

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ARZERRA safely and effectively. See full prescribing information for ARZERRA.

ARZERRA (ofatumumab)

Injection, for intravenous infusion

Initial U.S. Approval: 2009

WARNING: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

See full prescribing information for complete boxed warning.

- Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death. (5.2)
- Progressive Multifocal Leukoencephalopathy (PML) resulting in death. (5.4)

RECENT MAJOR CHANGES

Boxed Warning	09/2013
Indications and Usage (1)	04/2014
Dosage and Administration (2)	04/2014
Warnings and Precautions (5)	04/2014

INDICATIONS AND USAGE

ARZERRA (ofatumumab) is a CD20-directed cytolytic monoclonal antibody indicated:

- in combination with chlorambucil, for the treatment of previously untreated patients with chronic lymphocytic leukemia (CLL) for whom fludarabine-based therapy is considered inappropriate. (1.1)
- for the treatment of patients with CLL refractory to fludarabine and alemtuzumab. (1.2)

DOSAGE AND ADMINISTRATION

- Dilute and administer as an intravenous infusion. Do not administer subcutaneously or as an intravenous push or bolus. (2.1)
- Previously untreated CLL recommended dosage and schedule is:
 - 300 mg on Day 1 followed by 1,000 mg on Day 8 (Cycle 1)
 - 1,000 mg on Day 1 of subsequent 28-day cycles for a minimum of 3 cycles until best response or a maximum of 12 cycles. (2.1)
- Refractory CLL recommended dosage and schedule is:
 - 300 mg initial dose, followed 1 week later by
 - 2,000 mg weekly for 7 doses, followed 4 weeks later by

- 2,000 mg every 4 weeks for 4 doses. (2.1)
- Administer where facilities to adequately monitor and treat infusion reactions are available. (2.2)
- Premedicate with acetaminophen, antihistamine, and corticosteroid. (2.4)

DOSAGE FORMS AND STRENGTHS

- 100 mg/5 mL single-use vial for intravenous infusion. (3)
- 1,000 mg/50 mL single-use vial for intravenous infusion. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS and PRECAUTIONS

- Infusion Reactions: Premedicate with corticosteroid, acetaminophen, and an antihistamine. Monitor patients during infusions. Interrupt infusion if infusion reactions occur. (2.3, 2.4, 5.1)
- Tumor Lysis Syndrome: Anticipate TLS in high-risk patients; premedicate with anti-hyperuricemics and hydration. (5.5)
- Cytopenias: Neutropenia, anemia, and thrombocytopenia occur. Late-onset and prolonged neutropenia can also occur. Monitor complete blood counts at regular intervals. (5.6)

ADVERSE REACTIONS

- Previously Untreated CLL: Common adverse reactions ($\geq 10\%$) were infusion reactions and neutropenia. (6)
- Refractory CLL: Common adverse reactions ($\geq 10\%$) were neutropenia, pneumonia, pyrexia, cough, diarrhea, anemia, fatigue, dyspnea, rash, nausea, bronchitis, and upper respiratory tract infections. (6)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing Mothers: Published data suggest that consumption of breast milk does not result in substantial absorption of maternal antibodies into circulation. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2014

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1 FULL PRESCRIBING INFORMATION

2 **WARNING: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE** 3 **MULTIFOCAL LEUKOENCEPHALOPATHY**

- 4 • Hepatitis B Virus (HBV) reactivation can occur in patients receiving CD20-directed
5 cytolytic antibodies, including ARZERRA[®], in some cases resulting in fulminant
6 hepatitis, hepatic failure, and death [see *Warnings and Precautions (5.2)*].
- 7 • Progressive Multifocal Leukoencephalopathy (PML) resulting in death can occur in
8 patients receiving CD20-directed cytolytic antibodies, including ARZERRA [see
9 *Warnings and Precautions (5.4)*].

10 **1 INDICATIONS AND USAGE**

11 **1.1 Previously Untreated Chronic Lymphocytic Leukemia**

12 ARZERRA (ofatumumab) is indicated, in combination with chlorambucil, for the treatment of
13 previously untreated patients with chronic lymphocytic leukemia (CLL) for whom fludarabine-
14 based therapy is considered inappropriate [see *Clinical Studies (14.1)*].

16 **1.2 Refractory CLL**

17 ARZERRA is indicated for the treatment of patients with CLL refractory to fludarabine and
18 alemtuzumab [see *Clinical Studies (14.2)*].

19 **2 DOSAGE AND ADMINISTRATION**

20 **2.1 Recommended Dosage Regimen**

- 21 • Dilute and administer as an intravenous infusion according to the following schedules.
- 22 • Do not administer as an intravenous push or bolus or as a subcutaneous injection.
- 23 • Premedicate before each infusion [see *Dosage and Administration (2.4)*].

24
25 Previously Untreated CLL: The recommended dosage and schedule is:

- 26 • 300 mg on Day 1 followed 1 week later by 1,000 mg on Day 8 (Cycle 1) followed by
- 27 • 1,000 mg on Day 1 of subsequent 28-day cycles for a minimum of 3 cycles until best
28 response or a maximum of 12 cycles.

29
30 Refractory CLL: The recommended dosage and schedule is 12 doses administered as follows:

- 31 • 300 mg initial dose (Dose 1), followed 1 week later by
- 32 • 2,000 mg weekly for 7 doses (Doses 2 through 8), followed 4 weeks later by
- 33 • 2,000 mg every 4 weeks for 4 doses (Doses 9 through 12).

35 **2.2 Administration**

36 Administer ARZERRA in an environment where facilities to adequately monitor and treat
37 infusion reactions are available [see *Warnings and Precautions (5.1)*].

38

39 Prepare all doses in 1,000 mL of 0.9% Sodium Chloride Injection, USP [see *Dosage and*
40 *Administration (2.5)*].

41

42 Previously Untreated CLL:

- 43 • Cycle 1, Day 1 (300-mg dose): Initiate infusion at a rate of 3.6 mg/hour (12 mL/hour).
- 44 • Cycle 1, Day 8 and Cycles 2 through 12 (1,000-mg doses): Initiate infusion at a rate of
45 25 mg/hour (25 mL/hour). Initiate infusion at a rate of 12 mg/hour if a Grade 3 or greater
46 infusion-related adverse event was experienced during the previous infusion.

