

Final Draft Label

6-7-04

Rituxan® (Rituximab)

1 RITUXAN®
2 (Rituximab)

3

4 **WARNINGS**

5 **Fatal Infusion Reactions:** Deaths within 24 hours of RITUXAN infusion have been reported.

6 These fatal reactions followed an infusion reaction complex which included hypoxia,
7 pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular
8 fibrillation or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in
9 association with the first infusion. (See WARNINGS and ADVERSE REACTIONS.)

10

11 Patients who develop severe infusion reactions should have RITUXAN infusion discontinued
12 and receive medical treatment.

13

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

17

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

21

22

23 **DESCRIPTION**

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

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29 213 amino acids (based on cDNA analysis) and has an approximate molecular weight of
30 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

31

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

40

41 RITUXAN is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous
42 (IV) administration. RITUXAN is supplied at a concentration of 10 mg/mL in either 100 mg
43 (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for IV administration
44 in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL
45 polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5.

46

47 CLINICAL PHARMACOLOGY

48 General

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

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56 does not internalize upon antibody binding.⁶ Free CD20 antigen is not found in the
57 circulation.²

58

59 Preclinical Pharmacology and Toxicology

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

65

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

69

70 Human Pharmacokinetics/Pharmacodynamics

71 In patients given single doses at 10, 50, 100, 250 or 500 mg/m² as an IV infusion, serum
72 levels and the half-life of Rituximab were proportional to dose.⁹ In 14 patients given
73 375 mg/m² as an IV infusion for 4 weekly doses, the mean serum half-life was 76.3 hours
74 (range, 31.5 to 152.6 hours) after the first infusion and 205.8 hours (range, 83.9 to 407.0
75 hours); after the fourth infusion.^{10,11,12} The wide range of half-lives may reflect the variable
76 tumor burden among patients and the changes in CD20-positive (normal and malignant)
77 B-cell populations upon repeated administrations.

78

79 RITUXAN at a dose of 375 mg/m² was administered as an IV infusion at weekly intervals for
80 4 doses to 203 patients naive to RITUXAN. The mean C_{max} following the fourth infusion was
81 486 µg/mL (range, 77.5 to 996.6 µg/mL). The peak and trough serum levels of Rituximab
82 were inversely correlated with baseline values for the number of circulating CD20-positive
83 B cells and measures of disease burden. Median steady-state serum levels were higher for

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84 responders compared with nonresponders; however, no difference was found in the rate of
85 elimination as measured by serum half-life. Serum levels were higher in patients with
86 International Working Formulation (IWF) subtypes B, C, and D as compared with those with
87 subtype A. Rituximab was detectable in the serum of patients 3 to 6 months after completion
88 of treatment.

89

90 RITUXAN at a dose of 375 mg/m² was administered as an IV infusion at weekly intervals for 8
91 doses to 37 patients. The mean C_{max} after 8 infusions was 550 µg/mL (range, 171 to 1177
92 µg/mL). The mean C_{max} increased with each successive infusion through the eighth infusion
93 (Table 1).

94

95

Table 1

96

Rituximab C_{max} Values

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

97

98 The pharmacokinetic profile of RITUXAN when administered as 6 infusions of 375 mg/m² in
99 combination with 6 cycles of CHOP chemotherapy was similar to that seen with RITUXAN
100 alone.

101

102 Administration of RITUXAN resulted in a rapid and sustained depletion of circulating and
103 tissue-based B cells. Lymph node biopsies performed 14 days after therapy showed a
104 decrease in the percentage of B cells in seven of eight patients who had received single
105 doses of Rituximab ≥ 100 mg/m².⁹ Among the 166 patients in the pivotal study, circulating
106 B cells (measured as CD19-positive cells) were depleted within the first three doses with

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107 sustained depletion for up to 6 to 9 months post-treatment in 83% of patients. Of the
108 responding patients assessed (n = 80), 1% failed to show significant depletion of CD19-
109 positive cells after the third infusion of Rituximab as compared to 19% of the nonresponding
110 patients. B-cell recovery began at approximately 6 months following completion of treatment.
111 Median B-cell levels returned to normal by 12 months following completion of treatment.

