PRODUCT MONOGRAPH

Pr ARZERRA™

ofatumumab

100 mg/5 mL (20 mg/mL) Vial
1000 mg/50 mL (20 mg/mL) Vial

For Intravenous Use

Antineoplastic

Novartis Pharmaceuticals Canada Inc.
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
For Intravenous Infusion	Sterile Solution 100 mg per 5 mL vial 1000 mg per 50 mL vial (20 mg/mL)	There are no clinically relevant nonmedicinal ingredients. No preservatives are added. *For a complete listing see Dosage Forms, Composition and Packaging section.*

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 (see DOSAGE FORMS, COMPOSITION AND PACKAGING).

INDICATIONS AND CLINICAL USE

ARZERRA (ofatumumab) is indicated:

- in combination with chlorambucil, for the treatment of patients with chronic lymphocytic leukemia (CLL) who have not received prior therapy and for whom fludarabine-based therapy is considered inappropriate.

- for the treatment of patients with CLL refractory to fludarabine and alemtuzumab. The efficacy of ARZERRA in the treatment of refractory CLL is based on the demonstration of durable objective responses. No data demonstrate an improvement in disease related symptoms or increased survival with ARZERRA.

Pediatrics

The safety and effectiveness of ARZERRA in children has not been established. ARZERRA should not be used in children unless the benefit outweighs the risks (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

CONTRAINDICATIONS

- ARZERRA (ofatumumab) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or components of the container. For a complete list of excipients see the Dosage Forms, Composition and Packaging section of the Product Monograph.

- ARZERRA is also contraindicated in patients who have or have had progressive multifocal leukoencephalopathy (PML) (see WARNINGS AND PRECAUTIONS, Progressive Multifocal Leukoencephalopathy).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Infusion-related reactions**: ARZERRA administration can result in serious, including fatal infusion-related reactions (see WARNINGS AND PRECAUTIONS – Infusion-related reactions).
- **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 - Hepatitis B Infection and/or Reactivation).
- **Progressive Multifocal Leukoencephalopathy (PML)** resulting in death can occur in patients receiving CD20-directed cytolytic antibodies, including ARZERRA (see WARNINGS AND PRECAUTIONS - Progressive Multifocal Leukoencephalopathy).
- **Cardiovascular**: Serious and/or fatal cardiovascular events have been reported following the administration of ARZERRA (see WARNINGS AND PRECAUTIONS – Cardiovascular).
- **Infections**: Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of therapy with ARZERRA (see WARNINGS AND PRECAUTIONS – Infections).

General

Infusion-related reactions: Intravenous ARZERRA (ofatumumab) can cause infusion-related reactions. These reactions may result in temporary interruption or withdrawal of treatment or death. Premedication attenuates infusion-related reactions but these may still occur, predominantly during the first two infusions. Infusion-related reactions may include, but are not limited to, anaphylactoid/anaphylactic reactions, bronchospasm, cardiac events (e.g. myocardial ischaemia/infarction, bradycardia), chills/rigors, cough, cytokine release syndrome, diarrhoea, dyspnoea, fatigue, flushing, hypertension, hypotension, nausea, pain, pulmonary oedema, pruritis, pyrexia, rash, and urticaria. Even with premedication, severe reactions, including cytokine release syndrome, have been reported following ARZERRA use. In the events of severe infusion-related reaction, the infusion of ARZERRA must be interrupted immediately and symptomatic treatment instituted (see DOSAGE AND ADMINISTRATION).

If an anaphylactic reaction occurs, ARZERRA should be immediately and permanently discontinued and appropriate medical treatment should be initiated.

Infusion-related reactions occur predominantly during the first two infusions. Patients with a history of decreased pulmonary function may be at a greater risk for pulmonary complications from severe reactions and should be monitored closely during infusion of

ARZERRA (see ADVERSE REACTIONS, Infusion Reactions).

Tumour Lysis Syndrome: In patients with CLL, tumour lysis syndrome (TLS) can occur with use of ARZERRA. Patients with high tumour burden and/or high circulating lymphocyte counts (>25 x 10^9/L) are at greater risk for developing TLS. Consider tumour lysis prophylaxis with anti-hyperuricemics and hydration beginning 12 to 24 hours prior to infusion of ARZERRA. Management of TLS includes correction of electrolyte abnormalities, monitoring of renal function, maintenance of fluid balance and supportive care.

Cardiovascular

Serious and/or fatal cardiovascular events have been reported following administration of ARZERRA. Pulmonary oedema, hypertension, hypotension and myocardial ischemia/infarction have been reported with the administration of ARZERRA. Patients with a history of cardiac disease should be monitored closely during and after infusions and resuscitative measures should be available. ARZERRA should be discontinued in patients who experience serious or life-threatening cardiac arrhythmias.

Gastrointestinal

Bowel Obstruction: Bowel obstruction has been reported in patients receiving anti-CD20 monoclonal antibody therapy, including ofatumumab. Patients who present with abdominal pain, especially early in the course of ARZERRA therapy, should be evaluated and appropriate treatment instituted.

Haematologic

Cytopenia: Severe cytopenias, including prolonged (≥1 week) and late onset neutropenia and thrombocytopenia can occur with ARZERRA. Monitor complete blood counts, including neutrophil and platelet counts, prior to therapy and at regular intervals during therapy. Increase the frequency of monitoring in patients who develop worsening cytopenias (including anemia, neutropenia, or thrombocytopenia) or Grade 3 or 4 cytopenias. The duration of cytopenias caused by ARZERRA can extend months beyond the treatment period (see ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings).

Infections

Serious, including fatal, bacterial, fungal, and new or reactivated viral infections have occurred during and/or following the completion of therapy in clinical trials with ARZERRA (see ADVERSE REACTIONS, Infections).

Serious opportunistic infections such as aspergillioma, escherichia infection, fungal pneumonia, fusarium infection, pneumocystis jiroveci pneumonia, progressive multifocal leukoencephalopathy (PML), and systemic mycosis have occurred in patients receiving ARZERRA in clinical trials.

Discontinue ARZERRA for serious infections and institute appropriate anti-infective therapy. Appropriate antimicrobial treatment/prophylaxis or other interventions should be considered according to local practice and standards of care.

Hepatitis B Infection and/or Reactivation:

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.

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 has also 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 up to 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.

Progressive Multifocal Leukoencephalopathy: Progressive multifocal leukoencephalopathy (PML) resulting in death has occurred with ARZERRA. Consider PML in any patient treated with ARZERRA who reports the 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.

Immune

The safety of, and ability to generate a primary or anamnestic response to, immunization with live attenuated or inactivated vaccines during ARZERRA treatment has not been studied; therefore patients should be observed for failure to respond to a vaccine. Do not administer live viral vaccines to patients who have recently received ARZERRA. The risks and benefits of vaccinating patients with inactivated vaccines during ARZERRA therapy should be considered.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women to inform a product-associated risk. The effect on human pregnancy is unknown. Toxicology studies conducted in cynomolgus monkeys demonstrated that infants born to dams taking ARZERRA had decreased B-cell counts. In the absence of further testing, it is not known whether this finding would affect immune responses in human infants. In addition, it was not determined if and when the B-cell numbers would recover to normal levels. Since ofatumumab may cause fetal B-cell depletion, precautions should be undertaken to avoid pregnancy and adequate contraception (methods that result in less than 1 % pregnancy rates) should be used while using ARZERRA and for at least 6 months after the last ARZERRA treatment. ARZERRA should not be administered to pregnant women unless the possible benefit to the mother outweighs the possible risk to the foetus.

Nursing Women: The safe use of ARZERRA in humans during lactation has not been established. It is not known whether ARZERRA 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 ARZERRA are unknown, caution should be exercised when ARZERRA is administered to a nursing woman.

Pediatrics: Safety and effectiveness of ARZERRA have not been established in children (see ACTION AND CLINICAL PHARMACOLOGY, Pediatrics).

Geriatrics (>65 years of age): In Study 1, 68% of patients (148/217) receiving ARZERRA plus chlorambucil were 65 years of age or older. Compared with younger patients (<65 years) (n=69), there were no clinically significant differences in the common adverse reactions in patients 65 years and older (n=148). Patients age 65 years and older experienced a higher incidence of the following Grade 3 or greater adverse reactions compared with patients younger than 65 years of age: neutropenia (30% versus 17%) and pneumonia (5% versus 1%). In patients 65 years and older, 29% experienced serious adverse events compared with 13% of patients younger than 65 years. No clinically meaningful differences in the efficacy of ARZERRA plus chlorambucil were observed between older and younger patients.