47

48 In the absence of an infusion-related adverse event, the rate of infusion may be increased every
49 30 minutes (Table 1). Do not exceed the infusion rates in Table 1.

50

51 **Table 1. Infusion Rates for ARZERRA in Previously Untreated CLL**

Interval After Start of Infusion (min)	Cycle 1, Day 1 ^a (mL/hour)	Cycle 1, Day 8 ^b and Cycles 2-12 ^c (mL/hour)
0-30	12	25
31-60	25	50
61-90	50	100
91-120	100	200
121-150	200	400
151-180	300	400
>180	400	400

52 ^a Cycle 1, Day 1 = 300 mg; median duration of infusion = 5.2 hours.

53 ^b Cycle 1, Day 8 = 1,000 mg; median duration of infusion = 4.4 hours.

54 ^c Cycles 2 through 12 = 1,000 mg; median durations of infusion = 4.2 to 4.4 hours.

55

56 Refractory CLL:

- 57 • Dose 1 (300-mg dose): Initiate infusion at a rate of 3.6 mg/hour (12 mL/hour).
- 58 • Dose 2 (2,000-mg dose): Initiate infusion at a rate of 24 mg/hour (12 mL/hour).
- 59 • Doses 3 through 12 (2,000-mg doses): Initiate infusion at a rate of 50 mg/hour (25 mL/hour).

60

61 In the absence of an infusion-related adverse event, the rate of infusion may be increased every
62 30 minutes (Table 2). Do not exceed the infusion rates in Table 2.

63

64 **Table 2. Infusion Rates for ARZERRA in Refractory CLL**

Interval After Start of Infusion (min)	Dose 1 ^a (mL/hour)	Dose 2 ^b (mL/hour)	Doses 3-12 ^b (mL/hour)
0-30	12	12	25
31-60	25	25	50
61-90	50	50	100
91-120	100	100	200
>120	200	200	400

65 ^a Dose 1 = 300 mg; median duration of infusion = 6.8 hours.

66 ^b Doses 2 and 3 through 12 = 2,000 mg; median duration of infusion for Dose 2 = 6.8 hours;
67 median durations of infusion for Doses 3 through 12 = 4.2 to 4.4 hours.

68

69 **2.3 Infusion Rate Dose Modification for Infusion Reactions**

- 70 • Interrupt infusion for infusion reactions of any severity [*see Warnings and Precautions*
71 (*5.1*)]. Treatment can be resumed at the discretion of the treating physician. The following
72 infusion rate modifications can be used as a guide.
- 73 • If the infusion reaction resolves or remains less than or equal to Grade 2, resume infusion
74 with the following modifications according to the initial Grade of the infusion reaction.
 - 75 • Grade 1 or 2: Infuse at one-half of the previous infusion rate.
 - 76 • Grade 3 or 4: Infuse at a rate of 12 mL/hour.
- 77 • After resuming the infusion, the infusion rate may be increased according to Tables 1 and 2
78 above, based on patient tolerance.
- 79 • Consider permanent discontinuation of ARZERRA if the severity of the infusion reaction
80 does not resolve to less than or equal to Grade 2 despite adequate clinical intervention.
- 81 • Permanently discontinue therapy for patients who develop an anaphylactic reaction to
82 ARZERRA.

83

84 **2.4 Premedication**

85 Patients should receive the following premedication 30 minutes to 2 hours prior to each infusion
86 of ARZERRA:

87

88 Previously Untreated CLL:

- 89 • Oral acetaminophen 1,000 mg (or equivalent) plus
- 90 • Oral or intravenous antihistamine (diphenhydramine 50 mg or cetirizine 10 mg or equivalent)
91 plus
- 92 • Intravenous corticosteroid (prednisolone 50 mg or equivalent).

93

94 If the patient did not experience a Grade 3 or greater infusion-related adverse event during the
95 first 2 infusions of ARZERRA, the dose of corticosteroid may be reduced or omitted for
96 subsequent infusions.

97

98 Refractory CLL:

- 99 • Oral acetaminophen 1,000 mg (or equivalent) plus
100 • Oral or intravenous antihistamine (diphenhydramine 50 mg or cetirizine 10 mg or equivalent)
101 plus
102 • Intravenous corticosteroid (prednisolone 100 mg or equivalent).

103

104 Do not reduce corticosteroid dose for Doses 1, 2, and 9. Corticosteroid dose may be reduced as
105 follows:

- 106 • Doses 3 through 8: Corticosteroid may be reduced or omitted with subsequent infusions
107 if a Grade 3 or greater infusion reaction did not occur with the preceding dose.
108 • Doses 10 through 12: Administer prednisolone 50 mg to 100 mg or equivalent if a
109 Grade 3 or greater infusion reaction did not occur with Dose 9.

110

111 **2.5 Preparation and Administration**

- 112 • Do not shake product.
113 • Inspect parenteral drug products visually for particulate matter and discoloration prior to
114 administration. ARZERRA should be a clear to opalescent, colorless solution. The solution
115 should not be used if discolored or cloudy, or if foreign particulate matter is present.

116

117 Preparation of Solution:

- 118 • 300-mg dose: Withdraw and discard 15 mL from a 1,000-mL bag of 0.9% Sodium Chloride
119 Injection, USP. Withdraw 5 mL from each of 3 single-use 100-mg vials of ARZERRA and
120 add to the bag. Mix diluted solution by gentle inversion.
121 • 1,000-mg dose: Withdraw and discard 50 mL from a 1,000-mL bag of 0.9% Sodium
122 Chloride Injection, USP. Withdraw 50 mL from 1 single-use 1,000-mg vial of ARZERRA
123 and add to the bag. Mix diluted solution by gentle inversion.
124 • 2,000-mg dose: Withdraw and discard 100 mL from a 1,000-mL bag of 0.9% Sodium
125 Chloride Injection, USP. Withdraw 50 mL from each of 2 single-use 1,000-mg vials of
126 ARZERRA and add to the bag. Mix diluted solution by gentle inversion.
127 • Store diluted solution between 2° to 8°C (36° to 46°F).
128 • No incompatibilities between ARZERRA and polyvinylchloride or polyolefin bags and
129 administration sets have been observed.