112

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

117

118 CLINICAL STUDIES

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

123

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Table 2

125

Summary of RITUXAN Efficacy Data by Schedule and Clinical Setting

126

(See ADVERSE REACTIONS for Risk Factors Associated with Increased

127

Rates of Adverse Events.)

128

	Initial, Weekly x 4 N = 166	Initial, Weekly x 8 N = 37	Initial, Bulky, Weekly x 4 N = 39¹	Retreatment, Weekly x 4 N = 60
Overall Response Rate	48%	57%	36%	38%
Complete Response Rate	6%	14%	3%	10%
Median Duration Of Response ^{2,3,4} (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+]

129

¹ Six of these patients are included in the first column. Thus, data from 296 intent to treat patients are provided in this table.

130

² Kaplan-Meier projected with observed range.

131

³ "+" indicates an ongoing response.

132

⁴ Duration of response: interval from the onset of response to disease progression.

133

134

135

Initial Treatment, Weekly for 4 Doses

136

A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or

137

refractory low-grade or follicular B-cell NHL who received 375 mg/m² of RITUXAN given as

138

an IV infusion weekly for 4 doses.¹³ Patients with tumor masses >10 cm or with

139

>5,000 lymphocytes/ μ L in the peripheral blood were excluded from the study. The overall

140

response rate (ORR) was 48% with 6% complete response (CR) and 42% partial response

141

(PR) rates. The median time to onset of response was 50 days and the median duration of

142

response was 11.2 months (range, 1.9 to 42.1+). Disease-related signs and symptoms

143

(including B-symptoms) were present in 23% (39/166) of patients at study entry and resolved

144

in 64% (25/39) of those patients.

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

154

155 Initial Treatment, Weekly for 8 Doses

156 In a multicenter, single-arm study, 37 patients with relapsed or refractory, low-grade NHL
157 received 375 mg/m² of RITUXAN weekly for 8 doses. The ORR was 57% (CR 14%, PR
158 43%) with a projected median duration of response of 13.4 months (range, 2.5 to 36.5+).¹⁴
159 (For information on the higher incidence of Grade 3 and 4 adverse events, see ADVERSE
160 REACTIONS, Risk Factors Associated with Increased Rates of Adverse Events.)

161

162 Initial Treatment, Bulky Disease, Weekly for 4 Doses

163 In pooled data from multiple studies of RITUXAN, 39 patients with relapsed or refractory,
164 bulky disease (single lesion >10 cm in diameter), low-grade NHL received 375 mg/m² of
165 RITUXAN weekly for 4 doses. The ORR was 36% (CR 3%, PR 33%) with a median duration
166 of response of 6.9 months (range 2.8 to 25.0+). (For information on the higher incidence of
167 Grade 3 and 4 adverse events, see ADVERSE REACTIONS, Risk Factors Associated with
168 Increased Rates of Adverse Events.)

169

170 Retreatment, Weekly for 4 Doses

171 In a multi-center, single-arm study, 60 patients received 375 mg/m² of RITUXAN weekly for 4
172 doses.¹⁵ All patients had relapsed or refractory, low-grade or follicular B-cell NHL and had
173 achieved an objective clinical response to a prior course of RITUXAN. Of these 60 patients,

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174 55 received their second course of RITUXAN, 3 patients received their third course and 2
175 patients received their second and third courses of RITUXAN in this study. The ORR was
176 38% (10% CR and 28% PR) with a projected median duration of response of 15 months
177 (range, 3.0 to 25.1+ months).

178

179 INDICATIONS AND USAGE

180 RITUXAN® (Rituximab) is indicated for the treatment of patients with relapsed or refractory,
181 low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma.

182

183 CONTRAINDICATIONS

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

186

187 WARNINGS (See BOXED WARNINGS)

188 **Severe Infusion Reactions (See BOXED WARNINGS, ADVERSE REACTIONS and**
189 **Hypersensitivity Reactions):** RITUXAN has caused severe infusion reactions. In some
190 cases, these reactions were fatal. These severe reactions typically occurred during the first
191 infusion with time to onset of 30 to 120 minutes. Signs and symptoms of severe infusion
192 reactions may include hypotension, angioedema, hypoxia or bronchospasm, and may require
193 interruption of RITUXAN administration. The most severe manifestations and sequelae
194 include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction,
195 ventricular fibrillation, and cardiogenic shock. In the reported cases, the following factors
196 were more frequently associated with fatal outcomes: female gender, pulmonary infiltrates,
197 and chronic lymphocytic leukemia or mantle cell lymphoma.