In refractory CLL, clinical studies of ARZERRA did not include sufficient numbers of patients to determine whether those 65 and older would respond differently than those younger than 65 (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Renal Impairment: No formal studies of ARZERRA in patients with renal impairment have been performed. No dose adjustment is recommended for mild to moderate renal impairment (creatinine clearance >30 ml/min). (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Hepatic Impairment: No formal studies of ARZERRA in patients with hepatic impairment have been performed (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Monitoring and Laboratory Tests

Cytopenias, including prolonged and late-onset neutropenia, have been reported during ARZERRA therapy. Complete blood counts, including neutrophil and platelet counts, should be obtained prior to therapy and at regular intervals during therapy and more frequently in patients who develop cytopenias. Appropriate management should be considered should cytopenias occur (see WARNINGS AND PRECAUTIONS, Hematologic).

ADVERSE REACTIONS

Previously Untreated CLL:

The most common adverse reactions (≥10%) in patients in Study 1 (see CLINICAL TRIALS) were neutropenia, rash, nausea, pyrexia, diarrhea, fatigue, cough, vomiting, pruritus, dyspnea, and urticaria.

The most common serious adverse reaction (≥ 5%) in Study 1 was pneumonia.

Refractory CLL:

The most common adverse reactions (≥10%) in patients with refractory CLL (Study 2, see CLINICAL TRIALS) were cough, pyrexia, anemia, neutropenia, diarrhea, fatigue, dyspnea, pneumonia, chills, nausea, bronchitis, peripheral edema, back pain and upper respiratory tract infection.

The most common serious adverse reactions (≥ 5%) in Study 2 were pneumonia and neutropenia. Infections were the most common adverse reactions leading to drug discontinuation in Study 2.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Previously Untreated CLL

The safety of ARZERRA was evaluated in 1 study conducted in subjects previously untreated for CLL and considered inappropriate for fludarabine-based therapy. Study 1 was an open-label, parallel-arm, randomized study of 447 subjects who received either ARZERRA as monthly intravenous infusions (Cycle 1: 300 mg on day 1 and 1,000 mg on day 8; subsequent cycles: 1,000 mg on day 1 every 28 days) in combination with chlorambucil (10 mg/m^2 oral on days 1-7 every 28 days) or chlorambucil alone (10 mg/m^2 oral on days 1-7 every 28 days). The median number of cycles completed was 6 (total of 6,300 mg ofatumumab). The median age was 69 years (range: 35 to 92 years); 63% of subjects were male and 89% were White.

The adverse reactions described in Table 1 occurred in at least 5% of subjects in the ARZERRA plus chlorambucil arm and in at least 2% more subjects than observed in the chlorambucil alone treatment arm. The adverse reactions reporting period was from the first dose until 60 days after the last dose in Study 1.

Table 1 Adverse Reactions, Reported up to 60 Days After the Last Dose, Occurring in at Least 5% of Subjects in the ARZERRA Plus Chlorambucil Arm and in at Least 2% More Subjects Than Observed in the Chlorambucil Alone Treatment Arm

	ARZERRA plus Chlorambucil[c] (N = 217)		Chlorambucil (N = 227)	
	All Grades %	**Grade ≥3 %**	**All Grades %**	**Grade ≥3 %**
Blood and lymphatic system disorders				
Neutropenia	59 (27%)	57 (26%)	41 (18%)	33 (15%)
Leukopenia	14 (6%)	6 (3%)	4 (2%)	1 (<1%)
Gastrointestinal disorders				
Abdominal pain upper	10 (5%)	0	6 (3%)	0
General disorders and administrative site conditions				
Asthenia	18 (8%)	1 (<1%)	11 (5%)	0
Fatigue	34 (16%)	3 (1%)	40 (18%)	3 (1%)
Infections and infestations				
Herpes simplex[b]	14 (6%)	0	10 (4%)	1 (<1%)
Lower respiratory tract infection	11 (5%)	3 (1%)	7 (3%)	2 (<1%)
Injury, poisoning and procedural complications				
Infusion-related reactions[a]	146 (67%)	22 (10%)	0	0
Musculoskeletal and connective tissue disorders				
Arthralgia	11 (5%)	1 (<1%)	7 (3%)	0
Nervous system disorders				
Headache	20 (9%)	2 (<1%)	7 (3%)	0

[a]Includes events which occurred on the day of an infusion or within 24 hours of the end of an infusion and resulted in an interruption or discontinuation or treatment. Infusion-related reactions may include, but are not limited to chills, dyspnea, flushing, hypotension, nausea, pain, pruritus, pyrexia, rash, urticaria, diarrhea, hyperhidrosis, erythema, cough, and hypersensitivity.

[b]Includes: oral herpes, herpes virus infection, genital herpes, and herpes simplex.

[c]Safety data from Study 1 (see WARNINGS AND PRECAUTIONS)

Infusion-related reactions: Overall, 146 patients (67%) who received ofatumumab in combination with chlorambucil experienced one or more symptoms of infusion-related reactions (10% were Grade 3 or greater; none were fatal). Infusion-related reactions that were either Grade 3 or greater, serious, or led to treatment interruption or discontinuation occurred most frequently during Cycle 1 (56% on Day 1 [6% were Grade 3 or greater] and 23% on Day 8 [3% were Grade 3 or greater]) and decreased with subsequent

infusions. Infusion-related reactions led to discontinuation of treatment in 7 patients (3%). Serious adverse events of infusion-related reactions occurred in 6 patients (3%).

Neutropenia: Overall, 12 patients (3%) had neutropenia as a serious adverse event, reported up to 60 days after the last dose. One patient died with neutropenic sepsis and agranulocytosis. Prolonged neutropenia occurred in 12 patients (6%) receiving ARZERRA in combination with chlorambucil compared with 8 patients (4%) receiving chlorambucil. Late-onset neutropenia occurred in 9 patients (4%) receiving ARZERRA in combination with chlorambucil compared with 3 patients (1%) receiving chlorambucil alone.

Common Clinical Trial Adverse Drug Reactions occurring in ≥1% - <5% of patients treated with ARZERRA in combination with Chlorambucil

Other clinically relevant adverse reactions reported in ≥1% and <5% of patients treated with ARZERRA in combination with chlorambucil are presented below.

Cardiac disorders: Tachycardia (2%)

General disorders and administration site conditions: Chest discomfort (2%)

Immune system disorders: Drug hypersensitivitiy (2%), cytokine release syndrome (1%)

Investigations: Neutrophil count decreased (3%)

Metabolism and nutrition disorders: Tumour lysis syndrome (2%)

Respiratory, thoracic and mediastinal disorders: Nasal congestion (3%), bronchospasm (1%)

Skin and subcutaneous tissue disorders: Pruritic rash (3%), generalised rash (2%), generalised pruritus (3%)

Vascular disorders: Hypertension (4%), orthostatic hypotension (1%)

Less Common Clinical Trial Adverse Drug Reactions occurring in <1% of patients treated with ARZERRA in combination with Chlorambucil

Adverse reactions reported in <1% of patients treated with ARZERRA in combination with chlorambucil are presented below.

General disorders and administration site conditions: Infusion site urticaria

Immune system disorders: Anaphylactic reaction, including anaphylactic shock, immune system disorder

Infections and infestations: Hepatitis B

Investigations: Blood pressure decreased

Skin and subcutaneous tissue disorders: Rash maculo-papular, rash erythematous, rash papular

Vascular disorders: Hot flush

Refractory CLL

The safety of ARZERRA as monotherapy has been evaluated in 250 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 2 [n=223]) or 3 doses (Study 3 [n=27]).

The data described in Table 2, Table 3 and in the sections below are derived from the safety population for Study 2, which is comprised of 223 patients including 95 subjects who were included in the analysis of efficacy (see CLINICAL TRIALS, Table 9). Patients received an initial dose of ARZERRA 300 mg followed 1 week later by ARZERRA 2,000 mg once weekly for 7 infusions, followed 4 weeks later by ARZERRA 2,000 mg once every 4 weeks for 4 infusions, for a total of 12 infusions. The median age was 64 years (range: 41 to 87 years), 73% were male, and 96% were Caucasian. Patients received a median of 5 prior therapies, including rituximab (n=127/223, 57%) administered as monotherapy (n=51/223, 23%) or combination therapy (n=113/223, 51%). Of these 223 patients, 95 patients were refractory to fludarabine and alemtuzumab therapy (defined as failure to achieve at least a partial response with fludarabine or alemtuzumab treatment or disease progression within 6 months of the last dose of fludarabine or alemtuzumab). These 95 patients were included in the analysis of efficacy.