130

131 Administration Instructions:

- 132 • Do not mix ARZERRA with, or administer as an infusion with, other medicinal products.
133 • Administer using an infusion pump and an administration set.
134 • Flush the intravenous line with 0.9% Sodium Chloride Injection, USP before and after each
135 dose.
136 • Start infusion within 12 hours of preparation.
137 • Discard prepared solution after 24 hours.

138 **3 DOSAGE FORMS AND STRENGTHS**

- 139 • 100 mg/5 mL single-use vial for intravenous infusion.
140 • 1,000 mg/50 mL single-use vial for intravenous infusion.

141 **4 CONTRAINDICATIONS**

142 None.

143 **5 WARNINGS AND PRECAUTIONS**

144 **5.1 Infusion Reactions**

145 ARZERRA can cause serious, including fatal, infusion reactions manifesting as bronchospasm,
146 dyspnea, laryngeal edema, pulmonary edema, flushing, hypertension, hypotension, syncope,
147 cardiac events (e.g., myocardial ischemia/infarction, acute coronary syndrome, arrhythmia,
148 bradycardia), back pain, abdominal pain, pyrexia, rash, urticaria, angioedema, cytokine release
149 syndrome, and anaphylactoid/anaphylactic reactions. Infusion reactions occur more frequently
150 with the first 2 infusions. These reactions may result in temporary interruption or withdrawal of
151 treatment [see *Adverse Reactions (6.1)*].

152

153 Premedicate with acetaminophen, an antihistamine, and a corticosteroid [see *Dosage and*
154 *Administration (2.1, 2.4)*]. Infusion reactions may occur despite premedication. Interrupt
155 infusion with ARZERRA for infusion reactions of any severity. Institute medical management
156 for severe infusion reactions including angina or other signs and symptoms of myocardial
157 ischemia [see *Dosage and Administration (2.3)*]. If an anaphylactic reaction occurs, immediately
158 and permanently discontinue ARZERRA and initiate appropriate medical treatment.

159

160 **5.2 Hepatitis B Virus Reactivation**

161 Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic
162 failure, and death, has occurred in patients treated with ARZERRA. Cases have been reported in
163 patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are
164 HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation also has
165 occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative,
166 anti-HBc positive, and hepatitis B surface antibody [anti-HBs] positive).

167

168 HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid
169 increase in serum HBV DNA level or detection of HBsAg in a person who was previously
170 HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by
171 hepatitis, i.e., increase in transaminase levels and, in severe cases, increase in bilirubin levels,
172 liver failure, and death.

173

174 Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating
175 treatment with ARZERRA. For patients who show evidence of hepatitis B infection (HBsAg
176 positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult

177 physicians with expertise in managing hepatitis B regarding monitoring and consideration for
178 HBV antiviral therapy.

179

180 Monitor patients with evidence of current or prior HBV infection for clinical and laboratory
181 signs of hepatitis or HBV reactivation during and for several months following treatment with
182 ARZERRA. HBV reactivation has been reported for at least 12 months following completion of
183 therapy.

184

185 In patients who develop reactivation of HBV while receiving ARZERRA, immediately
186 discontinue ARZERRA and any concomitant chemotherapy, and institute appropriate treatment.
187 Resumption of ARZERRA in patients whose HBV reactivation resolves should be discussed
188 with physicians with expertise in managing hepatitis B. Insufficient data exist regarding the
189 safety of resuming ARZERRA in patients who develop HBV reactivation.

190

191 **5.3 Hepatitis B Virus Infection**

192 Fatal infection due to hepatitis B in patients who have not been previously infected has been
193 observed with ARZERRA. Monitor patients for clinical and laboratory signs of hepatitis.

194

195 **5.4 Progressive Multifocal Leukoencephalopathy**

196 Progressive multifocal leukoencephalopathy (PML) resulting in death has occurred with
197 ARZERRA. Consider PML in any patient with new onset of or changes in pre-existing
198 neurological signs or symptoms. If PML is suspected, discontinue ARZERRA and initiate
199 evaluation for PML including neurology consultation.

200

201 **5.5 Tumor Lysis Syndrome**

202 Tumor lysis syndrome (TLS), including the need for hospitalization, has occurred in patients
203 treated with ARZERRA. Patients with high tumor burden and/or high circulating lymphocyte
204 counts ($>25 \times 10^9/L$) are at greater risk for developing TLS. Consider tumor lysis prophylaxis
205 with anti-hyperuricemics and hydration beginning 12 to 24 hours prior to infusion of
206 ARZERRA. For treatment of TLS, administer aggressive intravenous hydration and anti-
207 hyperuricemic agents, correct electrolyte abnormalities, and monitor renal function.

208

209 **5.6 Cytopenias**

210 Severe cytopenias, including neutropenia, thrombocytopenia, and anemia, can occur with
211 ARZERRA. Pancytopenia, agranulocytosis, and fatal neutropenic sepsis have occurred in
212 patients who received ARZERRA in combination with chlorambucil. Grade 3 or 4 late-onset
213 neutropenia (onset at least 42 days after last treatment dose) and/or prolonged neutropenia (not
214 resolved between 24 and 42 days after last treatment dose) were reported in patients who
215 received ARZERRA [see *Adverse Reactions (6.1)*]. Monitor complete blood counts at regular

216 intervals during and after conclusion of therapy, and increase the frequency of monitoring in
217 patients who develop Grade 3 or 4 cytopenias.

218

219 **5.7 Immunizations**

220 The safety of immunization with live viral vaccines during or following administration of
221 ARZERRA has not been studied. Do not administer live viral vaccines to patients who have
222 recently received ARZERRA. The ability to generate an immune response to any vaccine
223 following administration of ARZERRA has not been studied.