198

199 *Management of severe infusion reactions:* The RITUXAN infusion should be interrupted for
200 severe reactions and supportive care measures instituted as medically indicated (e.g.,
201 intravenous fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and

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202 acetaminophen). In most cases, the infusion can be resumed at a 50% reduction in rate
203 (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Patients
204 requiring close monitoring during first and all subsequent infusions include those with
205 pre-existing cardiac and pulmonary conditions, those with prior clinically significant
206 cardiopulmonary adverse events and those with high numbers of circulating malignant cells
207 ($\geq 25,000/\text{mm}^3$) with or without evidence of high tumor burden.

208

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

210 Rapid reduction in tumor volume followed by acute renal failure, hyperkalemia, hypocalcemia,
211 hyperuricemia, or hyperphosphatasemia, have been reported within 12 to 24 hours after the
212 first RITUXAN infusion. Rare instances of fatal outcome have been reported in the setting of
213 TLS following treatment with RITUXAN. The risks of TLS appear to be greater in patients
214 with high numbers of circulating malignant cells ($\geq 25,000/\text{mm}^3$) or high tumor burden.
215 Prophylaxis for TLS should be considered for patients at high risk. Correction of electrolyte
216 abnormalities, monitoring of renal function and fluid balance, and administration of supportive
217 care, including dialysis, should be initiated as indicated. Following complete resolution of the
218 complications of TLS, RITUXAN has been tolerated when re-administered in conjunction with
219 prophylactic therapy for TLS in a limited number of cases.

220

221 **Hepatitis B Reactivation with Related Fulminant Hepatitis:** Hepatitis B virus (HBV)

222 reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some
223 patients with hematologic malignancies treated with RITUXAN. The majority of patients
224 received RITUXAN in combination with chemotherapy. The median time to the diagnosis of
225 hepatitis was approximately 4 months after the initiation of RITUXAN and approximately one
226 month after the last dose.

227

228 Persons at high risk of HBV infection should be screened before initiation of RITUXAN.

229 Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active

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230 HBV infection and for signs of hepatitis during and for up to several months following
231 RITUXAN therapy.

232

233 In patients who develop viral hepatitis, RITUXAN and any concomitant chemotherapy should
234 be discontinued and appropriate treatment including antiviral therapy initiated. There are
235 insufficient data regarding the safety of resuming RITUXAN therapy in patients who develop
236 hepatitis subsequent to HBV reactivation.

237

238 Hypersensitivity Reactions:

239 RITUXAN has been associated with hypersensitivity reactions (non-IgE-mediated reactions)
240 which may respond to adjustments in the infusion rate and in medical management.
241 Hypotension, bronchospasm, and angioedema have occurred in association with RITUXAN
242 infusion (see Severe Infusion Reactions). RITUXAN infusion should be interrupted for severe
243 hypersensitivity reactions and can be resumed at a 50% reduction in rate (e.g., from 100
244 mg/hr to 50 mg/hr) when symptoms have completely resolved. Treatment of these
245 symptoms with diphenhydramine and acetaminophen is recommended; additional treatment
246 with bronchodilators or IV saline may be indicated. In most cases, patients who have
247 experienced non-life-threatening hypersensitivity reactions have been able to complete the
248 full course of therapy. (See DOSAGE and ADMINISTRATION.) Medications for the
249 treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and corticosteroids,
250 should be available for immediate use in the event of a reaction during administration.

251

252 **Cardiovascular:** Infusions should be discontinued in the event of serious or life-threatening
253 cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo
254 cardiac monitoring during and after subsequent infusions of RITUXAN. Patients with pre-
255 existing cardiac conditions including arrhythmias and angina have had recurrences of these
256 events during RITUXAN therapy and should be monitored throughout the infusion and
257 immediate post-infusion period.

