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. (5.4)
• Progressive Multifocal Leukoencephalopathy (PML) resulting in death. (5.6)

----------RECENT MAJOR CHANGES----------

Boxed Warning	xx/xxxx
Dosage and Administration, Administration (2.2)	xx/xxxx
Warnings and Precautions, Tumor Lysis Syndrome (5.2)	xx/xxxx
Warnings and Precautions, Hepatitis B Virus Reactivation (5.4)	xx/xxxx
Warnings and Precautions, Hepatitis B Virus Infection (5.5)	xx/xxxx

----------INDICATIONS AND USAGE----------

ARZERRA (ofatumumab) is a CD20-directed cytolytic monoclonal antibody indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab. The effectiveness of ARZERRA is based on the demonstration of durable objective responses. No data demonstrate an improvement in disease-related symptoms or increased survival with ARZERRA. (1, 14)

---------- DOSAGE AND ADMINISTRATION ----------

- Dilute and administer as an intravenous infusion. Do not administer as an intravenous push or bolus. (2.1)
- Recommended dosage and schedule is 12 doses administered as follows:
  - 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 oral acetaminophen, oral or intravenous antihistamine, and intravenous corticosteroid. (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------

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

----------CONTRAINDICATIONS----------

None. (4)

---------- WARNINGS AND PRECAUTIONS----------

- Infusion Reactions: Premedicate with an intravenous corticosteroid (as appropriate), oral acetaminophen, and an oral or intravenous antihistamine. Monitor patients closely during infusions. Interrupt infusion if infusion reactions occur. (2.3, 2.4, 5.1)
- Tumor Lysis Syndrome: Administer aggressive intravenous hydration and anti-hyperuricemic agents, correct electrolyte abnormalities, and monitor renal function. (5.2)
- Cytopenias: Monitor blood counts at regular intervals. (5.3)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (≥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: xx/xxxx

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- Hepatitis B Virus (HBV) reactivation can occur in patients receiving CD20-directed cytolytic antibodies, including ARZERRA, in some cases resulting in fulminant hepatitis, hepatic failure, and death *[see Warnings and Precautions (5.4)]*.
- Progressive Multifocal Leukoencephalopathy (PML) resulting in death can occur in patients receiving CD20-directed cytolytic antibodies, including ARZERRA *[see Warnings and Precautions (5.6)]*.

1 INDICATIONS AND USAGE

ARZERRA® (ofatumumab) is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab.

The effectiveness of ARZERRA is based on the demonstration of durable objective responses *[see Clinical Studies (14)]*. No data demonstrate an improvement in disease-related symptoms or increased survival with ARZERRA.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage Regimen

- Do not administer as an intravenous push or bolus.
- Premedicate before each infusion *[see Dosage and Administration (2.4)]*.
- Administer with an in-line filter set supplied with product.

The recommended dosage and schedule is 12 doses administered as follows:

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

2.2 Administration

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

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

- Dose 1: Initiate infusion at a rate of 3.6 mg/hour (12 mL/hour).
- Dose 2: Initiate infusion at a rate of 24 mg/hour (12 mL/hour).
- Doses 3 through 12: Initiate infusion at a rate of 50 mg/hour (25 mL/hour).

In the absence of infusional toxicity, the rate of infusion may be increased every 30 minutes as described in Table 1. Do not exceed the infusion rates in Table 1.

Table 1. Infusion Rates for ARZERRA

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

[a] Dose 1 = 300 mg (0.3 mg/mL).
[b] Doses 2 and 3-12 = 2,000 mg (2 mg/mL).

2.3 Dose Modification

- Interrupt infusion for infusion reactions of any severity *[see Warnings and Precautions (5.1)]*.
- For Grade 4 infusion reactions, do not resume the infusion.
- For Grade 1, 2, or 3 infusion reaction, if the infusion reaction resolves or remains less than or equal to Grade 2, resume infusion with the following modifications according to the initial Grade of the infusion reaction.
  - Grade 1 or 2: Infuse at one-half of the previous infusion rate.
  - Grade 3: Infuse at a rate of 12 mL/hour.
- After resuming the infusion, the infusion rate may be increased according to Table 1 above, based on patient tolerance.