224 **6 ADVERSE REACTIONS**

225 The following serious adverse reactions are discussed in greater detail in other sections of the
226 labeling:

- 227 • Infusion Reactions [*see Warnings and Precautions (5.1)*]
- 228 • Hepatitis B Virus Reactivation [*see Warnings and Precautions (5.2)*]
- 229 • Hepatitis B Virus Infection [*see Warnings and Precautions (5.3)*]
- 230 • Progressive Multifocal Leukoencephalopathy [*see Warnings and Precautions (5.4)*]
- 231 • Tumor Lysis Syndrome [*see Warnings and Precautions (5.5)*]
- 232 • Cytopenias [*see Warnings and Precautions (5.6)*]

233

234 Previously Untreated CLL: The most common adverse reactions ($\geq 10\%$) were infusion
235 reactions and neutropenia (Table 3).

236

237 Refractory CLL: The most common adverse reactions ($\geq 10\%$) were neutropenia, pneumonia,
238 pyrexia, cough, diarrhea, anemia, fatigue, dyspnea, rash, nausea, bronchitis, and upper
239 respiratory tract infections (Table 5). The most common serious adverse reactions were
240 infections (including pneumonia and sepsis), neutropenia, and pyrexia. Infections were the most
241 common adverse reactions leading to drug discontinuation.

242

243 **6.1 Clinical Trials Experience**

244 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
245 observed in the clinical trials of a drug cannot be directly compared with rates in the clinical
246 trials of another drug and may not reflect the rates observed in practice.

247

248 Previously Untreated CLL: The safety of ARZERRA was evaluated in an open-label, parallel-
249 arm, randomized trial (Study 1) in 444 patients with previously untreated CLL. Patients were
250 randomized to receive either ARZERRA as an intravenous infusion every 28 days in
251 combination with chlorambucil (n = 217) or chlorambucil as a single agent (n = 227). In both
252 arms, patients received chlorambucil 10 mg/m² orally on Days 1 to 7 every 28 days. The infusion
253 schedule for ARZERRA was 300 mg administered on Cycle 1 Day 1, 1,000 mg administered on

254 Cycle 1 Day 8, and 1,000 mg administered on Day 1 of subsequent 28-day cycles. The median
255 number of cycles of ARZERRA completed was 6.

256

257 The data described in Table 3 include relevant adverse reactions occurring up to 60 days after the
258 last dose of study medication; Table 4 includes relevant hematologic laboratory abnormalities.

259

260 **Table 3. Adverse Reactions With $\geq 5\%$ Incidence in Patients Receiving ARZERRA Plus**
261 **Chlorambucil and Also $\geq 2\%$ More Than Patients Receiving Chlorambucil**

Adverse Reactions	ARZERRA Plus Chlorambucil (N = 217)		Chlorambucil (N = 227)	
	All Grades %	Grade ≥ 3 %	All Grades %	Grade ≥ 3 %
Infusion reactions ^a	67	10	0	0
Neutropenia	27	26	18	14
Asthenia	8	<1	5	0
Headache	7	<1	3	0
Leukopenia	6	3	2	<1
Herpes simplex ^b	6	0	4	<1
Lower respiratory tract infection	5	1	3	<1
Arthralgia	5	<1	3	0
Upper abdominal pain	5	0	3	0

262 ^a Includes events which occurred on the day of an infusion or within 24 hours of the end of an
263 infusion and resulted in an interruption or discontinuation of treatment. Infusion reactions may
264 include, but are not limited to, chills, dyspnea, flushing, hypotension, nausea, pain, pruritus,
265 pyrexia, rash, and urticaria.

266 ^b Includes oral herpes, herpes, herpes virus infection, genital herpes, and herpes simplex.

267

268 **Table 4. Post-baseline Hematologic Laboratory Abnormalities Occurring With $\geq 5\%$**
269 **Incidence in Patients Receiving ARZERRA Plus Chlorambucil and Also $\geq 2\%$ More Than**
270 **Patients Receiving Chlorambucil**

	ARZERRA plus Chlorambucil (N = 217)		Chlorambucil (N = 227)	
	All Grades %	Grade ≥ 3 %	All Grades %	Grade ≥ 3 %
Leukopenia	67	23	28	4
Neutropenia	66	29	56	24
Lymphopenia	52	29	20	7

271

272 Infusion Reactions: Overall, 67% of patients who received ARZERRA in combination with
273 chlorambucil experienced one or more symptoms of infusion reactions (10% were Grade 3 or

274 greater; none were fatal). Infusion reactions that were either Grade 3 or greater, serious, or led to
275 treatment interruption or discontinuation occurred most frequently during Cycle 1 (56% on
276 Day 1 [6% were Grade 3 or greater] and 23% on Day 8 [3% were Grade 3 or greater]) and
277 decreased with subsequent infusions. Infusion reactions led to discontinuation of treatment in 3%
278 of patients. Serious adverse events of infusion reactions occurred in 2% of patients.

279

280 **Neutropenia:** Overall, 3% of patients had neutropenia as a serious adverse event, reported up to
281 60 days after the last dose. One patient died with neutropenic sepsis and agranulocytosis.

282 Prolonged neutropenia occurred in 6% of patients receiving ARZERRA in combination with
283 chlorambucil compared with 4% of patients receiving chlorambucil. Late-onset neutropenia
284 occurred in 6% of patients receiving ARZERRA in combination with chlorambucil compared
285 with 1% of patients receiving chlorambucil alone.

286

287 **Refractory CLL:** The safety of monotherapy with ARZERRA was evaluated in 181 patients
288 with relapsed or refractory CLL in 2 open-label, non-randomized, single-arm studies. In these
289 studies, ARZERRA was administered at 2,000 mg beginning with the second dose for 11 doses
290 (Study 2 [n = 154]) or 3 doses (Study 3 [n = 27]).