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259 **Renal:** RITUXAN administration has been associated with severe renal toxicity including
260 acute renal failure requiring dialysis and in some cases, has led to a fatal outcome. Renal
261 toxicity has occurred in patients with high numbers of circulating malignant cells
262 ($>25,000/\text{mm}^3$) or high tumor burden who experience tumor lysis syndrome (see Tumor
263 Lysis Syndrome) and in patients administered concomitant cisplatin therapy during clinical
264 trials. The combination of cisplatin and RITUXAN is not an approved treatment regimen. If
265 this combination is used in clinical trials *extreme caution* should be exercised; patients should
266 be monitored closely for signs of renal failure. Discontinuation of RITUXAN should be
267 considered for those with rising serum creatinine or oliguria.

268

269 **Severe Mucocutaneous Reactions (See BOXED WARNINGS and ADVERSE**
270 **REACTIONS):** Mucocutaneous reactions, some with fatal outcome, have been reported in
271 patients treated with RITUXAN. These reports include paraneoplastic pemphigus (an
272 uncommon disorder which is a manifestation of the patient's underlying malignancy),¹⁶
273 Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic
274 epidermal necrolysis. The onset of the reaction in the reported cases has varied from 1 to 13
275 weeks following RITUXAN exposure. Patients experiencing a severe mucocutaneous
276 reaction should not receive any further infusions and seek prompt medical evaluation. Skin
277 biopsy may help to distinguish among different mucocutaneous reactions and guide
278 subsequent treatment. The safety of readministration of RITUXAN to patients with any of
279 these mucocutaneous reactions has not been determined.

280

281 **PRECAUTIONS**

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

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

287

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

291

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

300

301 **Immunization:** The safety of immunization with live viral vaccines following RITUXAN
302 therapy has not been studied. The ability to generate a primary or anamnestic humoral
303 response to vaccination is currently being studied.

304

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

310

311 **Pregnancy Category C:** Animal reproduction studies have not been conducted with
312 RITUXAN. It is not known whether RITUXAN can cause fetal harm when administered to a

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313 pregnant woman or whether it can affect reproductive capacity. Human IgG is known to pass
314 the placental barrier, and thus may potentially cause fetal B-cell depletion; therefore,
315 RITUXAN should be given to a pregnant woman only if clearly needed.

316

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

322

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

325

326 **Geriatric Use:** Among the 331 patients enrolled in clinical studies of single agent RITUXAN,
327 24% were 65 to 75 years old and 5% were 75 years old and older. The overall response
328 rates were higher in older (age \geq 65 years) vs. younger (age $<$ 65 years) patients (52% vs.
329 44%, respectively). However, the median duration of response, based on Kaplan-Meier
330 estimates, was shorter in older vs. younger patients: 10.1 months (range, 1.9 to 36.5+) vs.
331 11.4 months (range, 2.1 to 42.1+), respectively. This shorter duration of response was not
332 statistically significant. Adverse reactions, including incidence, severity and type of adverse
333 reaction were similar between older and younger patients.

334

335 **ADVERSE REACTIONS**

336 The most serious adverse reactions caused by RITUXAN include infusion reactions, tumor
337 lysis syndrome, mucocutaneous reactions, hypersensitivity reactions, cardiac arrhythmias
338 and angina, and renal failure. Please refer to the BOXED WARNINGS and WARNINGS
339 sections for detailed descriptions of these reactions. Infusion reactions and lymphopenia are
340 the most commonly occurring adverse reactions.

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342 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
343 observed in the clinical trials of a drug cannot be directly compared to rates in the clinical
344 trials of another drug and may not reflect the rates observed in practice. The adverse
345 reaction information from clinical trials does, however, provide a basis for identifying the
346 adverse events that appear to be related to drug use and for approximating rates.

