10 cm (N=195): abdominal pain, anemia, dyspnea, hypotension, and

711 neutropenia.

712 Previously Untreated, Follicular, CD20-Positive, B-Cell NHL

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

719 Patients in the R-CVP arm had higher incidences of infusional toxicity and
720 of neutropenia as compared to those in the CVP arm. The following
721 adverse events occurred more frequently ($\geq 5\%$) in patients receiving
722 R-CVP compared to CVP alone: rash (17% vs. 5%), cough
723 (15% vs. 6%), flushing (14% vs. 3%), rigors (10% vs. 2%), pruritis
724 (10% vs. 1%), neutropenia (8% vs. 3%), and chest tightness (7% vs. 1%).

725 Previously Untreated, Low-Grade, CD20-Positive, B-Cell NHL

726 Safety data were obtained in a single, multi-center, randomized study of
727 322 patients of whom 161 received Rituxan and 161 received no treatment
728 following 6–8 cycles of CVP chemotherapy. Ninety-five patients (59%)
729 received the maximum number of doses (16) of Rituxan.

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

732 The following adverse events were reported more frequently ($\geq 5\%$) in
733 patients receiving Rituxan following CVP compared with those who
734 received no further therapy: fatigue (39% vs. 14%), anemia
735 (35% vs. 20%), peripheral sensory neuropathy (30% vs. 18%), infections
736 (19% vs. 9%), pulmonary toxicity (18% vs. 10%), hepato-biliary toxicity
737 (17% vs. 7%), rash and/or pruritis (17% vs. 5%), arthralgia (12% vs. 3%),
738 and weight gain (11% vs. 4%). Neutropenia was the only Grade 3 or
739 4 adverse event that occurred more frequently ($\geq 2\%$) in the Rituxan arm
740 compared with those who received no further therapy (4% vs. 1%).

741 Rituxan in Combination with Chemotherapy for DLBCL

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

747 The population varied from 18–92 years of age and 55% were male; racial
748 distribution was collected only for Study 6 (see **CLINICAL STUDIES**
749 section) where 90% of patients were Caucasian, 5% were Black, 3% were
750 Hispanic and 2% were from other racial groups. Patients received
751 4–8 doses of Rituxan at 375 mg/m².

752 The following adverse events, regardless of severity, were reported more
753 frequently (≥5%) in patients age ≥60 years receiving R-CHOP as
754 compared to CHOP alone: pyrexia (56% vs. 46%), lung disorder (31% vs.
755 24%), cardiac disorder (29% vs. 21%), and chills (13% vs. 4%). In one of
756 these studies (Study 7), more detailed assessment of cardiac toxicity
757 revealed that supraventricular arrhythmias or tachycardia accounted for
758 most of the difference in cardiac disorders, with 4.5% vs. 1.0% incidences
759 for R-CHOP and CHOP, respectively.

760 The following Grade 3 or 4 adverse events were reported more frequently
761 among patients in the R-CHOP arm compared with those in the CHOP
762 arm: thrombocytopenia (9% vs. 7%) and lung disorder (6% vs. 3%).

763 Other severe adverse events reported more commonly among patients
764 receiving R-CHOP in one or more studies were viral infection,
765 neutropenia and anemia.

766 Adverse Reactions in Patients with Rheumatoid Arthritis

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

770 **ADVERSE REACTIONS**). Specific safety considerations in this
 771 indication are discussed below.

772 Where specific percentages are noted, these data are based on 938 patients
 773 treated in Phase 2 and 3 studies of Rituxan (2 × 1000 mg) or placebo
 774 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.