291

292 The data described in Table 5 and other sections below are derived from 154 patients in Study 2.
293 All patients received 2,000 mg weekly from the second dose onward. Ninety percent of patients
294 received at least 8 infusions of ARZERRA and 55% received all 12 infusions. The median age
295 was 63 years (range: 41 to 86 years), 72% were male, and 97% were white.

296

297 **Table 5. Incidence of All Adverse Reactions Occurring in ≥5% of Patients and in the**
298 **Fludarabine- and Alemtuzumab-refractory Subset**

Adverse Reaction	Total Population (N = 154)		Fludarabine- and Alemtuzumab-refractory (N = 59)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Pneumonia ^a	23	14	25	15
Pyrexia	20	3	25	5
Cough	19	0	19	0
Diarrhea	18	0	19	0
Anemia	16	5	17	8
Fatigue	15	0	15	0
Dyspnea	14	2	19	5
Rash ^b	14	<1	17	2
Bronchitis	11	<1	19	2
Nausea	11	0	12	0
Upper respiratory tract infection	11	0	3	0
Edema peripheral	9	<1	8	2
Back pain	8	1	12	2
Chills	8	0	10	0
Nasopharyngitis	8	0	8	0
Sepsis ^c	8	8	10	10
Urticaria	8	0	5	0
Insomnia	7	0	10	0
Headache	6	0	7	0
Herpes zoster	6	1	7	2
Hyperhidrosis	5	0	5	0
Hypertension	5	0	8	0
Hypotension	5	0	3	0
Muscle spasms	5	0	3	0
Sinusitis	5	2	3	2
Tachycardia	5	<1	7	2

299 ^a Includes pneumonia, lung infection, lobar pneumonia, and bronchopneumonia.

300 ^b Includes rash, rash macular, and rash vesicular.

301 ^c Includes sepsis, neutropenic sepsis, bacteremia, and septic shock.

302

303 **Infusion Reactions:** Infusion reactions occurred in 44% of patients on the day of the first
304 infusion (300 mg), 29% on the day of the second infusion (2,000 mg), and less frequently during
305 subsequent infusions.

306

307 **Infections:** A total of 108 patients (70%) experienced bacterial, viral, or fungal infections. A
308 total of 45 patients (29%) experienced Grade 3 or greater infections, of which 19 (12%) were

309 fatal. The proportion of fatal infections in the fludarabine- and alemtuzumab-refractory group
310 was 17%.

311

312 Neutropenia: Of 108 patients with normal neutrophil counts at baseline, 45 (42%) developed
313 Grade 3 or greater neutropenia. Nineteen (18%) developed Grade 4 neutropenia. Some patients
314 experienced new onset Grade 4 neutropenia >2 weeks in duration.

315

316 **6.2 Immunogenicity**

317 There is a potential for immunogenicity with therapeutic proteins such as ofatumumab. Serum
318 samples from more than 300 patients with CLL were tested during and after treatment for
319 antibodies to ARZERRA. There was no formation of anti-ofatumumab antibodies in patients
320 with CLL after treatment with ofatumumab.

321

322 Immunogenicity assay results are highly dependent on several factors including assay sensitivity
323 and specificity, assay methodology, sample handling, timing of sample collection, concomitant
324 medications, and underlying disease. For these reasons, comparison of incidence of antibodies to
325 ARZERRA with the incidence of antibodies to other products may be misleading.

326

327 **6.3 Postmarketing Experience**

328 The following adverse reactions have been identified during post-approval use of ARZERRA.
329 Because these reactions are reported voluntarily from a population of uncertain size, it is not
330 always possible to reliably estimate their frequency or establish a causal relationship to drug
331 exposure.

332 Infusion-related Cardiac Events: Cardiac arrest.

333 Mucocutaneous Reactions: Stevens-Johnson syndrome, porphyria cutanea tarda.

334 **7 DRUG INTERACTIONS**

335 Coadministration of ARZERRA with chlorambucil did not result in clinically relevant effects on
336 the pharmacokinetics of chlorambucil or its active metabolite, phenylacetic acid mustard.

337 **8 USE IN SPECIFIC POPULATIONS**

338 **8.1 Pregnancy**

339 Pregnancy Category C: There are no adequate or well-controlled studies of ofatumumab in
340 pregnant women. A reproductive study in pregnant cynomolgus monkeys that received
341 ofatumumab at doses up to 3.5 times the maximum recommended human dose (2,000 mg) of
342 ofatumumab did not demonstrate maternal toxicity or teratogenicity. Ofatumumab crossed the
343 placental barrier, and fetuses exhibited depletion of peripheral B cells and decreased spleen and
344 placental weights. ARZERRA should be used during pregnancy only if the potential benefit to
345 the mother justifies the potential risk to the fetus.

346

347 There are no human or animal data on the potential short- and long-term effects of perinatal
348 B-cell depletion in offspring following in utero exposure to ofatumumab. Ofatumumab does not
349 bind normal human tissues other than B lymphocytes. It is not known if binding occurs to unique
350 embryonic or fetal tissue targets. In addition, the kinetics of B-lymphocyte recovery are
351 unknown in offspring with B-cell depletion [*see Nonclinical Toxicology (13.3)*].

352

353 **8.3 Nursing Mothers**

354 It is not known whether ofatumumab is secreted in human milk; however, human IgG is secreted
355 in human milk. Published data suggest that neonatal and infant consumption of breast milk does
356 not result in substantial absorption of these maternal antibodies into circulation. Because the
357 effects of local gastrointestinal and limited systemic exposure to ofatumumab are unknown,
358 caution should be exercised when ARZERRA is administered to a nursing woman.

359

360 **8.4 Pediatric Use**

361 Safety and effectiveness of ARZERRA have not been established in children.

362

363 **8.5 Geriatric Use**

364 In Study 1, 68% of patients (148/217) receiving ARZERRA plus chlorambucil were 65 years and
365 older. Patients age 65 years and older experienced a higher incidence of the following Grade 3 or
366 greater adverse reactions compared with patients younger than 65 years of age: neutropenia
367 (30% versus 17%) and pneumonia (5% versus 1%) [*see Adverse Reactions (6.1)*]. In patients
368 65 years and older, 29% experienced serious adverse events compared with 13% of patients
369 younger than 65 years. No clinically meaningful differences in the effectiveness of ARZERRA
370 plus chlorambucil were observed between older and younger patients [*see Clinical Studies*
371 *(14.1)*].