2.4 Premedication

- Premedicate 30 minutes to 2 hours prior to each dose with oral acetaminophen 1,000 mg (or equivalent), oral or intravenous antihistamine (cetirizine 10 mg or equivalent), and intravenous corticosteroid (prednisolone 100 mg or equivalent).
- Do not reduce corticosteroid dose for Doses 1, 2, and 9.
- Corticosteroid dose may be reduced as follows for Doses 3 through 8 and 10 through 12:
  - Doses 3 through 8: Gradually reduce corticosteroid dose with successive infusions if a Grade 3 or greater infusion reaction did not occur with the preceding dose.
  - Doses 10 through 12: Administer prednisolone 50 mg to 100 mg or equivalent if a Grade 3 or greater infusion reaction did not occur with Dose 9.

2.5 Preparation and Administration

- Do not shake product.

- Inspect parenteral drug products visually for particulate matter and discoloration prior to administration. ARZERRA should be a clear to opalescent, colorless solution and may contain a small amount of visible translucent-to-white, amorphous, ofatumumab particles. The solution should not be used if discolored or cloudy, or if foreign particulate matter is present.

Preparation of Solution:

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

Administration Instructions:

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

3 DOSAGE FORMS AND STRENGTHS

- 100 mg/5 mL single-use vial.
- 1,000 mg/50 mL single-use vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

ARZERRA can cause serious infusion reactions manifesting as bronchospasm, dyspnea, laryngeal edema, pulmonary edema, flushing, hypertension, hypotension, syncope, cardiac ischemia/infarction, back pain, abdominal pain, pyrexia, rash, urticaria, and angioedema. Infusion reactions occur more frequently with the first 2 infusions *[see Adverse Reactions (6.1)]*.

Premedicate with acetaminophen, an antihistamine, and a corticosteroid *[see Dosage and Administration (2.1, 2.4)]*. Interrupt infusion with ARZERRA for infusion reactions of any severity. Institute medical management for severe infusion reactions including angina or other signs and symptoms of myocardial ischemia *[see Dosage and Administration (2.3)]*.

In a study of patients with moderate to severe chronic obstructive pulmonary disease, an indication for which ARZERRA is not approved, 2 of 5 patients developed Grade 3 bronchospasm during infusion.

5.2 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) has occurred in patients treated with CD20-directed cytolytic antibodies, including ARZERRA. Administer aggressive intravenous hydration and anti-hyperuricemic agents, correct electrolyte abnormalities, and monitor renal function.

5.3 Cytopenias

Prolonged (≥1 week) severe neutropenia and thrombocytopenia can occur with ARZERRA. Monitor complete blood counts (CBC) and platelet counts at regular intervals during therapy, and increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias.

5.4 Hepatitis B Virus Reactivation

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

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

Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with ARZERRA. For patients who show evidence of hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy.

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

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

5.5 Hepatitis B Virus Infection

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

5.6 Progressive Multifocal Leukoencephalopathy

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

5.7 Intestinal Obstruction

Obstruction of the small intestine can occur in patients receiving ARZERRA. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur.

5.8 Immunizations

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

6 ADVERSE REACTIONS

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

- Infusion Reactions *[see Warnings and Precautions (5.1)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.2)]*
- Cytopenias *[see Warnings and Precautions (5.3)]*
- Hepatitis B Virus Reactivation *[see Warnings and Precautions (5.4)]*
- Hepatitis B Virus Infection *[see Warnings and Precautions (5.5)]*

- Progressive Multifocal Leukoencephalopathy *[see Warnings and Precautions (5.6)]*
- Intestinal Obstruction *[see Warnings and Precautions (5.7)]*

The most common adverse reactions (≥10%) in Study 1 were neutropenia, pneumonia, pyrexia, cough, diarrhea, anemia, fatigue, dyspnea, rash, nausea, bronchitis, and upper respiratory tract infections.

The most common serious adverse reactions in Study 1 were infections (including pneumonia and sepsis), neutropenia, and pyrexia. Infections were the most common adverse reactions leading to drug discontinuation in Study 1.

6.1 Clinical Trials Experience

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

The safety of monotherapy with ARZERRA was evaluated in 181 patients with relapsed or refractory CLL in 2 open-label, non-randomized, single-arm studies. In these studies, ARZERRA was administered at 2,000 mg beginning with the second dose for 11 doses (Study 1 [n = 154]) or 3 doses (Study 2 [n = 27]).