347

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

354

355 Where specific percentages are noted, these data are based on 356 patients treated in
356 nonrandomized, single-arm studies of RITUXAN administered as a single agent. Most
357 patients received RITUXAN 375 mg/m² weekly for 4 doses. These include 39 patients with
358 bulky disease (lesions \geq 10 cm) and 60 patients who received more than 1 course of
359 RITUXAN. Thirty-seven patients received 375 mg/m² for 8 doses and 25 patients received
360 doses other than 375 mg/m² for 4 doses and up to 500 mg/m² single dose in the Phase 1
361 setting. Adverse events of greater severity are referred to as "Grade 3 and 4 events" defined
362 by the commonly used National Cancer Institute Common Toxicity Criteria.¹⁷

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Table 3

365

Incidence of Adverse Events \geq 5% of Patients in Clinical Trials (N = 356)

366

(Adverse Events were followed for a period of 12 months following

367

RITUXAN therapy)

	All Grades (%)	Grade 3 and 4 (%)
Any Adverse Events	99	57
Body as a Whole	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
Cardiovascular System	25	3
Hypotension	10	1
Hypertension	6	1
Digestive System	37	2
Nausea	23	1
Diarrhea	10	1
Vomiting	10	1
Hemic and Lymphatic System	67	48
Lymphopenia	48	40
Leukopenia	14	4
Neutropenia	14	6
Thrombocytopenia	12	2
Anemia	8	3
Metabolic and Nutritional Disorders	38	3
Angioedema	11	1
Hyperglycemia	9	1
Peripheral Edema	8	0
LDH Increase	7	0
Musculoskeletal System	26	3
Myalgia	10	1
Arthralgia	10	1
Nervous System	32	1
Dizziness	10	1
Anxiety	5	1
Respiratory System	38	4
Increased Cough	13	1
Rhinitis	12	1

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	All Grades (%)	Grade 3 and 4 (%)
Bronchospasm	8	1
Dyspnea	7	1
Sinusitis	6	0
Skin and Appendages	44	2
Night Sweats	15	1
Rash	15	1
Pruritus	14	1
Urticaria	8	1

368
369
370

371 **Risk Factors Associated with Increased Rates of Adverse Events:** Administration of
372 RITUXAN weekly for 8 doses resulted in higher rates of Grade 3 and 4 adverse events¹⁷
373 overall (70%) compared with administration weekly for 4 doses (57%). The incidence of
374 Grade 3 or 4 adverse events was similar in patients retreated with RITUXAN compared with
375 initial treatment (58% and 57%, respectively). The incidence of the following clinically
376 significant adverse events was higher in patients with bulky disease (lesions ≥ 10 cm) (N = 39)
377 versus patients with lesions
378 < 10 cm (N = 195): abdominal pain, anemia, dyspnea, hypotension, and neutropenia.

379

380 **Infusion Reactions (See BOXED WARNINGS and WARNINGS):** Mild to moderate infusion
381 reactions consisting of fever and chills/rigors occurred in the majority of patients during the
382 first RITUXAN infusion. Other frequent infusion reaction symptoms included nausea,
383 pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation,
384 rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and hypertension. These reactions
385 generally occurred within 30 to 120 minutes of beginning the first infusion, and resolved with
386 slowing or interruption of the RITUXAN infusion and with supportive care (diphenhydramine,
387 acetaminophen, IV saline, and vasopressors). In an analysis of data from 356 patients with
388 relapsed or refractory, low-grade NHL who received 4 (N = 319) or 8 (N = 37) weekly
389 infusions of RITUXAN, the incidence of infusion reactions was highest during the first infusion
390 (77%) and decreased with each subsequent infusion (30% with fourth infusion and 14% with
391 eighth infusion).

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393 **Infectious Events:** RITUXAN induced B-cell depletion in 70% to 80% of patients and was
394 associated with decreased serum immunoglobulins in a minority of patients; the lymphopenia
395 lasted a median of 14 days (range, 1 to 588 days). Infectious events occurred in 31% of
396 patients: 19% of patients had bacterial infections, 10% had viral infections, 1% had fungal
397 infections, and 6% were unknown infections. Incidence is not additive because a single
398 patient may have had more than one type of infection. Serious infectious events (Grade 3 or
399 4),¹⁷ including sepsis, occurred in 2% of patients.

400

401 **Hematologic Events:** In clinical trials, Grade 3 and 4 cytopenias¹⁷ were reported in 48% of
402 patients treated with RITUXAN; these include: lymphopenia (40%), neutropenia (6%),
403 leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of
404 lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2
405 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two
406 occurrences of hemolytic anemia following RITUXAN therapy were reported.