372

373 In refractory CLL, clinical studies of ARZERRA did not include sufficient numbers of subjects
374 aged 65 years and older to determine whether they respond differently from younger subjects
375 [*see Clinical Pharmacology (12.3)*].

376

377 **8.6 Renal Impairment**

378 No formal studies of ARZERRA in patients with renal impairment have been conducted [*see*
379 *Clinical Pharmacology (12.3)*].

380

381 **8.7 Hepatic Impairment**

382 No formal studies of ARZERRA in patients with hepatic impairment have been conducted.

383 **10 OVERDOSAGE**

384 No data are available regarding overdosage with ARZERRA.

385 **11 DESCRIPTION**

386 ARZERRA (ofatumumab) is an IgG1 κ human monoclonal antibody with a molecular weight of
387 approximately 149 kDa. The antibody was generated via transgenic mouse and hybridoma
388 technology and is produced in a recombinant murine cell line (NS0) using standard mammalian
389 cell cultivation and purification technologies.

390

391 ARZERRA is a sterile, clear to opalescent, colorless, preservative-free liquid concentrate for
392 intravenous administration. ARZERRA is supplied at a concentration of 20 mg/mL in single-use
393 vials. Each single-use vial contains either 100 mg ofatumumab in 5 mL of solution or 1,000 mg
394 ofatumumab in 50 mL of solution.

395

396 Inactive ingredients include: 10 mg/mL arginine, diluted hydrochloric acid, 0.019 mg/mL edetate
397 disodium, 0.2 mg/mL polysorbate 80, 6.8 mg/mL sodium acetate, 2.98 mg/mL sodium chloride,
398 and Water for Injection, USP. The pH is 5.5.

399 **12 CLINICAL PHARMACOLOGY**

400 **12.1 Mechanism of Action**

401 Ofatumumab binds specifically to both the small and large extracellular loops of the CD20
402 molecule. The CD20 molecule is expressed on normal B lymphocytes (pre-B- to mature
403 B-lymphocyte) and on B-cell CLL. The CD20 molecule is not shed from the cell surface and is
404 not internalized following antibody binding.

405

406 The Fab domain of ofatumumab binds to the CD20 molecule and the Fc domain mediates
407 immune effector functions to result in B-cell lysis in vitro. Data suggest that possible
408 mechanisms of cell lysis include complement-dependent cytotoxicity and antibody-dependent,
409 cell-mediated cytotoxicity.

410

411 **12.2 Pharmacodynamics**

412 B-Cell Depletion: In patients with previously untreated CLL, at 6 months after the last dose, the
413 median reductions in CD19-positive B cells were >99% (n = 155) for ARZERRA in combination
414 with chlorambucil and 94% (n = 121) for chlorambucil alone.

415

416 In patients with CLL refractory to fludarabine and alemtuzumab, the median decrease in
417 circulating CD19-positive B cells was 91% (n = 50) with the 8th infusion and 85% (n = 32) with
418 the 12th infusion. The time to recovery of lymphocytes, including CD19-positive B cells, to
419 normal levels has not been determined.

420

421 Although the depletion of B-cells in the peripheral blood is a measurable pharmacodynamic
422 effect, it is not directly correlated with the depletion of B cells in solid organs or in malignant
423 deposits. B-cell depletion has not been shown to be directly correlated to clinical response.

424

425 Cardiac Electrophysiology: The effect of multiple doses of ARZERRA on the QTc interval
426 was evaluated in a pooled analysis of 3 open-label studies in patients with CLL (N = 85).
427 Patients received ARZERRA 300 mg on Day 1 followed by either 1,000 mg or 2,000 mg for
428 subsequent doses. No large changes in the mean QTc interval (i.e., >20 milliseconds) were
429 detected in the pooled analysis.

430

431 **12.3 Pharmacokinetics**

432 Ofatumumab is eliminated through both a target-independent route and a B cell-mediated route.
433 Ofatumumab exhibited dose-dependent clearance in the dose range of 100 to 2,000 mg. Due to
434 the depletion of B cells, the clearance of ofatumumab decreased substantially after subsequent
435 infusions compared with the first infusion.

436

437 Pharmacokinetic data were obtained after repeated administration (4, 5, 8, or 12 infusions) of
438 1,000 mg or 2,000 mg doses in 381 patients with CLL (Studies 1, 2, and 3). The geometric mean
439 (%CV) values for clearance, volume of distribution at steady state (V_{ss}), and half-life for
440 ofatumumab in these patients were 12.9 mL/hour (76%), 5.7 L (65%), and 15.6 days (90%). The
441 pharmacokinetic profile was similar across doses in patients with CLL.

442

443 Specific Populations: Effects of Body Size, Gender, Age, and Renal Impairment: Based
444 on population pharmacokinetic analyses, body size, gender, age, and renal impairment (evaluated
445 in patients with a calculated creatinine clearance ≥ 30 mL/min) do not have a clinically
446 meaningful effect on the pharmacokinetics of ofatumumab.

447 **13 NONCLINICAL TOXICOLOGY**

448 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

449 No carcinogenicity or mutagenicity studies of ofatumumab have been conducted. In a
450 repeat-dose toxicity study, no tumorigenic or unexpected mitogenic responses were noted in
451 cynomolgus monkeys treated for 7 months with up to 3.5 times the maximum human dose
452 (2,000 mg) of ofatumumab. Effects on male and female fertility have not been evaluated in
453 animal studies.