The data described in Table 2 and other sections below are derived from 154 patients in Study 1. All patients received 2,000 mg weekly from the second dose onward. Ninety percent of patients received at least 8 infusions of ARZERRA and 55% received all 12 infusions. The median age was 63 years (range: 41 to 86 years), 72% were male, and 97% were White.

Table 2. Incidence of All Adverse Reactions Occurring in ≥5% of Patients in Study 1 and in the Fludarabine- and Alemtuzumab-Refractory Subset of Study 1 (MedDRA 9.0)

Body System/Adverse Event	Total Population (n = 154)		Fludarabine- and Alemtuzumab-Refractory (n = 59)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Infections and infestations				
Pneumonia[a]	23	14	25	15
Upper respiratory tract infection	11	0	3	0
Bronchitis	11	<1	19	2
Sepsis[b]	8	8	10	10
Nasopharyngitis	8	0	8	0
Herpes zoster	6	1	7	2
Sinusitis	5	2	3	2
Blood and lymphatic system disorders				
Anemia	16	5	17	8
Psychiatric disorders				
Insomnia	7	0	10	0
Nervous system disorders				
Headache	6	0	7	0
Cardiovascular disorders				
Hypertension	5	0	8	0
Hypotension	5	0	3	0
Tachycardia	5	<1	7	2
Respiratory, thoracic, and mediastinal disorders				
Cough	19	0	19	0
Dyspnea	14	2	19	5
Gastrointestinal disorders				
Diarrhea	18	0	19	0
Nausea	11	0	12	0
Skin and subcutaneous tissue disorders				
Rash[c]	14	<1	17	2
Urticaria	8	0	5	0
Hyperhidrosis	5	0	5	0
Musculoskeletal and connective tissue disorders				
Back pain	8	1	12	2
Muscle spasms	5	0	3	0
General disorders and administration site conditions				
Pyrexia	20	3	25	5
Fatigue	15	0	15	0
Edema peripheral	9	<1	8	2
Chills	8	0	10	0

[a] Pneumonia includes pneumonia, lung infection, lobar pneumonia, and bronchopneumonia.
[b] Sepsis includes sepsis, neutropenic sepsis, bacteremia, and septic shock.
[c] Rash includes rash, rash macular, and rash vesicular.

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

Infections: A total of 108 patients (70%) experienced bacterial, viral, or fungal infections. A total of 45 patients (29%) experienced ≥Grade 3 infections, of which 19 (12%) were fatal. The proportion of fatal infections in the fludarabine- and alemtuzumab-refractory group was 17%.

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

6.2 Immunogenicity

There is a potential for immunogenicity with therapeutic proteins such as ofatumumab. Serum samples from patients with CLL in Study 1 were tested by enzyme-linked immunosorbent assay (ELISA) for anti-ofatumumab antibodies during and after the 24-week treatment period. Results were negative in 46 patients after the 8th infusion and in 33 patients after the 12th infusion.

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

7 DRUG INTERACTIONS

No formal drug-drug interaction studies have been conducted with ARZERRA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical studies of ARZERRA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

No data are available regarding overdosage with ARZERRA.

11 DESCRIPTION

ARZERRA (ofatumumab) is an IgG1κ human monoclonal antibody with a molecular weight of approximately 149 kDa. The antibody was generated via transgenic mouse and hybridoma technology and is produced in a recombinant murine cell line (NS0) using standard mammalian cell cultivation and purification technologies.

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

Pharmacokinetic data were obtained from 146 patients with refractory CLL who received a 300-mg initial dose followed by 7 weekly and 4 monthly infusions of 2,000 mg. The C_{max} and $AUC_{(0-\infty)}$ after the 8^{th} infusion in Study 1 were approximately 40% and 60% higher than after the 4^{th} infusion in Study 2. The mean volume of distribution at steady-state (V_{ss}) values ranged from 1.7 to 5.1 L. Ofatumumab is eliminated through both a target-independent route and a B cell-mediated route. Ofatumumab exhibited dose-dependent clearance in the dose range of 100 to 2,000 mg. Due to the depletion of B cells, the clearance of ofatumumab decreased substantially after subsequent infusions compared to the first infusion. The mean clearance between the 4^{th} and 12^{th} infusions was approximately 0.01 L/hr and exhibited large inter-subject variability with CV% greater than 50%. The mean $t_{1/2}$ between the 4^{th} and 12^{th} infusions was approximately 14 days (range: 2.3 to 61.5 days).