407

408 In addition, there have been a limited number of postmarketing reports of prolonged
409 pancytopenia, marrow hypoplasia, and late onset neutropenia (defined as occurring 40 days
410 after the last dose of RITUXAN) in patients with hematologic malignancies. In reported cases
411 of late onset neutropenia (NCI-CTC Grade 3 and 4), the median duration of neutropenia was
412 10 days (range 3 to 148 days). Documented resolution of the neutropenia was described in
413 approximately one-half of the reported cases; of those with documented recovery,
414 approximately half received growth factor support. In the remaining cases, information on
415 resolution was not provided. More than half of the reported cases of delayed onset
416 neutropenia occurred in patients who had undergone a prior autologous bone marrow
417 transplantation. In an adequately designed, controlled, clinical trial, the reported incidence of
418 NCI-CTC Grade 3 and 4 neutropenia was higher in patients receiving RITUXAN in

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419 combination with fludarabine as compared to those receiving fludarabine alone (76% [39/51]
420 vs. 39% [21/53]).¹⁸

421

422 **Cardiac Events (See BOXED WARNINGS):** Grade 3 or 4 cardiac-related events include
423 hypotension. Rare, fatal cardiac failure with symptomatic onset weeks after RITUXAN has
424 also been reported. Patients who develop clinically significant cardiopulmonary events
425 should have RITUXAN infusion discontinued.

426

427 **Pulmonary Events (See BOXED WARNINGS):** 135 patients (38%) experienced pulmonary
428 events in clinical trials. The most common respiratory system adverse events experienced
429 were increased cough, rhinitis, bronchospasm, dyspnea, and sinusitis. In both clinical
430 studies and post-marketing surveillance, there have been a limited number of reports of
431 bronchiolitis obliterans presenting up to 6 months post-RITUXAN infusion and a limited
432 number of reports of pneumonitis (including interstitial pneumonitis) presenting up to 3
433 months post-RITUXAN infusion, some of which resulted in fatal outcomes. The safety of
434 resumption or continued administration of RITUXAN in patients with pneumonitis or
435 bronchiolitis obliterans is unknown.

436

437 **Immune/Autoimmune Events:** Immune/autoimmune events have been reported, including
438 uveitis, optic neuritis in a patient with systemic vasculitis, pleuritis in a patient with a lupus-like
439 syndrome, serum sickness with polyarticular arthritis, and vasculitis with rash.

440

441 **Less Commonly Observed Events:** In clinical trials, < 5% and > 1% of the patients
442 experienced the following events regardless of causality assessment: agitation, anorexia,
443 arthritis, conjunctivitis, depression, dyspepsia, edema, hyperkinesia, hypertonia, hypesthesia,
444 hypoglycemia, injection site pain, insomnia, lacrimation disorder, malaise, nervousness,
445 neuritis, neuropathy, paresthesia, somnolence, vertigo, weight decrease.

446

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447 **OVERDOSAGE**

448 There has been no experience with overdosage in human clinical trials. Single doses of up to
449 500 mg/m² have been given in controlled clinical trials.¹⁰

450

451 **DOSAGE AND ADMINISTRATION**

452 **Initial Therapy:** RITUXAN is given at 375 mg/m² IV infusion once weekly for 4 or 8 doses.

453

454 **Retreatment Therapy:** Patients who subsequently develop progressive disease may be
455 safely retreated with RITUXAN 375 mg/m² IV infusion once weekly for 4 doses. Currently
456 there are limited data concerning more than 2 courses.

457

458 **RITUXAN as a Component of Zevalin™ (Ibritumomab Tiuxetan) Therapeutic Regimen:**

459 As a required component of the Zevalin therapeutic regimen, RITUXAN 250 mg/m² should be
460 infused within 4 hours prior to the administration of Indium-111- (In-111-) Zevalin and within 4
461 hours prior to the administration of Yttrium-90- (Y-90-) Zevalin. Administration of RITUXAN
462 and In-111-Zevalin should precede RITUXAN and Y-90-Zevalin by 7-9 days. Refer to the
463 Zevalin package insert for full prescribing information regarding the Zevalin therapeutic
464 regimen.