Most Common Adverse Reactions: Table 2 lists adverse reactions, regardless of causality, occurring in ≥5% of 223 patients with CLL who received up to 12 infusions of ARZERRA in Study 2. Table 2 also lists the incidence of these reactions in the group of patients with CLL that was refractory to both fludarabine and alemtuzumab.

Table 2 Incidence of All Adverse Reactions Occurring in ≥5% of Patients in Study 2 and in the Fludarabine- and Alemtuzumab-Refractory Subset of Study 2

Body System/ Adverse Event	Total Population (n = 223)		Fludarabine- and Alemtuzumab-Refractory (n = 95)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Infections and infestations				
Pneumonia	34 (15%)	23 (10%)	15 (16%)	10 (11%)
Bronchitis	26 (12%)	1 (<1%)	14 (15%)	1 (1%)
Upper respiratory tract infection	23 (10%)	0	4 (4%)	0
Nasopharyngitis	21 (9%)	0	10 (11%)	0
Lower respiratory tract infection	14 (6%)	1 (<1%)	5 (5%)	0
Sinusitis	15 (7%)	4 (2%)	7 (7%)	2 (2%)
Urinary tract infection	13 (6%)	3 (1%)	4 (4%)	2 (2%)
Herpes zoster	12 (5%)	2 (<1%)	6 (6%)	1 (1%)
Rhinitis	11 (5%)	0	6 (6%)	0
Sepsis	11 (5%)	11 (5%)	5 (5%)	5 (5%)
Septic Events**	20 (9%)	20 (9%)	13 (14%)	13 (14%)
Pharyngitis	7 (3%)	0	6 (6%)	0
Blood and lymphatic system disorders				
Anemia	39 (17%)	11 (5%)	17 (18%)	7 (7%)
Neutropenia	37 (17%)	29 (13%)	19 (20%)	15 (16%)
Thrombocytopenia	10 (4%)	8 (4%)	7 (7%)	6 (6%)
Lymph node pain	7 (3%)	0	5 (5%)	0
Events* related to decreased neutrophil counts	46 (21%)	38 (17%)	22 (23%)	18 (19%)
Psychiatric disorders				
Insomnia	15 (7%)	0	7 (7%)	0
Nervous system disorders				
Headache	14 (6%)	0	8 (8%)	0
Paraesthesia	12 (5%)	0	5 (5%)	0
Metabolism and nutrition disorders				
Decreased Appetite	12 (5%)	0	8 (8%)	0

Body System/ Adverse Event	Total Population (n = 223)		Fludarabine- and Alemtuzumab-Refractory (n = 95)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Cardiovascular disorders				
Hypotension	14 (6%)	0	7 (7%)	0
Tachycardia	11 (5%)	1 (<1%)	6 (6%)	1 (1%)
Hypertension	9 (4%)	0	6 (6%)	0
Respiratory, thoracic, and mediastinal disorders				
Cough	52 (23%)	0	23 (24%)	0
Dyspnea	34 (15%)	4 (2%)	19 (20%)	4 (4%)
Epistaxis	9 (4%)	0	5 (5%)	0
Oropharyngeal pain	9 (4%)	0	5 (5%)	0
Productive cough	7 (3%)	0	5 (5%)	0
Nasal congestion	6 (3%)	0	5 (5%)	0
Gastrointestinal disorders				
Diarrhea	37 (17%)	1 (<1%)	16 (17%)	0
Nausea	29 (13%)	0	13 (14%)	0
Vomiting	15 (7%)	0	7 (7%)	0
Abdominal pain	13 (6%)	1 (<1%)	5 (5%)	0
Constipation	11 (5%)	0	2 (2%)	0
Skin and subcutaneous tissue disorders				
Rash	30 (13%)	1 (<1%)	17 (18%)	1 (1%)
Hyperhidrosis	15 (7%)	0	6 (6%)	0
Urticaria	16 (7%)	0	5 (5%)	0
Musculoskeletal and connective tissue disorders				
Back pain	22 (10%)	2 (<1%)	13 (14%)	1 (1%)
Muscle spasms	13 (6%)	0	4 (4%)	0
Arthralgia	11 (5%)	1 (<1%)	8 (8%)	1 (1%)
Immune system disorders				
Cytokine release syndrome	10 (4%)	1 (<1%)	5 (5%)	0
Hypersensitivity	8 (4%)	2 (<1%)	7 (7%)	1 (1%)
General disorders and administration site conditions				
Pyrexia	47 (21%)	5 (2%)	22 (23%)	4 (4%)
Fatigue	35 (16%)	0	12 (13%)	0
Chills	28 (13%)	0	13 (14%)	0
Edema peripheral	24 (11%)	1 (<1%)	9 (9%)	1 (1%)
Asthenia	8 (4%)	0	6 (6%)	0

*Includes febrile neutropenia, neutropenia, neutropenic sepsis, and neutrophil count decrease.
**includes neutropenic sepsis, sepsis, septic shock, Escherichia sepsis.

Table 3 lists treatment-related adverse reactions, occurring in ≥1% of 223 patients with CLL who received up to 12 infusions of ARZERRA in Study 2. Table 3 also lists the incidence of these reactions in the group of patients with CLL that was refractory to both fludarabine and alemtuzumab.

Table 3 Incidence of Treatment Related Adverse Reactions Occurring in ≥1% of Patients in Study 1 and in the Fludarabine- and Alemtuzumab-Refractory Subset of Study 2

Body System/ Adverse Event	Total Population (n = 223)		Fludarabine- and Alemtuzumab-Refractory (n = 95)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Any Event	149 (67%)	55 (25%)	62 (65%)	25 (26%)
General disorders and administration site conditions				
Any Event	54 (24%)	1 (<1%)	22 (23%)	1 (1%)
Chills	21 (9%)		7 (7%)	
Pyrexia	15 (7%)	1 (<1%)	7 (7%)	1 (1%)
Fatigue	15 (7%)		3 (3%)	
Feeling hot	5 (2%)		2 (2%)	
Oedema peripheral	5 (2%)		1 (1%)	
Chest discomfort	3 (1%)		3 (3%)	
Infusion related reaction	3 (1%)		0	
Influenza like illness	2 (<1)		2 (2%)	
Oedema	1 (<1%)		1 (1%)	
Asthenia	1 (<1%)		1 (1%)	
Chest Pain	1 (<1%)		1 (1%)	
Gait Disturbance	1 (<1%)		1 (1%)	
Infusion site reaction	1 (<1%)		1 (1%)	
Pain	1 (<1%)		1 (1%)	
Skin and subcutaneous tissue disorders				
Any Event	52 (23%)	1 (<1%)	23 (24%)	1 (1%)
Rash	20 (9%)		13 (14%)	
Urticaria	15 (7%)		5 (5%)	
Hyperhidrosis	13 (6%)		5 (5%)	
Pruritus	9 (4%)		4 (4%)	
Erythema	5 (2%)		2 (2%)	
Ecchymosis	1 (<1%)		1 (1%)	
Generalized rash	1 (<1%)	1 (<1%)	1 (1%)	1 (1%)