Special Populations: Cross-study analyses were performed on data from patients with a variety of conditions, including 162 patients with CLL, who received multiple infusions of ARZERRA as a single agent at doses ranging from 100 to 2,000 mg. The effects of various covariates (e.g.,

body size [weight, height, body surface area], age, gender, baseline creatinine clearance) on ofatumumab pharmacokinetics were assessed in a population pharmacokinetic analysis.

Body Weight: Volume of distribution and clearance increased with body weight. However, this increase was not clinically significant. No dosage adjustment is recommended based on body weight.

Age: Age did not significantly influence ofatumumab pharmacokinetics in patients ranging from 21 to 86 years of age. No pharmacokinetic data are available in pediatric patients.

Gender: Gender had a modest effect on ofatumumab pharmacokinetics (14% to 25% lower clearance and volume of distribution in female patients compared to male patients) in a cross-study population analysis (41% of the patients in this analysis were male and 59% were female). These effects are not considered clinically important, and no dosage adjustment is recommended.

Renal Impairment: Creatinine clearance at baseline did not have a clinically important effect on ofatumumab pharmacokinetics in patients with calculated creatinine clearance values ranging from 33 to 287 mL/min.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

13.3 Reproductive and Developmental Toxicology

Pregnant cynomolgus monkeys dosed with 0.7 or 3.5 times the human dose of ofatumumab weekly during the period of organogenesis (gestation days 20 to 50) had no maternal toxicity or teratogenicity. Both dose levels of ofatumumab depleted circulating B cells in the dams, with signs of initial B cell recovery 50 days after the final dose. Following Caesarean section at gestational day 100, fetuses from ofatumumab-treated dams exhibited decreases in mean peripheral B-cell counts (decreased to approximately 10% of control values), splenic B-cell counts (decreased to approximately 15 to 20% of control values), and spleen weights (decreased by 15% for the low-dose and by 30% for the high-dose group, compared to control values). Fetuses from treated dams exhibiting anti-ofatumumab antibody responses had higher B cell counts and higher spleen weights compared to the fetuses from other treated dams, indicating partial recovery in those animals developing anti-ofatumumab antibodies. When compared to control animals, fetuses from treated dams in both dose groups had a 10% decrease in mean

placental weights. A 15% decrease in mean thymus weight compared to the controls was also observed in fetuses from dams treated with 3.5 times the human dose of ofatumumab. The biological significance of decreased placental and thymic weights is unknown.

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

14 CLINICAL STUDIES

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

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

The investigator-determined overall response rate in patients with CLL refractory to fludarabine and alemtuzumab was 42% (99% CI: 26, 60) with a median duration of response of 6.5 months (95% CI: 5.8, 8.3). There were no complete responses. Anti-tumor activity was also observed in additional patients in Study 1 and in a multicenter, open-label, dose-escalation study (Study 2) conducted in patients with relapsed or refractory CLL.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

ARZERRA is available as follows:

Carton Contents	NDC
3 single-use 100 mg/5 mL vials with 2 in-line filter sets	Vial: NDC 0173-0821-02 Carton of 3 vials: NDC 0173-0821-33
1 single-use 1,000 mg/50 mL vial with 2 in-line filter sets	Vial and Carton: NDC 0173-0821-01

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

17 PATIENT COUNSELING INFORMATION

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

- Signs and symptoms of infusion reactions including fever, chills, rash, or breathing problems within 24 hours of infusion *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*
- Bleeding, easy bruising, petechiae, pallor, worsening weakness, or fatigue *[see Warnings and Precautions (5.3)]*
- Signs of infections including fever and cough *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*
- Symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes *[see Warnings and Precautions (5.4, 5.5)]*
- New neurological symptoms such as confusion, dizziness or loss of balance, difficulty talking or walking, or vision problems *[see Warnings and Precautions (5.6)]*
- New or worsening abdominal pain or nausea or a significant increase in feeling unwell *[see Warnings and Precautions (5.2, 5.7)]*
- Pregnancy or nursing *[see Use in Specific Populations (8.1, 8.3)]*

Advise patients of the need for:

- Periodic monitoring for blood counts *[see Warnings and Precautions (5.3)]*
- Avoiding vaccination with live viral vaccines *[see Warnings and Precautions (5.8)]*

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