454

455 **13.3 Reproductive and Developmental Toxicology**

456 Pregnant cynomolgus monkeys dosed with 0.7 or 3.5 times the maximum human dose
457 (2,000 mg) of ofatumumab weekly during the period of organogenesis (gestation days 20 to 50)
458 had no maternal toxicity or teratogenicity. Both dose levels of ofatumumab depleted circulating
459 B cells in the dams, with signs of initial B cell recovery 50 days after the final dose. Following
460 Caesarean section at gestational day 100, fetuses from ofatumumab-treated dams exhibited
461 decreases in mean peripheral B-cell counts (decreased to approximately 10% of control values),
462 splenic B-cell counts (decreased to approximately 15% to 20% of control values), and spleen

463 weights (decreased by 15% for the low-dose and by 30% for the high-dose group, compared with
464 control values). Fetuses from treated dams exhibiting anti-ofatumumab antibody responses had
465 higher B cell counts and higher spleen weights compared with the fetuses from other treated
466 dams, indicating partial recovery in those animals developing anti-ofatumumab antibodies. When
467 compared with control animals, fetuses from treated dams in both dose groups had a 10%
468 decrease in mean placental weights. A 15% decrease in mean thymus weight compared with the
469 controls was also observed in fetuses from dams treated with 3.5 times the human dose of
470 ofatumumab. The biological significance of decreased placental and thymic weights is unknown.

471

472 The kinetics of B-lymphocyte recovery and the potential long-term effects of perinatal B-cell
473 depletion in offspring from ofatumumab-treated dams have not been studied in animals.

474 **14 CLINICAL STUDIES**

475 **14.1 Previously Untreated CLL**

476 The efficacy of ARZERRA was evaluated in a randomized, open-label, parallel-arm study;
477 447 patients previously untreated for CLL were randomized to receive either ARZERRA as
478 monthly intravenous infusions (Cycle 1: 300 mg on Day 1 and 1,000 mg on Day 8; subsequent
479 cycles: 1,000 mg on Day 1 every 28 days) in combination with chlorambucil (10 mg/m² orally
480 on Days 1 to 7 every 28 days) or chlorambucil alone (10 mg/m² orally on Days 1 to 7 every 28
481 days). Patients received treatment for a minimum of 3 cycles. Treatment was continued for
482 3 cycles beyond maximal response (2 consecutive response assessments of stable disease, partial
483 response, or complete response) for up to 12 cycles. Approximately 60% of patients received 3
484 to 6 cycles of ARZERRA and 30% received 7 to 12 cycles.

485

486 This trial enrolled patients for whom fludarabine-based therapy was considered to be
487 inappropriate by the investigator for reasons that included advanced age or presence of co-
488 morbidities. In the overall trial population, the median age was 69 years (range: 35 to 92 years)
489 and 69% of patients in both arms were at least 65 years of age. In the overall trial population,
490 72% of patients had 2 or more co-morbidities and 48% of patients had a creatinine clearance of
491 less than 70 mL/min. Sixty-three percent of patients were male and 89% were white. Elevated
492 beta-2 microglobulin (β 2m) >3,500 mcg/L was present in 72% of patients at baseline.

493

494 The primary endpoint was progression-free-survival (PFS) as assessed by a blinded Independent
495 Review Committee (IRC) using the International Workshop for Chronic Lymphocytic Leukemia
496 (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines
497 (2008). ARZERRA plus chlorambucil resulted in statistically significant improvement in IRC-
498 assessed median PFS compared with chlorambucil alone (22.4 months versus 13.1 months;
499 hazard ratio: 0.57 [0.45, 0.72]) (Table 6; Figure 1).

500

501 Secondary efficacy endpoints, including overall response (OR), complete response (CR), and
 502 duration of response, were also assessed by the IRC using the 2008 IWCLL Guidelines
 503 (Table 6).

504
 505 **Table 6. IRC-assessed Efficacy Results in Previously Untreated CLL (ITT Population^a)**

Primary and Key Secondary Endpoints	ARZERRA Plus Chlorambucil (N = 221)	Chlorambucil (N = 226)
Progression-free survival (PFS) Median, months (95% CI)	22.4 (19.0, 25.2)	13.1 (10.6, 13.8)
Hazard ratio ^b (95% CI) Stratified log rank <i>P</i> value	0.57 (0.45, 0.72) <i>P</i> <0.001	
Overall response, % (95% CI) <i>P</i> value	82.4 (76.7, 87.1)	68.6 (62.1, 74.6)
Complete response, %	12	1
Duration of response Median, months (95% CI)	22.1 (19.1, 24.6)	13.2 (10.8, 16.4)