775

776 **Infusion Reactions**

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

Combined

Reference

779 first infusion, compared to 23% of placebo-treated patients receiving their
780 first infusion. The incidence of adverse events during the 24-hour period
781 following the second infusion, Rituxan or placebo, decreased to 11% and
782 13%, respectively. Acute infusion reactions (manifested by fever, chills,
783 rigors, pruritus, urticaria/rash, angioedema, sneezing, throat irritation,
784 cough, and/or bronchospasm, with or without associated hypotension or
785 hypertension) were experienced by 27% of Rituxan-treated patients
786 following their first infusion, compared to 19% of placebo-treated patients
787 receiving their first placebo infusion. The incidence of these acute
788 infusion reactions following the second infusion of Rituxan or placebo
789 decreased to 9% and 11%, respectively. Serious acute infusion reactions
790 were experienced by <1% of patients in either treatment group. Acute
791 infusion reactions required dose modification (stopping, slowing or
792 interruption of the infusion) in 10% and 2% of patients receiving
793 Rituximab or placebo, respectively, after the first course. The proportion
794 of patients experiencing acute infusion reactions decreased with
795 subsequent courses of Rituxan. The administration of IV glucocorticoids
796 prior to Rituxan infusions reduced the incidence and severity of such
797 reactions, however, there was no clear benefit from the administration of
798 oral glucocorticoids for the prevention of acute infusion reactions.
799 Patients in clinical studies also received antihistamines and acetaminophen
800 prior to Rituxan infusions.

801 Infections

802 In RA clinical studies, 39% of patients in the Rituxan group experienced
803 an infection of any type compared to 34% of patients in the placebo group.
804 The most common infections were nasopharyngitis, upper respiratory tract
805 infections, urinary tract infections, bronchitis, and sinusitis. The only
806 infections to show an absolute increase over placebo of at least 1% were
807 upper respiratory tract infections, which affected 7% of Rituxan-treated
808 patients and 6% of placebo-treated patients and rhinitis, which affected
809 3% of Rituxan-treated patients and 2% of placebo-treated patients.

Combined

Reference

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

814 Cardiac Events

815 The incidence of serious cardiovascular events in the double-blind part of
816 the clinical trials was 1.7% and 1.3% in Rituxan and placebo treatment
817 groups, respectively. Three cardiovascular deaths occurred during the
818 double-blind period of the RA studies including all Rituximab regimens
819 (3/769=0.4%) as compared to none in the placebo treatment group
820 (0/389).

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

825 Immunogenicity

826 A total of 54/990 patients (5%) with RA tested positive for HACA.
827 Of these, most became positive by week 24. Following the first course,
828 however, some became positive at week 16 or after 24 weeks. Some
829 patients tested positive after the second course of treatment. Limited data
830 are available on the safety or efficacy of Rituxan retreatment in patients
831 who develop HACA. One of 10 HACA-positive patients who received
832 retreatment with Rituxan experienced a serious acute infusion reaction
833 (bronchospasm). The clinical relevance of HACA formation in
834 Rituximab-treated patients is unclear.

835 Post-Marketing Reports

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

Combined

Reference

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

844 *Hematologic:* prolonged pancytopenia, marrow hypoplasia, and late onset
845 neutropenia, hyperviscosity syndrome in Waldenstrom's
846 macroglobulinemia.

847 *Cardiac:* fatal cardiac failure.

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

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

852 *Skin:* severe mucocutaneous reactions.

853 *Gastrointestinal:* bowel obstruction and perforation.

854 **OVERDOSAGE**

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

858 **DOSAGE AND ADMINISTRATION**

859 **Relapsed or Refractory, Low-Grade or Follicular,** 860 **CD20-Positive, B-Cell Non-Hodgkin's Lymphoma**

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

863 **Retreatment Therapy**

864 The recommended dose of Rituxan is 375 mg/m² IV infusion once weekly
865 for 4 doses in responding patients who develop progressive disease after

Combined

Reference

866 previous Rituxan therapy. Currently there are limited data concerning
867 more than 2 courses.

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

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

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

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

875 **Diffuse Large B-Cell NHL**

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

878 **Rheumatoid Arthritis**

879 Rituxan is given as two-1000 mg IV infusions separated by 2 weeks.
880 Glucocorticoids administered as methylprednisolone 100 mg IV or its
881 equivalent 30 minutes prior to each infusion are recommended to reduce
882 the incidence and severity of infusion reactions. Safety and efficacy of
883 retreatment have not been established in controlled trials (see
884 **PRECAUTIONS: [Retreatment in patients with RA](#)**).