Body System/ Adverse Event	Total Population (n = 223)		Fludarabine- and Alemtuzumab-Refractory (n = 95)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Infections and infestations				
Any Event	47 (21%)	18 (8%)	20 (21%)	10 (11%)
Pneumonia	10 (4%)	6 (3%)	5 (5%)	3 (3%)
Bronchitis	6 (3%)		3 (3%)	
Lower respiratory tract infection	4 (2%)		2 (2%)	
Herpes zoster	3 (1%)		0	
Infection	3 (1%)	2 (<1%)	2 (2%)	1 (1%)
Oral Herpes	3 (1%)		0	
Sepsis	3 (1%)	3 (1%)	0	
Septic Events*	4 (2%)	4 (2%)	1 (1%)	1 (1%)
Sinusitis	3 (1%)		0	
Urinary tract infection	3 (1%)	1 (<1%)	1 (1%)	1 (1%)
Lung Infection	1 (<1%)		1 (1%)	
Neutropenic sepsis	1 (<1%)	1 (<1%)	1 (1%)	1 (1%)
Candidiasis	1 (<1%)		1 (1%)	
Escherichia infection	1 (<1%)	1 (<1%)	1 (1%)	1 (1%)
Herpes virus infection	1 (<1%)		1 (1%)	
Influenza	1 (<1%)		1 (1%)	
Pharyngitis	1 (<1%)		1 (1%)	
Pneumocystis jiroveci pneumonia	1 (<1%)	1 (<1%)	1 (1%)	1 (1%)
Progressive multifocal leukoencephalopathy	1 (<1%)	1 (<1%)	1 (1%)	1 (1%)
Pseudomonas infection	1 (<1%)	1 (<1%)	1 (1%)	1 (1%)
Pneumonia primary atypical	1 (<1%)		1 (1%)	
Blood and lymphatic system disorders				
Any event	42 (19%)	29 (13%)	20 (21%)	14 (15%)
Neutropenia	30 (13%)	23 (10%)	17 (18%)	13 (14%)
Anaemia	10 (4%)	2 (<1%)	4 (4%)	
Lymph node pain	5 (2%)		3 (3%)	
Thrombocytopenia	2 (<1%)	1 (<1%)	1 (1%)	
Febrile Neutopenia	2 (<1%)	2 (<1%)	1 (1%)	1 (1%)
Leukopenia	2 (<1%)	1 (<1%)	1 (1%)	
Respiratory, thoracic and mediastinal disorders				
Any event	40 (18%)	4 (2%)	22 (23%)	1 (1%)
Dyspnoea	13 (6%)	1 (<1%)	7 (7%)	1 (1%)
Cough	12 (5%)		6 (6%)	
Throat irritation	5 (2%)	2 (<1%)	2 (2%)	
Bronchospasm	4 (2%)	1 (<1%)	2 (2%)	1 (1%)
Nasal congestion	4 (2%)		4 (4%)	

Body System/ Adverse Event	Total Population (n = 223)		Fludarabine- and Alemtuzumab-Refractory (n = 95)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Sneezing	4 (2%)		3 (3%)	
Dry throat	3 (1%)		2 (2%)	
Hypoxia	3 (1%)		3 (3%)	
Oropharyngeal pain	3 (1%)		2 (2%)	
Productive cough	2 (<1%)		1 (1%)	
Nasal discomfort	1 (<1%)		1 (1%)	
Epstaxis	1 (<1%)		1 (1%)	
Sinus congestion	1 (<1%)		1 (1%)	
Throat tightness	1 (<1%)		1 (1%)	
Gastrointestinal disorders				
Any event	37 (17%)	1 (<1%)	14 (15%)	
Nausea	14 (6%)		5 (5%)	
Diarrhoea	12 (5%)	1 (<1%)	6 (6%)	
Vomiting	7 (3%)		3 (3%)	
Abdominal pain	5 (2%)		3 (3%)	
Abdominal discomfort	4 (2%)		1 (1%)	
Abdominal pain upper	2 (<1%)		1 (1%)	
Stomatitis	2 (<1%)		1 (1%)	
Dyspepsia	1 (<1%)		1 (1%)	
Feces discoloured	1 (<1%)		1 (1%)	
Gingivitis	1 (<1%)		1 (1%)	
Tooth loss	1 (<1%)		1 (1%)	
Nervous system disorders				
Any event	29 (13%)		13 (14%)	
Paraesthesia	8 (4%)		4 (4%)	
Headache	6 (3%)		4 (4%)	
Peripheral sensory neuropathy	5 (2%)		2 (2%)	
Hypoaesthesia	3 (1%)		1 (1%)	
Lethargy	2 (<1%)		1 (1%)	
Neuropathy peripheral	2 (<1%)		2 (2%)	
Polyneuropathy	1 (<1%)		1 (1%)	
Vascular disorders				
Any event	22 (10%)	1 (<1%)	10 (11%)	1 (1%)
Hypotension	11 (5%)		5 (5%)	
Flushing	7 (3%)		3 (3%)	
Hypertension	4 (2%)		2 (2%)	
Hot flush	2 (<1%)		1 (1%)	
Deep vein thrombosis	1 (<1%)	1 (<1)	1 (1%)	1 (1%)
Musculoskeletal and connective tissue disorders				
Any event	21 (9%)	1 (<1%)	8 (8%)	1 (1%)
Back pain	7 (3%)	1 (<1%)	3 (3%)	1 (1%)
Muscle spasms	5 (2%)		2 (2%)	

Body System/ Adverse Event	Total Population (n = 223)		Fludarabine- and Alemtuzumab-Refractory (n = 95)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Musculoskeletal pain	4 (2%)		1 (1%)	
Bone pain	2 (<1%)		1 (1%)	
Flank pain	1 (<1%)		1 (1%)	
Muscle tightness	1 (<1%)		1 (1%)	
Immune system disorders				
Any event	20 (9%)	4 (2%)	12 (13%)	1 (1%)
Cytokine release syndrome	10 (4%)	1 (<1%)	5 (5%)	
Hypersensitivity	8 (4%)	2 (<1%)	7 (7%)	1 (1%)
Investigations				
Any event	14 (6%)	4 (2%)	3 (3%)	2 (2%)
Neutrophil count decrease	4 (2%)	4 (2%)	2 (2%)	2 (2%)
Blood creatinine increased	3 (1%)		1 (1%)	
Haemoglobin decreased	3 (1%)	1 (<1%)	0	
Platelet count decrease	2 (<1%)	1 (<1%)	1 (1%)	
Lymphocyte count decrease	1 (<1%)	1 (<1%)	1 (1%)	1 (1%)
WBC count decrease	1 (<1%)	1 (<1%)	1 (1%)	1 (1%)
Cardiac disorders				
Any event	9 (4%)	1 (<1%)	6 (6%)	1 (1%)
Tachycardia	6 (3%)	1 (<1%)	4 (4%)	1 (1%)
Bradycardia	1 (<1%)		1 (1%)	
Sinus Tachycardis	2 (<1%)		1 (1%)	
Eye Disorders				
Any event	3 (1%)		2 (2%)	
Dry eye	1 (<1%)		1 (1%)	
Eyelid oedema	1 (<1%)		1 (1%)	
Ear and Labyrinth Disorders				
Any event	2 (<1%)		1 (1%)	
Vertigo	2 (<1%)		1 (1%)	
Reproductive System and Breast Disorders				
Any event	1 (<1%)		1 (1%)	
Gynaecomastia	1 (<1%)		1 (1%)	

*includes neutropenic sepsis, sepsis, septic shock, Escherichia sepsis.

Infusion-related reactions: In Study 2, infusion-related reactions occurred in 69% (153/223) of patients that received one or more doses of ofatumumab. Infusion-related reactions were more common during the first two infusions with 43% (95/223) and 31% (68/216) of patients having reactions during infusions one and two, respectively (see WARNINGS AND PRECAUTIONS, Infusion-related reactions). Serious infusion-related reactions (≥Grade 3) were experienced by 6% (14/223) of patients.

Infections: In Study 2, of the 223 patients enrolled, a total of 162 patients (73%) experienced 1 or more bacterial, viral, or fungal infections. During the treatment and follow-up phases of the study, 43 patients (19%) experienced Grade 3 infections and 15 patients (7%) experienced Grade 4 infections. In total, 72 patients (32%) experienced 1 or more infections that were classified as serious adverse events. A total of 21 patients (9%) had fatal infections including 13 patients (14%) in the fludarabine- and alemtuzumab-refractory group (n=95). In Study 2, one case of John Cunningham (JC) virus infection resulting in fatal progressive multifocal leukoencephalopathy (PML) was reported (see WARNINGS AND PRECAUTIONS, Infections).

In Study 2, infections of the lower respiratory tract were more common than upper respiratory tract infections. Pneumonias were the most common lower respiratory tract infections (46 [21%] patients). The second most frequently reported events were bronchitis (26 [12%] patients), followed by septic complications (20 [9%] patients). Fatal infection occurred in 21 [9%] patients during treatment or follow-up. During extended follow up, an additional 24 patients died due to infection (7 with pneumonia/lower respiratory infection, 13 with sepsis, 1 with aspergillus infection, 1 with fusarium infection, 1 with progressive multifocal leukoencephalopathy, and one with systemic mycosis).