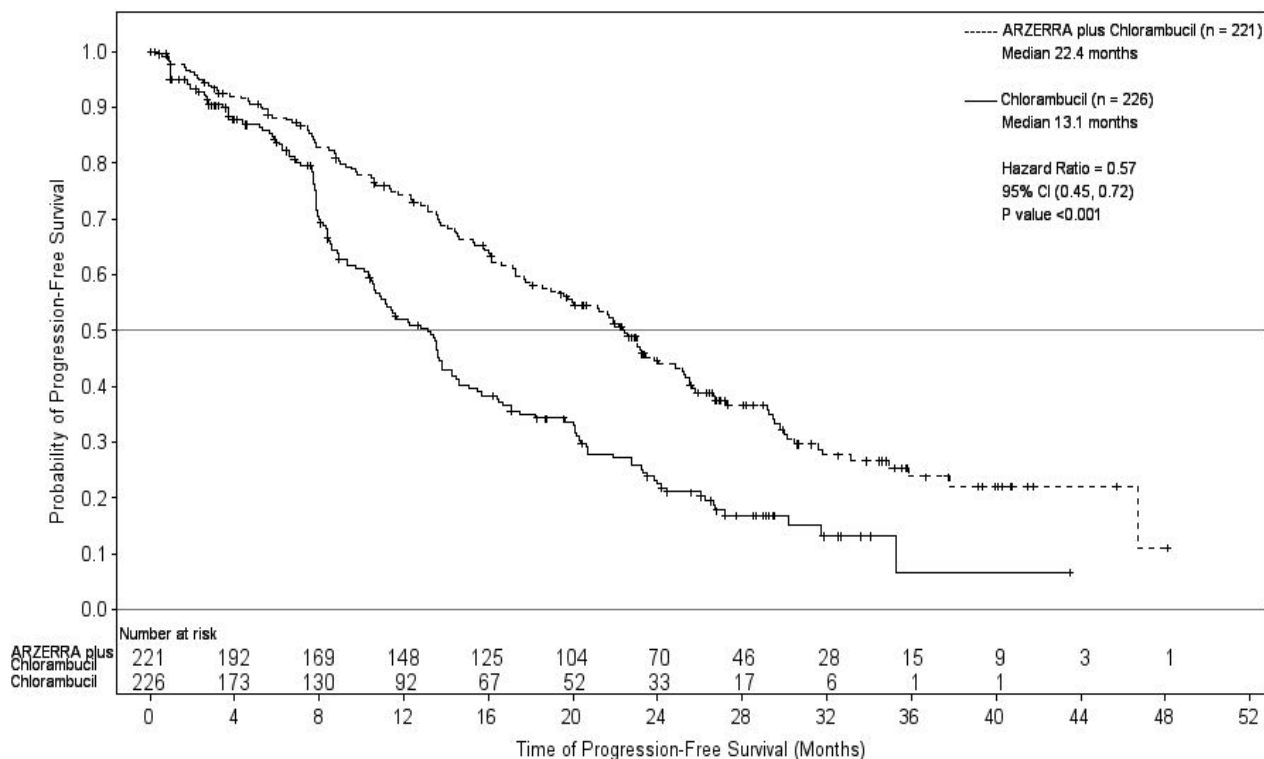
506 IRC = Independent Review Committee; ITT = intention to treat; CI = confidence interval.

507 ^a Intention-to-treat population includes all 447 randomized patients.

508 ^b Pike Estimator.

509

510 **Figure 1. Kaplan-Meier Estimates of IRC-assessed Progression-free Survival**



511
512

513 **14.2 Refractory CLL**

514 Study 2 was a single-arm, multicenter study in 154 patients with relapsed or refractory CLL.
 515 ARZERRA was administered by intravenous infusion according to the following schedule:
 516 300 mg (Week 0), 2,000 mg weekly for 7 infusions (Weeks 1 through 7), and 2,000 mg every
 517 4 weeks for 4 infusions (Weeks 12 through 24). Patients with CLL refractory to fludarabine and
 518 alemtuzumab (n = 59) comprised the efficacy population. Drug refractoriness was defined as
 519 failure to achieve at least a partial response to, or disease progression within 6 months of, the last
 520 dose of fludarabine or alemtuzumab. The main efficacy outcome was durable objective tumor
 521 response rate. Objective tumor responses were determined using the 1996 NCI-WG Guidelines
 522 for CLL.

523

524 In patients with CLL refractory to fludarabine and alemtuzumab, the median age was 64 years
 525 (range: 41 to 86 years), 75% were male, and 95% were white. The median number of prior
 526 therapies was 5; 93% received prior alkylating agents, 59% received prior rituximab, and all
 527 received prior fludarabine and alemtuzumab. Eighty-eight percent of patients received at least
 528 8 infusions of ARZERRA and 54% received 12 infusions.

529

530 The investigator-determined overall response rate in patients with CLL refractory to fludarabine
 531 and alemtuzumab was 42% (99% CI: 26, 60) with a median duration of response of 6.5 months
 532 (95% CI: 5.8, 8.3). There were no complete responses. Anti-tumor activity was also observed in

533 additional patients in Study 2 and in a multicenter, open-label, dose-escalation study (Study 3)
534 conducted in patients with relapsed or refractory CLL.

535 **16 HOW SUPPLIED/STORAGE AND HANDLING**

536 ARZERRA (ofatumumab) is a sterile, clear to opalescent, colorless, preservative-free liquid
537 concentrate (20 mg/mL) for dilution and intravenous administration provided in single-use glass
538 vials with a rubber stopper (not made with natural rubber latex) and an aluminum overseal. Each
539 vial contains either 100 mg ofatumumab in 5 mL of solution or 1,000 mg ofatumumab in 50 mL
540 of solution.

541

542 ARZERRA is available as follows:

Carton Contents	NDC
3 single-use 100 mg/5 mL vials	Vial: NDC 0173-0821-02 Carton of 3 vials: NDC 0173-0821-33
1 single-use 1,000 mg/50 mL vial	Vial and Carton: NDC 0173-0821-01

543

544 Store ARZERRA refrigerated between 2° to 8°C (36° to 46°F). Do not freeze. Vials should be
545 protected from light.

546 **17 PATIENT COUNSELING INFORMATION**

547 Advise patients to contact a healthcare professional for any of the following:

- 548 • Signs and symptoms of infusion reactions including fever, chills, rash, or breathing problems
549 within 24 hours of infusion [see *Warnings and Precautions (5.1)*, *Adverse Reactions (6.1)*]
- 550 • Symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes
551 [see *Warnings and Precautions (5.2, 5.3)*]
- 552 • New neurological symptoms such as confusion, dizziness or loss of balance, difficulty
553 talking or walking, or vision problems [see *Warnings and Precautions (5.4)*]
- 554 • Bleeding, easy bruising, petechiae, pallor, worsening weakness, or fatigue [see *Warnings and*
555 *Precautions (5.6)*]
- 556 • Signs of infections including fever and cough [see *Warnings and Precautions (5.6)*, *Adverse*
557 *Reactions (6.1)*]
- 558 • Pregnancy or nursing [see *Use in Specific Populations (8.1, 8.3)*]

559

560 Advise patients of the need for:

- 561 • Monitoring and possible need for treatment if they have a history of hepatitis B infection
562 (based on the blood test) [see *Warnings and Precautions (5.2)*].
- 563 • Periodic monitoring for blood counts [see *Warnings and Precautions (5.6)*]
- 564 • Avoiding vaccination with live viral vaccines [see *Warnings and Precautions (5.7)*]

565

566 ARZERRA is a registered trademark of the GSK group of companies.

567

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