885 Rituxan is given in combination with methotrexate.

886 **Rituxan as a Component of Zevalin[®] (Ibritumomab tiuxetan)** 887 **Therapeutic Regimen**

888 As a required component of the Zevalin therapeutic regimen, Rituxan
889 250 mg/m² should be infused within 4 hours prior to the administration of
890 Indium-111- (In-111-) Zevalin and within 4 hours prior to the
891 administration of Yttrium-90- (Y-90-) Zevalin. Administration of Rituxan
892 and In-111-Zevalin should precede Rituxan and Y-90-Zevalin by
893 7–9 days. Refer to the Zevalin package insert for full prescribing
894 information regarding the Zevalin therapeutic regimen.

895 Rituxan may be administered in an outpatient setting. DO NOT
896 ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. (See
897 **Administration**).

898 **Instructions for Administration**

899 Preparation for Administration

900 Use appropriate aseptic technique. Withdraw the necessary amount of
901 Rituxan and dilute to a final concentration of 1 to 4 mg/mL into an
902 infusion bag containing either 0.9% Sodium Chloride, USP, or
903 5% Dextrose in Water, USP. Gently invert the bag to mix the solution.
904 Discard any unused portion left in the vial. Parenteral drug products
905 should be inspected visually for particulate matter and discoloration prior
906 to administration.

907 Rituxan solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for
908 24 hours. Rituxan solutions for infusion have been shown to be stable for
909 an additional 24 hours at room temperature. However, since Rituxan
910 solutions do not contain a preservative, diluted solutions should be stored
911 refrigerated (2°C–8°C). No incompatibilities between Rituxan and
912 polyvinylchloride or polyethylene bags have been observed.

913 **Administration: DO NOT ADMINISTER AS AN INTRAVENOUS** 914 **PUSH OR BOLUS**

915 Infusion reactions may occur (see **BOXED WARNINGS**, **WARNINGS**,
916 and **ADVERSE REACTIONS**). Premedication consisting of
917 acetaminophen and an antihistamine should be considered before each
918 infusion of Rituxan. Premedication may attenuate infusion reactions.
919 Since transient hypotension may occur during Rituxan infusion,
920 consideration should be given to withholding antihypertensive
921 medications 12 hours prior to Rituxan infusion.

922 First Infusion

923 The Rituxan solution for infusion should be administered intravenously at
924 an initial rate of 50 mg/hr. Rituxan should not be mixed or diluted with

Combined

Reference

925 other drugs. If infusion reactions do not occur, escalate the infusion rate
926 in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
927 If an infusion reaction develops, the infusion should be temporarily
928 slowed or interrupted (see **BOXED WARNINGS** and **WARNINGS**).
929 The infusion can continue at one-half the previous rate upon improvement
930 of patient symptoms.

931 Subsequent Infusions

932 If the patient tolerated the first infusion well, subsequent Rituxan infusions
933 can be administered at an initial rate of 100 mg/hr, and increased by
934 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr
935 as tolerated. If the patient did not tolerate the first infusion well, follow
936 the guidelines under First Infusion.