Neutropenia: Of 154 patients with normal neutrophil counts at baseline who were part of Study 2, 44 (29%) had a Grade 3, and 22 (14%) had a Grade 4 neutropenic episode during the study. Neutropenia was considered the primary cause of death for one patient in Study 2 (see WARNINGS AND PRECAUTIONS, Hematologic).

Less Common Treatment Related Clinical Trial Adverse Drug Reactions (<1%)

General disorders and administration site conditions: hyperthermia, mucosal inflammation.

Skin and subcutaneous tissue disorders: dry skin, eczema, skin lesion.

Infections and infestations: nasopharyngitis, rhinitis, abscess, aspergilloma, bronchopneumonia, cellulitis, cystitis, ear infection, eye infection, mucocutaneouscandidiasis, nocardiosis, oral fungal infection, tinea infection, upper respiratory tract infection.

Blood and lymphatic system disorders: agranulocytosis, haemolytic anaemia, lymphopenia.

Respiratory, thoracic and mediastinal disorders: pleural effusion, rhinitis allergic, tachypnoea.

Gastrointestinal disorders: abdominal distension, dry mouth, mouth ulceration, palatal dysplasia, salivary hypersecretion.

Nervous system disorders: dizziness, cerebral ischaemia, dysgeusia, intercostal neuralgia, presyncope, sensory disturbance, sinus headache.

Vascular disorders: pallor.

Musculoskeletal and connective tissue disorders: myalgia, pain in extremity, neck pain.

Immune system disorders: anaphylactic reaction, anaphylactoid reaction (including anaphylactic shock), immunodeficiency.

Investigations: alanine aminotransferase increased, blood alkaline phosphatase increased, blood uric acid increased, electrocardiogram QT prolonged, heart rate increased, immunoglobulins decreased, international normalised ratio increased, liver function test abnormal.

Cardiac disorders: palpitations.

Metabolism and nutrition disorders: hyperuricaemia, hyponatraemia, metabolic acidosis.

Eye disorders: conjunctivitis.

Renal and urinary disorders: haematuria, pollakiuria, renal pain.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): Hodgkin's disease, tumour lysis syndrome.

Psychiatric disorders: cognitive disorder, restlessness.

Endocrine disorders: hyperthyroidism.

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory safety (clinical chemistry) data were graded according to the Common Terminology Criteria for Adverse Events (NCI CTCAE version 3.0). Hematologic data were graded based on the IWCLL Grading Scale for Hematological Toxicity in CLL Studies for Study 1 and according to the NCI CTCAE version 3.0 for Study 2. Worst case changes from baseline for any post-baseline were analysed. For Study 1, a clinically significant change from baseline was defined as any lab parameter that was observed in 5% or more subjects in the O+Chl arm and for which the addition of ofatumumab resulted in a 2% higher incidence compared to CHL alone arm. For Study 2, a clinically significant change from baseline was defined as any lab parameter that was observed in 5% or more subjects in the DR group. The number (%) of patients with a clinically significant finding was summarized for each lab parameter in Table 4 and Table 5.

Table 4 Significant Laboratory Changes from Baseline – Study 1

Parameters	ARZERRA plus Chlorambucil (N = 217)	ARZERRA plus Chlorambucil (N = 217)	Chlorambucil (N = 227)	Chlorambucil (N = 227)
	All grades	Grade 3,4	All grades	Grade 3,4
BIOCHEMISTRY				
Alanine aminotransferase (GPT, ALT)	65 (30%)	1 (<1%)	43 (19%)	3 (1%)
Alkaline Phosphatase	34 (16%)	3 (1%)	21 (9%)	0
Aspartate aminotransferase (AST)	46 (21%)	2 (<1%)	29 (13%)	2 (<1%)
Calcium (low)	13 (6%)	3 (1%)	5 (2%)	2 (<1%)
Creatine Kinase	38 (18%)	1 (<1%)	21 (9%)	0
Glucose (random, low)	133 (62%)	11 (5%)	128 (57%)	9 (4%)
Sodium (high)	59 (28%)	1 (<1%)	45 (20%)	0
HEMATOLOGY				
Leukocytes	152 (71%)	55 (25%)	66 (29%)	13 (6%)
Lymphocytes	120 (56%)	62 (29%)	47 (21%)	18 (8%)
Neutrophils	155 (72%)	71 (33%)	129 (58%)	57 (25%)

Changes from baseline are shown for parameters for which the addition of ofatumumab resulted in a 2% higher incidence for all grades in the O+CHL arm compared to CHL alone arm (cut-off of 5% in the O+CHL arm) at any post-baseline visit.

Table 5 Significant Laboratory Changes from Baseline – Study 2

Parameters	ARZERRA DR (n=95)	ARZERRA DR (n=95)	ARZERRA Total (n=223)	ARZERRA Total (n=223)
	All grades	Grade 3,4	All grades	Grade 3,4
BIOCHEMISTRY				
Alanine aminotransferase (GPT, ALT)	14 (16%)	1 (1%)	38 (18%)	1 (<1%)
Alkaline Phosphatase	11 (12%)	1 (1%)	30 (14%)	1 (<1%)
Bilirubin Total	14 (16%)	3 (3%)	30 (14%)	3 (1%)
Creatinine	7 (8%)	0	30 (14%)	0
Glucose (random)	7 (8%)	0	13 (6%)	0
Potassium	23 (26%)	6 (6%)	50 (24%)	9 (4%)
Sodium	11 (12%)	1 (1%)	34 (16%)	3 (1%)
HEMATOLOGY				
Hemoglobin	30 (32%)	11 (12%)	73 (33%)	24 (11%)
Leukocytes	46 (49%)	13 (14%)	98 (45%)	23 (11%)
Lymphocytes	34 (37%)	7 (8%)	72 (33%)	11 (5%)
Neutrophils	61 (66%)	40 (43%)	140 (64%)	95 (43%)
Platelets	38 (40%)	19 (20%)	79 (36%)	36 (16%)

Changes from baseline are shown for parameters with a 5% or higher incidence for all grades in the DR group.
DR=Fludarabine- and Alemtuzumab-Refractory

POST-MARKET ADVERSE DRUG REACTIONS

The adverse drug reactions reported during the post-marketing experience with ofatumumab are consistent with those described in the Clinical Trial Adverse Drug Reactions section of this monograph and no new safety concerns have been identified.

Infections and infestations*:*

Cases of fulminant and fatal hepatitis B virus (HBV) infection and reactivation have been reported rarely in patients receiving ARZERRA (see WARNINGS AND PRECAUTIONS).

Reports of progressive multifocal leukoencephalopathy (PML) and death have been received for patients treated with ARZERRA (see WARNINGS AND PRECAUTIONS).

Cardiac:

Reports of bradycardia in the setting of infusion-related reactions have been reported for patients treated with ARZERRA (see WARNINGS AND PRECAUTIONS). A case of cardiac arrest in the setting of an infusion-related reaction has also been reported.

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

Respiratory, thoracic and mediastinal disorders:

Reports of pulmonary oedema in the setting of infusion-related reactions have been reported for patients treated with ARZERRA (see WARNINGS AND PRECAUTIONS).

DRUG INTERACTIONS

Drug-Drug Interactions: In limited drug-drug interaction studies, ofatumumab did not have an observable clinically relevant effect on the pharmacokinetics of bendamustine, chlorambucil or its active metabolite, phenylacetic acid mustard.

Drug-Laboratory Test Interactions: No formal drug-laboratory test interaction studies have been conducted with ARZERRA (ofatumumab).

DOSAGE AND ADMINISTRATION

Dosing Considerations

- ARZERRA (ofatumumab) is administered via intravenous (IV) infusion and must be diluted prior to administration. Do not administer as an intravenous push or bolus.
- ARZERRA should be administered under the supervision of a physician experienced in the use of cancer therapy and in an environment where full resuscitation facilities are immediately available.

Patients should be closely monitored during administration of ARZERRA for the onset of infusion-related reactions, including cytokine release syndrome, particularly during the first two infusions.

Premedications:

Patients should receive the following premedications 30 minutes to 2 hours prior to each infusion.

Previously Untreated CLL:

Patients should be premedicated with oral acetaminophen 1,000 mg (or equivalent), oral or intravenous antihistamine (diphenhydramine 50 mg or cetirizine 10 mg or equivalent) plus intravenous corticosteroid (prednisolone 50 mg or equivalent).