465

466 RITUXAN may be administered in an outpatient setting. **DO NOT ADMINISTER AS AN**
467 **INTRAVENOUS PUSH OR BOLUS. (See Administration.)**

468

469 **Instructions for Administration**

470 **Preparation for Administration:** Use appropriate aseptic technique. Withdraw the
471 necessary amount of RITUXAN and dilute to a final concentration of 1 to 4 mg/mL into an
472 infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP.
473 Gently invert the bag to mix the solution. Discard any unused portion left in the vial.

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474 Parenteral drug products should be inspected visually for particulate matter and discoloration
475 prior to administration.

476

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

482

483 **Administration: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.**

484 Infusion and hypersensitivity reactions may occur (see BOXED WARNINGS, WARNINGS,
485 and ADVERSE REACTIONS). Premedication consisting of acetaminophen and
486 diphenhydramine should be considered before each infusion of RITUXAN. Premedication
487 may attenuate infusion reactions. Since transient hypotension may occur during RITUXAN
488 infusion, consideration should be given to withholding antihypertensive medications 12 hours
489 prior to RITUXAN infusion.

490

491 **First Infusion:** The RITUXAN solution for infusion should be administered intravenously at an
492 initial rate of 50 mg/hr. RITUXAN should not be mixed or diluted with other drugs. If
493 hypersensitivity or infusion reactions do not occur, escalate the infusion rate in 50 mg/hr
494 increments every 30 minutes, to a maximum of 400 mg/hr. If a hypersensitivity (non-IgE-
495 mediated) or an infusion reaction develops, the infusion should be temporarily slowed or
496 interrupted (see BOXED WARNINGS and WARNINGS). The infusion can continue at
497 one-half the previous rate upon improvement of patient symptoms.

498

499 **Subsequent Infusions:** If the patient tolerated the first infusion well, subsequent RITUXAN
500 infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr

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501 increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated. If the patient did
502 not tolerate the first infusion well, follow the guidelines under First Infusion.

503

504 **Stability and Storage:** RITUXAN vials are stable at 2–8°C (36–46°F). Do not use beyond
505 expiration date stamped on carton. RITUXAN vials should be protected from direct sunlight.

506 Refer to the “Preparation and Administration” section for information on the stability and
507 storage of solutions of RITUXAN diluted for infusion.

508

509 **HOW SUPPLIED**

510 RITUXAN® (Rituximab) is supplied as 100 mg and 500 mg of sterile, preservative-free,
511 single-use vials.

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

513 NDC 50242-051-21

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

515 NDC 50242-053-06

516

517 **REFERENCES**

518 1. Valentine MA, Meier KE, Rossie S, et al. Phosphorylation of the CD20 phosphoprotein in
519 resting B lymphocytes. *J Biol Chem* 1989 264(19): 11282–11287.

520

521 2. Einfeld DA, Brown JP, Valentine MA, et al. Molecular cloning of the human B cell CD20
522 receptor predicts a hydrophobic protein with multiple transmembrane domains. *EMBO J*
523 1988 7(3):711–717.

524

525 3. Anderson KC, Bates MP, Slaughenhaupt BL, et al. Expression of human B cell-associated
526 antigens on leukemias and lymphomas: A model of human B cell differentiation. *Blood*
527 1984 63(6):1424–1433.

528

Rituxan® (Rituximab)