937 **Stability and Storage**

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

943 **HOW SUPPLIED**

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

946 Single unit 100 mg carton: Contains one 10 mL vial of Rituxan
947 (10 mg/mL).

948 NDC 50242-051-21

949 Single unit 500 mg carton: Contains one 50 mL vial of Rituxan
950 (10 mg/mL).

951 NDC 50242-053-06

952 **REFERENCES**

- 953 1. Valentine MA, Meier KE, Rossie S, et al. Phosphorylation of the
954 CD20 phosphoprotein in resting B lymphocytes. *J Biol Chem*
955 1989;264(19): 11282–7.
- 956 2. Einfeld DA, Brown JP, Valentine MA, et al. Molecular cloning of
957 the human B cell CD20 receptor predicts a hydrophobic protein
958 with multiple transmembrane domains. *EMBO J* 1988;7(3):711–7.
- 959 3. Anderson KC, Bates MP, Slaughenhoupt BL, et al. Expression of
960 human B cell-associated antigens on leukemias and lymphomas: A
961 model of human B-cell differentiation. *Blood* 1984;63(6):1424–33.
- 962 4. Tedder TF, Boyd AW, Freedman AS, et al. The B cell surface
963 molecule B1 is functionally linked with B-cell activation and
964 differentiation. *J Immunol* 1985;135(2):973–9.
- 965 5. Tedder TF, Zhou LJ, Bell PD, et al. The CD20 surface molecule of
966 B lymphocytes functions as a calcium channel. *J Cell Biochem*
967 1990;14D:195.
- 968 6. Press OW, Applebaum F, Ledbetter JA, Martin PJ, Zarling J, Kidd
969 P, et al. Monoclonal antibody 1F5 (anti-CD20) serotherapy of
970 human B-cell lymphomas. *Blood* 1987;69(2):584–91.
- 971 7. Dorner, T, Rumester, G. The role of B-cells in rheumatoid arthritis:
972 mechanisms and therapeutic targets. *Curr Op Rheum*
973 2003;15:246–52.
- 974 8. Reff ME, Carner C, Chambers KS, Chinn PC, Leonard JE, Raab R,
975 et al. Depletion of B cells in vivo by a chimeric mouse human
976 monoclonal antibody to CD20. *Blood* 1994;83(2):435–45.
- 977 9. Demidem A, Lam T, Alas S, Hariharan K, Hanna N, and Bonavida
978 B. Chimeric anti-CD20 (IDEC-C2B8) monoclonal antibody
979 sensitizes a B cell lymphoma cell line to cell killing by cytotoxic
980 drugs. *Cancer Biotherapy & Radiopharmaceuticals*
981 1997;12(3):177–86.
- 982 10. Maloney DG, Liles TM, Czerwinski C, Waldichuk J, Rosenberg J,
983 Grillo-López A, et al. Phase I clinical trial using escalating
984 single-dose infusion of chimeric anti-CD20 monoclonal antibody
985 (IDEC-C2B8) in patients with recurrent B-cell lymphoma. *Blood*
986 1994;84(8):2457–66.

CombinedReference

- 987 11. Berinstein NL, Grillo-López AJ, White CA, Bence-Bruckler I,
988 Maloney D, Czuczman M, et al. Association of serum Rituximab
989 (IDEC-C2B8) concentration and anti-tumor response in the
990 treatment of recurrent low-grade or follicular non-Hodgkin's
991 lymphoma. *Annals of Oncology* 1998;9:995–1001.
- 992 12. Maloney DG, Grillo-López AJ, Bodkin D, White CA, Liles T-M,
993 Royston I, et al. IDEC-C2B8: Results of a phase I multiple-dose
994 trial in patients with relapsed non-Hodgkin's lymphoma. *J Clin*
995 *Oncol* 1997;15(10):3266–74.
- 996 13. Maloney DG, Grillo-López AJ, White CA, Bodkin D, Schilder RJ,
997 Neidhart JA, et al. IDEC-C2B8 (Rituximab) anti-CD20
998 monoclonal antibody therapy in patients with relapsed low-grade
999 non-Hodgkin's lymphoma. *Blood* 1997;90(6):2188–95.
- 1000 14. McLaughlin P, Grillo-López AJ, Link BK, Levy R, Czuczman MS,
1001 Williams ME, et al. Rituximab chimeric anti-CD20 monoclonal
1002 antibody therapy for relapsed indolent lymphoma: half of patients
1003 respond to a four-dose treatment program. *J Clin Oncol*
1004 1998;16(8):2825–33.
- 1005 15. Piro LD, White CA, Grillo-López AJ, Janakiraman N, Saven A,
1006 Beck TM, et al. Extended Rituximab (anti-CD20 monoclonal
1007 antibody) therapy for relapsed or refractory low-grade or follicular
1008 non-Hodgkin's lymphoma. *Annals of Oncology* 1999;10:655–61.
- 1009 16. Data on file.
- 1010 17. Davis TA, White CA, Grillo-López AJ, Velasquez WS, Lin B,
1011 Maloney DG, et al. Single-agent monoclonal antibody efficacy in
1012 bulky Non-Hodgkin's lymphoma: results of a phase II trial of
1013 rituximab. *JCO* 1999;17:1851–7.
- 1014 18. Davis TA, Grillo-López AJ, White CA, McLaughlin P, Czuczman
1015 MS, Link BK, Maloney DG, Weaver RL, Rosenberg J, Levy R.
1016 Rituximab anti-CD20 monoclonal antibody therapy in
1017 non-hodgkin's lymphoma: safety and efficacy of re-treatment. *J*
1018 *Clin Oncol* 2000;18(17):3135–43.
- 1019 19. Anhalt GJ, Kim SC, Stanley JR, Korman NJ, Jabs DA, Kory M,
1020 Izumi H, Rattie H, Mutasim D, Ariss-Abdo L, Labib RS.
1021 Paraneoplastic Pemphigus, an autoimmune mucocutaneous disease
1022 associated with neoplasia. *NEJM* 1990;323(25):1729–35.