- Do not reduce corticosteroid dose for doses 1 and 2 (cycle 1)

- If the patient does not experience a Grade 3 or greater infusion reaction following the first and second dose, the dose of corticosteriod for subsequent infusions may be reduced or omitted at the discretion of the physician.

Refractory CLL:

Patients should be premedicated with oral acetaminophen 1,000 mg (or equivalent), oral or intravenous antihistamine (cetirizine 10 mg or equivalent) plus 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 at the discretion of the physician:
    - 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.

Recommended Dose and Dosage Adjustment

Recommended Dosage Regimen:

Previously Untreated CLL:

The recommended dose of ARZERRA is:

- Cycle 1: 300 mg for the first infusion on day 1 and 1000 mg on day 8.
- Subsequent cycles (until best response or a maximum of 12 cycles): 1000 mg on day 1 (every 28 days).

Each cycle lasts 28 days and is counted from day 1 of the cycle.

- First infusion: Administer over 4.5 hours through a peripheral line or indwelling catheter. The initial rate of the first infusion of ARZERRA should be 12 mL/h. During infusion, the rate should be increased every 30 minutes to a maximum of 400 mL/h (see Table 6). If an infusion-related ADR is observed during an infusion, see sub-section **Dose modification and reinitiation of therapy in patients with previously untreated CLL or refractory CLL**.
- Subsequent infusions: If the first infusion has been completed without severe infusion related adverse drug reactions (ADR), the remaining infusions (2-13) of 1000 mg should be administered over 4 hours through a peripheral line or

indwelling catheter. Initiate infusion at a rate of 25 mL/h. The rate of infusion should be doubled every 30 minutes up to a maximum of 400 mL/h (see Table 6).

Table 6 Infusion Rates for ARZERRA

Time (min)	Infusion 1 (mL/hour)	Infusions 2 to 13 (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

Refractory CLL:

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

- 300 mg on day 1 followed 1 week later by
- 2,000 mg weekly for 7 doses (infusions 2 through 8) followed 4 weeks later by
- 2,000 mg every 28 days for 4 doses (infusions 9 through 12).

- First and second infusions: Administer over 6.5 hours through a peripheral linear indwelling catheter. The initial rate of the first and second infusion of ARZERRA should be 12 mL/h (see Table 7). During infusion, the rate should be doubled every 30 minutes to a maximum of 200 mL/h. If an infusion-related ADR is observed during an infusion, see sub-section **Dose modification and reinitiation of therapy in patients with previously untreated CLL or refractory CLL.**
- Subsequent infusions: If the second infusion has been completed without severe infusion related adverse drug reactions (ADRs), the remaining infusions (3-12) should be administered over 4 hours through a peripheral line or indwelling catheter. Initiate infusion at a rate of 25 mL/h. In the absence of infusional toxicity, the rate of infusion may be increased every 30 minutes up to a maximum of 400 mL/h (see Table 7).

Table 7 Infusion Rates for ARZERRA

Time (min)	Infusions 1 and 2 (mL/hour)	Infusions 3 to 12 (mL/hour)
0 - 30	12	25
31 - 60	25	50
61 - 90	50	100
91 - 120	100	200
>120	200	400

Dose modification and reinitiation of therapy in patients with previously untreated CLL or refractory CLL: Slower infusion rates may be required when patients experience infusion related ADRs.

- In the event of a mild or moderate ADR, the infusion should be interrupted and restarted at half of the infusion rate at the time of interruption, once the patient's condition is stable. If the infusion rate had not been increased from the starting rate of 12 mL/hour prior to interruption due to an ADR, the infusion should be restarted at 12 mL/hour, the standard starting infusion rate. The infusion rate can continue to be increased according to the standard procedure, to physician discretion and to patient tolerance (not to exceed doubling the rate every 30 mins).

- In the event of a severe ADR, the infusion should be interrupted and restarted at 12 mL/hour, once the patient's condition is stable. The infusion rate can continue to be increased according to the standard procedure, to physician discretion and to patient tolerance (not to exceed doubling the rate every 30 mins).

Therapy should be permanently discontinued in patients who develop an anaphylactic reaction to ARZERRA.

Missed Dose

Missed or delayed doses should not be omitted but administered at a later time point, based on professional judgment observing the total number of planned doses and the planned interval between doses.

Preparation and Administration

Check the ARZERRA concentrate for particulate matter and discoloration prior to dilution. ARZERRA should be a clear to opalescent, colourless to pale yellow solution. Do not use the ARZERRA concentrate if there is discolouration. The concentrate should be practically free of visible particles.

Do not shake the ARZERRA vial for this inspection.

Preparation of Solution:

The ARZERRA concentrate must be diluted in saline prior to administration, using an aseptic technique.

- 300 mg dose: Use 3 x 5 mL vials (15 mL in total): Withdraw and discard 15 mL from a 1,000 mL bag of 0.9% sodium chloride for infusion. Withdraw 5 mL of ARZERRA solution from each of the 3 vials and inject into the 1,000 mL bag. Do not shake. Mix the diluted solution by gentle inversion.

- 1000 mg dose: Use 1 x 50 mL vial (50 mL in total): Withdraw and discard 50 mL from a 1,000 mL bag of 0.9% sodium chloride for infusion. Withdraw 50 mL of ARZERRA solution from the vial (50 mL in total) and inject into the 1,000 mL bag. Do not shake. Mix the diluted solution by gentle inversion.

- 2,000 mg dose: Use 2 x 50 mL vials (100 mL in total): Withdraw and discard 100 mL from a 1,000 mL bag of 0.9% sodium chloride for infusion. Withdraw 50 mL of ARZERRA solution from each of the 2 vials (100 mL in total) and inject into the 1,000 mL bag. Do not shake. Mix the diluted solution by gentle inversion.

Dilution:

Dose	Vial Size	Number of vials	Approximate Available Volume	Nominal Concentration per mL
300 mg	100 mg/5 mL in 10 mL vial	3	1000 mL = 1 bag	0.3 mg/mL
1000 mg	1000 mg/50 mL in 60 mL vial	1	1000 mL = 1 bag	1 mg/mL
2000 mg	1000 mg/50 mL in 60 mL vial	2	1000 mL = 1 bag	2 mg/mL

Administration Instructions:

- ARZERRA must not be administered as a bolus. Administer using an i.v. infusion pump and an administration set.
- Store diluted solution at 2º to 8º C. Use within 24 h of preparation and discard any unused solution after 24 h.
- ARZERRA must not be mixed with, or administered as an infusion with, other medicinal products or intravenous solutions. Flush line before and after ARZERRA administration with 0.9% sodium chloride to avoid this.

OVERDOSAGE

No data are available regarding overdosage with ARZERRA.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ofatumumab is a human monoclonal antibody (IgG1κ) that binds specifically to a distinct epitope encompassing both the small and large extracellular loops of the CD20 molecule. The CD20 molecule is a transmembrane phosphoprotein expressed on B lymphocytes from the pre-B to mature B lymphocyte stage and on B cell CLL cells. The CD20 molecule is not shed from the cell surface and is not internalised following antibody binding.

The binding of ofatumumab to the membrane-proximal epitope of the CD20 molecule induces recruitment and activation of the complement pathway at the cell surface, leading to complement-dependent cytotoxicity (CDC) and resultant lysis of tumour cells. Ofatumumab has been shown to induce appreciable lysis of cells with high expression levels of complement defense molecules. In addition, the binding of ofatumumab induces cell death through antibody-dependent cell-mediated cytotoxicity (ADCC). Ofatumumab has also been shown to induce cell lysis in both high and low CD20 expressing cells and in rituximab-resistant cells.

Pharmacodynamics

B-cell depletion

Previously Untreated CLL

In patients with previously untreated CLL, when ofatumumab was administered in combination with chlorambucil, the median decreases in B-cell counts after the first cycle and prior to the sixth monthly cycle were 94% and >99%. At 6 months after the last dose, the median reductions in B-cell counts were >99%.

Refractory CLL

Peripheral B cell counts decreased after the first ofatumumab infusion in patients with haematologic malignancies. When ofatumumab was administered as single agent in patients with refractory CLL, the median decrease in B cell counts was 22% (DR: 17%, BFR 23%) after the first infusion and 92% (DR: 93%, BFR: 92%) after the eighth infusion. Peripheral B cell counts remained low throughout the remainder of therapy in most patients, then gradually recovered (median decrease in B cell counts was 69% below baseline 3 months after the end of ofatumumab therapy) (see Figure 1-Figure 2). Significant B cell depletion may continue for up to 3-12 months after the last ofatumumab infusion.