- 529 4. Tedder TF, Boyd AW, Freedman AS, et al. The B cell surface molecule B1 is functionally
530 linked with B cell activation and differentiation. *J Immunol* 1985 135(2):973–979.
531
- 532 5. Tedder TF, Zhou LJ, Bell PD, et al. The CD20 surface molecule of B lymphocytes
533 functions as a calcium channel. *J Cell Biochem* 1990 14D:195.
534
- 535 6. Press OW, Applebaum F, Ledbetter JA, Martin PJ, Zarling J, Kidd P, et al. Monoclonal
536 antibody 1F5 (anti-CD20) serotherapy of human B-cell lymphomas. *Blood* 1987
537 69(2):584–591.
538
- 539 7. Reff ME, Carner C, Chambers KS, Chinn PC, Leonard JE, Raab R, et al. Depletion of B
540 cells in vivo by a chimeric mouse human monoclonal antibody to CD20. *Blood* 1994
541 83(2):435–445.
542
- 543 8. Demidem A, Lam T, Alas S, Hariharan K, Hanna N, and Bonavida B. Chimeric anti-CD20
544 (IDEC-C2B8) monoclonal antibody sensitizes a B cell lymphoma cell line to cell killing by
545 cytotoxic drugs. *Cancer Biotherapy & Radiopharmaceuticals* 1997 12(3):177–186.
546
- 547 9. Maloney DG, Liles TM, Czerwinski C, Waldichuk J, Rosenberg J, Grillo-López A, et al.
548 Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20
549 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. *Blood*
550 1994 84(8):2457–2466.
551
- 552 10. Berinstein NL, Grillo-López AJ, White CA, Bence-Bruckler I, Maloney D, Czuczman M, et
553 al. Association of serum Rituximab (IDEC-C2B8) concentration and anti-tumor response
554 in the treatment of recurrent low-grade or follicular non-Hodgkin's lymphoma. *Annals of*
555 *Oncology* 1998, 9:995–1001.
556

Rituxan® (Rituximab)

- 557 11. Maloney DG, Grillo-López AJ, Bodkin D, White CA, Liles T-M, Royston I, et al.
558 IDEC-C2B8: Results of a phase I multiple-dose trial in patients with relapsed
559 non-Hodgkin's lymphoma. *J Clin Oncol* 1997 15(10):3266–3274.
560
- 561 12. Maloney DG, Grillo-López AJ, White CA, Bodkin D, Schilder RJ, Neidhart JA, et al.
562 IDEC-C2B8 (Rituximab) anti-CD20 monoclonal antibody therapy in patients with
563 relapsed low-grade non-Hodgkin's lymphoma. *Blood* 1997 90(6):2188–2195.
564
- 565 13. McLaughlin P, Grillo-López AJ, Link BK, Levy R, Czuczman MS, Williams ME, et al.
566 Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent
567 lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol*
568 1998 16(8):2825–2833.
569
- 570 14. Piro LD, White CA, Grillo-López AJ, Janakiraman N, Saven A, Beck TM, et al. Extended
571 Rituximab (anti-CD20 monoclonal antibody) therapy for relapsed or refractory low-grade
572 or follicular non-Hodgkin's lymphoma. *Annals of Oncology* 1999 10:655–661.
573
- 574 15. Davis TA, Grillo-López AJ, White CA, McLaughlin P, Czuczman MS, Link BK, Maloney
575 DG, Weaver RL, Rosenberg J, Levy R. Rituximab anti-CD20 monoclonal antibody
576 therapy in non-hodgkin's lymphoma: safety and efficacy of re-treatment. *J Clin Oncol*
577 2000 18(17):3135–3143.
578
- 579 16. Anhalt GJ, Kim SC, Stanley JR, Korman NJ, Jabs DA, Kory M, Izumi H, Rattie H,
580 Mutasim D, Ariss-Abdo L, Labib RS. Paraneoplastic Pemphigus, an autoimmune
581 mucocutaneous disease associated with neoplasia. *NEJM* 1990 323(25): 1729–1735.
582
- 583 17. National Institutes of Health (US), National Cancer Institute. Common Toxicity Criteria.
584 [Bethesda, MD.] : National Institutes of Health, National Cancer Institute; c1998. 73p.

Rituxan® (Rituximab)

585 18. Byrd JC, Peterson BL, Morrison VA, Park K, Jacobson R, Hoke E, Vardiman JW, Rai K,
586 Schiffer CA, Larson RA. Randomized phase 2 study of fludarabine with concurrent
587 versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell
588 chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712
589 (CALGB 9712). *Blood* 2003 101(1): 6-14.

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Jointly Marketed by:

IDEC Pharmaceuticals Corporation

11011 Torreyana Road

San Diego, CA 92121

Genentech, Inc.

1 DNA Way

South San Francisco, CA 94080-4990

4809705

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