Combined

Reference

- 1023 20. National Institutes of Health (US), National Cancer Institute.
1024 Common Toxicity Criteria. [Bethesda, MD.] : National Institutes of
1025 Health, National Cancer Institute; c1998;73p.

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

Rituxan[®]
(Rituximab)

Manufactured by: 4835500

Genentech, Inc. Initial US Approval November 26, 1997

1 DNA Way

South San Francisco, CA 94080-4990 Revision Date September 29, 2006

©2006 Biogen Idec Inc. and Genentech, Inc.

1026

1027

Patient Information

1028

Rituxan[®] (ri-tuk'-san)

1029

(Rituximab)

1030 Read this patient information leaflet when you have been prescribed

1031 Rituxan and each time you are scheduled to receive a Rituxan infusion.

1032 This information does not take the place of talking to your doctor about

1033 your medical condition or your treatment. Talk with your doctor if you

1034 have any questions about your treatment with Rituxan.

1035 **What is the most important safety information I should know about**

1036 **Rituxan?**

1037 **Rituxan can cause the following serious side effects, some of which**

1038 **could be life-threatening:**

1039 • **Infusion reactions.** Tell your doctor or get medical treatment right
1040 away if you get hives, swelling, dizziness, blurred vision, drowsiness,
1041 headache, cough, wheezing, or have trouble breathing while receiving
1042 or after receiving Rituxan.

1043 • **Tumor Lysis Syndrome (TLS).** TLS is caused by the fast
1044 breakdown of certain blood cancers. TLS can cause kidney failure
1045 and the need for dialysis treatment. Patients receiving Rituxan for
1046 non-Hodgkin's lymphoma may get TLS.

1047 • **Severe skin reactions.** Tell your doctor or get medical treatment
1048 right away if you get painful sores, ulcers, blisters, or peeling skin
1049 while receiving or after receiving Rituxan.

1050 Also, see “What are possible side-effects with Rituxan?” for other serious
1051 side effects, some of which could be life-threatening.

1052 **What is Rituxan?**

1053 Rituxan is a biologic medicine used in adults:

- 1054 • alone or with other anti-cancer medicines to treat certain types of
1055 non-Hodgkin’s lymphoma (NHL).
- 1056 • with another medicine called methotrexate to reduce the signs and
1057 symptoms of Rheumatoid Arthritis (RA) after at least one other
1058 medicine called a tumor necrosis factor (TNF) inhibitor has been used
1059 and did not work well.

1060 Rituxan has not been studied in children.

1061 **How does Rituxan work?**

1062 Rituxan works by getting rid of certain B-cells in the blood. B-cells are a
1063 type of white blood cell found in the blood. B-cells usually help the body
1064 fight infection. B-cells play an important role in diseases such as NHL
1065 and RA. Rituxan may also get rid of healthy B-cells and this can give you
1066 a higher chance for getting infections.

1067 **Who should not receive Rituxan?**

1068 Do not receive Rituxan if you ever had an allergic reaction to Rituxan.

1069 **What should I tell my doctor before treatment with Rituxan?**

1070 Tell your doctor about all of your medical conditions, including if you:

- 1071 • have an infection or have an infection that will not go away or that
1072 keeps coming back.
- 1073 • are scheduled to have surgery.
- 1074 • have had hepatitis B virus infection or are a carrier of hepatitis B
1075 virus. Your doctor should check you closely for signs of a hepatitis
1076 infection during treatment with Rituxan and for several months after
1077 treatment ends.