Figure 1 **CD5+ CD19 Cells in Peripheral Blood in DR Patients (Study 2)**

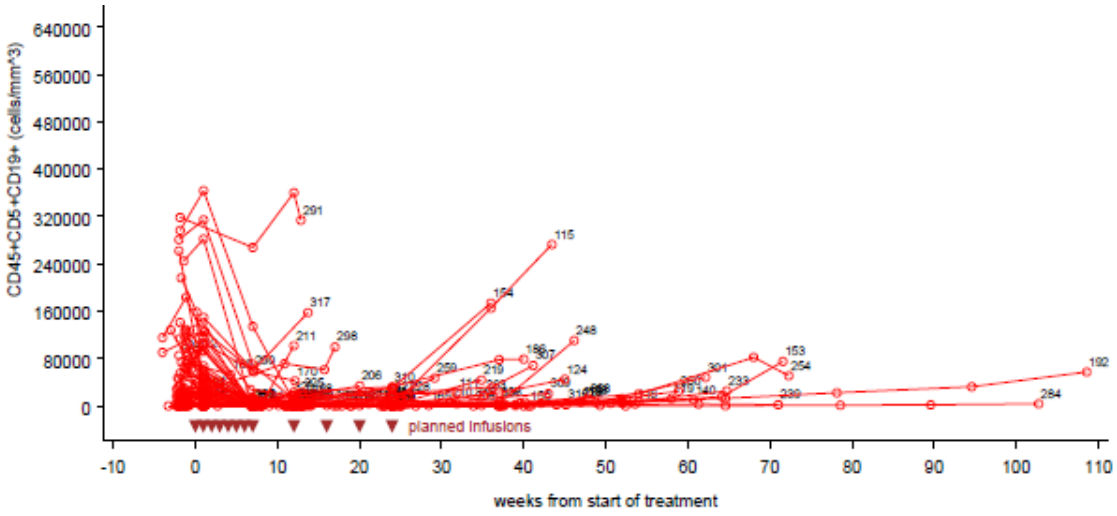
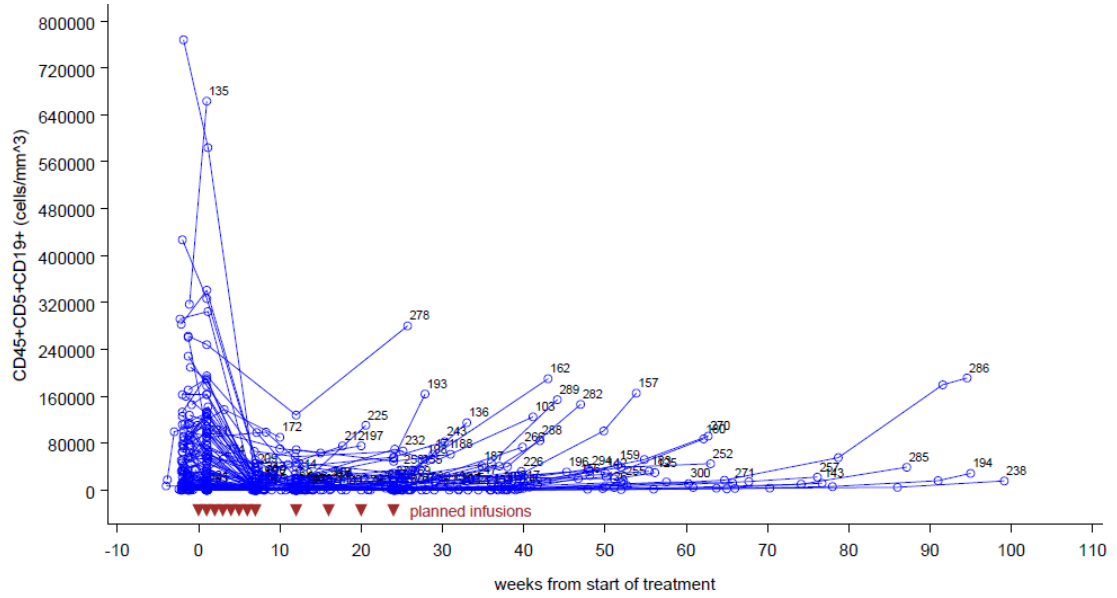


Figure 2 **CD5+ CD19+ Cells in Peripheral Blood in BFR Patients (Study 2)**



Immunogenicity: There is a potential for immunogenicity with therapeutic proteins such as ofatumumab. Serum samples from more than 1000 patients across the CLL clinical program were tested for anti-ofatumumab antibodies during and after treatment periods ranging from 8 weeks to 2 years. Formation of anti-ofatumumab antibodies was observed for less than 0.5% of patients with CLL after treatment with ofatumumab.

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

Pharmacokinetics

Previously Untreated CLL:

In patients with previously untreated CLL receiving ofatumumab and chlorambucil, the geometric mean C_{max} values after the first infusion (300 mg), the 1000 mg infusion on day 8, and the 1000 mg infusion at the fourth monthly cycle were 52 μg/mL, 241 μg/mL, and 285 μg/mL, respectively; the geometric mean $AUC_{(0-\tau)}$ value at the fourth cycle was 65,100 μg.h/mL.

The geometric mean CL and $t_{½}$ values were 15.4 mL/h (range 4.1-146 mL/h) and 18.5 days (range 2.7-82.6 days) after the fourth cycle.

Refractory CLL:

Ofatumumab pharmacokinetic parameter values in the initial clinical study of four weekly infusions in patients with relapsed or refractory CLL (Study 3) are summarized in Table 8, and the concentration-time data in patients with fludarabine-refractory CLL (Study 2) are displayed in Figure 3 and Figure 4.

Table 8 Summary of Ofatumumab Serum Pharmacokinetic Parameter Values after the First and Fourth Infusions (Study 3)

	First Infusion (500 mg)		Fourth Weekly Infusion (2000 mg)	
	n	Geometric mean (%CVb)	n	Geometric mean (%CVb)
C_{max} (μg/mL)	27	136 (56)	26	1061 (30)
$AUC_{(0-\infty)}$ (μg.h/mL)	27	7848 (141)	24	420,840 (103)
CL (mL/h)	27	63.7 (140)	24	8.5 (98)
V_{ss} (L)	27	3.24 (44)	24	1.73 (44)
$t_{½}$ (days)	27	1.3 (109)	24	11.5 (77)

%CVb = between-subject coefficient of variation.

Ofatumumab undergoes non-specific clearance like other IgG molecules and target-mediated clearance via binding to B cells. There was a rapid and sustained depletion of B cells after the first ofatumumab infusion, leaving a reduced number of B cells available for the antibody to bind at subsequent infusions. As a result, ofatumumab clearance values were lower and $t_{½}$ values were greater after later infusions than after the initial infusion.

Figure 3 Serum Ofatumumab Concentration-Time Data in DR Patients (Study 2)