Combined

Reference

- 1078 • have any scheduled vaccinations. It is not known if Rituxan affects
1079 your ability to respond to vaccines.
- 1080 • have heart or lung problems.
- 1081 • are pregnant or planning to become pregnant. It is not known if
1082 Rituxan can harm your unborn baby.
- 1083 • are breastfeeding. It is not known if Rituxan passes into human breast
1084 milk. You should not breastfeed while being treated with Rituxan.
- 1085 Tell your doctor about all the other medicines you take, including
1086 prescription and nonprescription medicines, vitamins, or herbal
1087 supplements. If you have RA, tell your doctor if you are taking or took
1088 another biologic medicine called a TNF inhibitor or a DMARD (disease
1089 modifying anti-rheumatic drug).

1090 **How do I receive Rituxan?**

- 1091 • Rituxan is given through a needle placed in a vein (IV infusion), in
1092 your arm. Rituxan therapy is given in different ways for NHL and
1093 RA. Talk to your doctor about how you will receive Rituxan.
- 1094 • Your doctor may prescribe other medicines before each infusion of
1095 Rituxan to prevent or reduce pain, or to reduce fever and allergic
1096 reactions.
- 1097 • Your doctor should do regular blood tests to check for side effects or
1098 reactions to Rituxan.

1099 **What are possible side effects with Rituxan?**

- 1100 Rituxan can cause the following serious side effects, some of which could
1101 be life-threatening side effects, including (See “What is the most
1102 important safety information I should know about Rituxan?”)
- 1103 • Infusion reactions
- 1104 • Tumor Lysis Syndrome (TLS)
- 1105 • Severe skin reactions

1106 **Other serious side effects with Rituxan include:**

- 1107 • **Hepatitis B virus reactivation.** Tell your doctor if you had
1108 Hepatitis B virus or are a carrier of Hepatitis B virus. Rituxan may
1109 make you sick with Hepatitis B virus again and cause serious liver
1110 problems. People with active liver disease due to Hepatitis B should
1111 stop receiving Rituxan.
- 1112 • **Heart Problems.** Tell your doctor about any heart problems you
1113 have including chest pain (angina) and irregular heart beats. Rituxan
1114 can cause chest pain and irregular heart beats which may require
1115 treatment.
- 1116 • **Infections.** Rituxan can increase your chances for getting infections.
1117 Call your doctor right away if you have a persistent cough, fever,
1118 chills, congestion, or any flu-like symptoms while receiving Rituxan.
1119 These symptoms may be signs of a serious infection.
- 1120 • **Stomach and bowel problems.** Serious stomach and bowel
1121 problems have been seen when Rituxan has been used with
1122 anti-cancer medicines in some patients with non-Hodgkin's
1123 lymphoma. Call your doctor right away if you have any stomach area
1124 pain during treatment with Rituxan.

1125 **Common side effects with Rituxan include:**

1126 Fever, chills, shakes, itching, hives, sneezing, swelling, throat irritation or
1127 tightness, and cough. These usually occur within 24 hours after the first
1128 infusion. Other common side effects include headache, nausea, upper
1129 respiratory tract infection, and aching joints. If you have any of these
1130 symptoms, tell your doctor or nurse.

1131 **What if I still have questions?**

1132 If you have any questions about Rituxan or your health, talk with your
1133 doctor. You can also visit the Rituxan internet sites at www.Rituxan.com
1134 or the companies' internet sites at www.Gene.com or
1135 www.Biogenidec.com or call 1-877-4-Rituxan (877-474-8892).

1136 Jointly Marketed by: Biogen Idec Inc. and Genentech, Inc.

Combined

Reference

- 1137 Manufactured by:
1138 Genentech, Inc.
1139 1 DNA Way
1140 South San Francisco, CA 94080-4990
1141 ©2006 Biogen Idec Inc. and Genentech, Inc.

1142 Patient Information Approval February 28, 2006