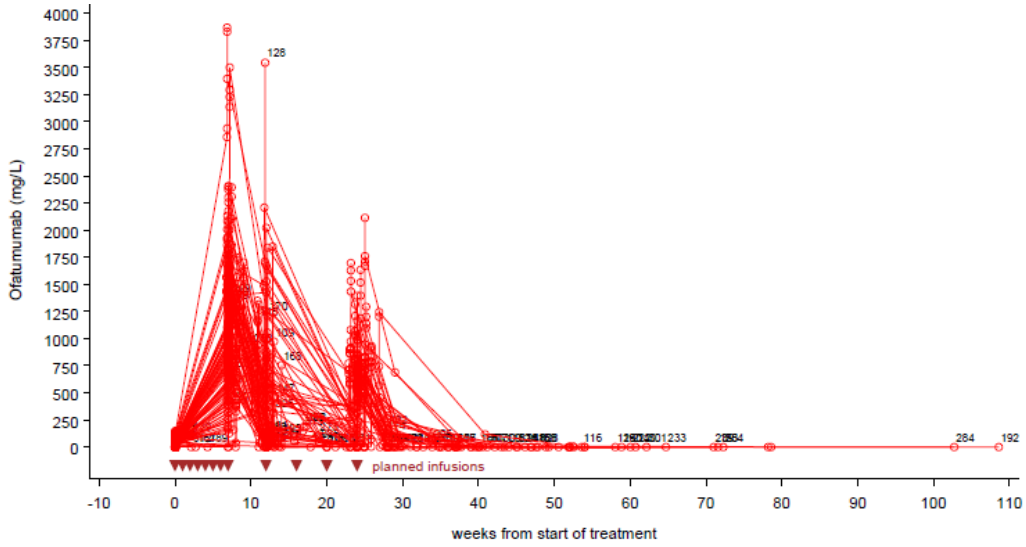
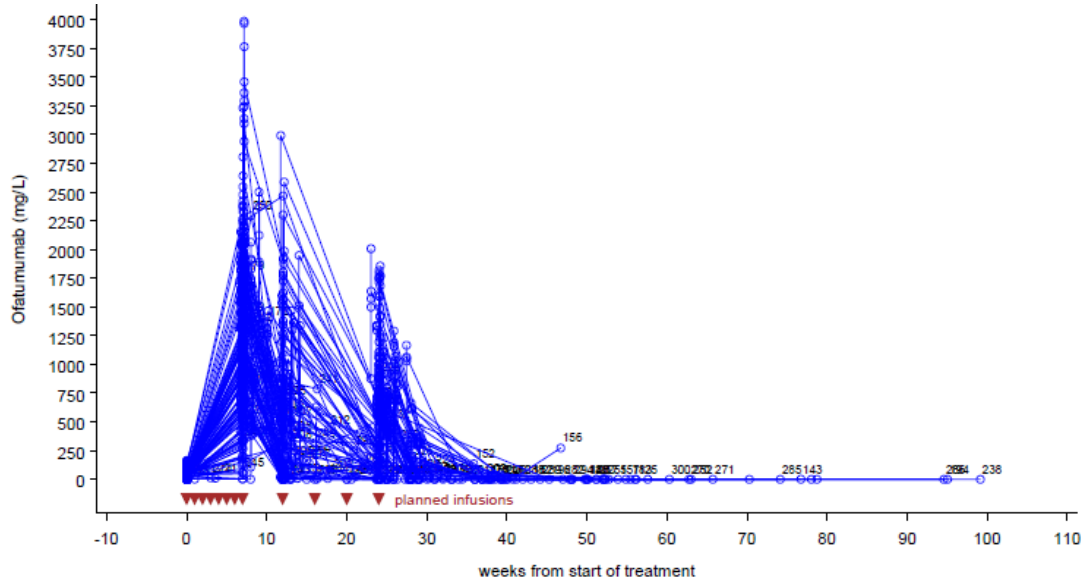


Figure 4 Serum Ofatumumab Concentration-Time Data in BFR Patients (Study 2)



In Study 2 the geometric mean C_{max} value was 63 µg/mL after the first infusion (300 mg); after the eighth weekly infusion (seventh infusion of 2,000 mg), the geometric mean C_{max} value was 1,482 µg/mL; after the twelfth infusion (fourth monthly infusion; 2,000 mg), the geometric mean C_{max} value was 881 µg/mL.

Special Populations and Conditions

Pediatrics: No pharmacokinetic data are available in pediatric patients (see WARNINGS AND PRECAUTIONS, Pediatrics).

Geriatrics: Age was not found to be a significant factor on ofatumumab pharmacokinetics in a cross-study population pharmacokinetic analysis of patients ranging in age from 21 to 87 years of age (see WARNINGS AND PRECAUTIONS, Geriatrics).

Gender: Gender had a modest effect (12%) on ofatumumab central volume of distribution in a cross-study population analysis, with higher C_{max} and AUC values observed in female patients (48% of the patients in this analysis were male and 52% were female); these effects are not considered clinically relevant, and no dose adjustment is recommended.

Hepatic Insufficiency: No formal studies were conducted to examine the effect of hepatic impairment. IgG1 molecules such as ofatumumab are catabolised by ubiquitous proteolytic enzymes, which are not restricted to hepatic tissue; therefore, changes in hepatic function are unlikely to have any effect on the elimination of ofatumumab (see WARNINGS AND PRECAUTIONS, Hepatic Impairment).

Renal Insufficiency: Baseline calculated creatinine clearance was not found to be a significant factor on ofatumumab pharmacokinetics in a cross-study population analysis in patients with calculated creatinine clearance values as low as 26 mL/min. No dose adjustment is recommended for mild to moderate renal impairment (creatinine clearance >30 mL/min). There are limited pharmacokinetic data in patients with severe renal impairment (creatinine clearance <30 mL/min) (see WARNINGS AND PRECAUTIONS, Renal Impairment).

STORAGE AND STABILITY

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

SPECIAL HANDLING INSTRUCTIONS

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater, and disposal through household waste should be avoided. Use established ‘collection systems’ if available in your location.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

ARZERRA (ofatumumab) is a sterile, clear to opalescent, colourless to pale yellow, preservative free liquid concentrate (20 mg/mL) for dilution and intravenous administration. ARZERRA liquid concentrate should be practically free of visible particles. ARZERRA is provided in single-use glass vials with a latex-free rubber stopper and an aluminum overseal. It is presented in a 10 or 60 mL vial with a nominal fill volume of 5 or 50 mL, respectively. Each single use vial contains either 100 mg ofatumumab in 5 mL of solution or 1,000 mg ofatumumab in 50 mL of solution.

Composition

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.

Other Ingredients

Excipients

Arginine, sodium acetate, sodium chloride, polysorbate 80, edetate disodium, hydrochloric acid, water for injection.

Packaging

ARZERRA 100 mg/5 mL is available as follows:

Carton of 3 single-use vials.

ARZERRA 1,000 mg/50 mL is available as follows:

Carton of 1 single-use vial.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

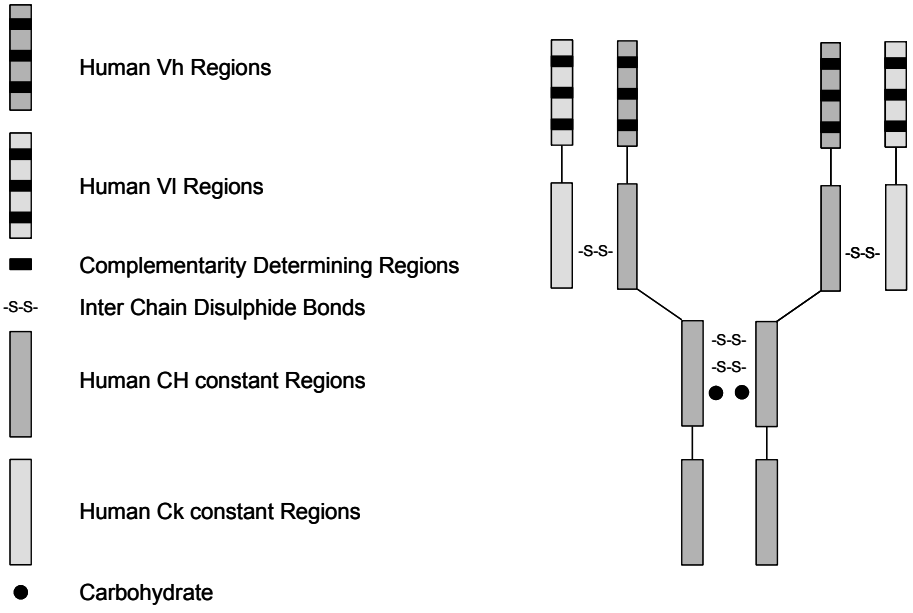
Proper name: Ofatumumab

Chemical name: Immunoglobulin G1, anti-(human CD20 (antigen)) (human monoclonal HuMax-CD20 heavy chain), disulfide linked with human monoclonal HuMax-CD20 κ-chain, dimer

Molecular formula and molecular mass: Approximately 149 kDa. Carbohydrates constitute approximately 2% of the molecular weight of the ofatumumab antibody

Structural formula:

Schematic Representation of Ofatumumab Indicating the Disulphide Bridges



CLINICAL TRIALS

The clinical efficacy and safety of ARZERRA (ofatumumab) has been evaluated in one clinical study in previously untreated CLL patients who are considered inappropriate for a fludarabine-based treatment (Study 1), and one clinical study (Study 2) in previously treated CLL patients who were refractory to fludarabine and alemtuzumab.

Table 9 Trial Design and Patient Demographics for Clinical Trials in Specific Indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects[2] (number)	Median age (Range)	Gender
1	Phase III, Multicenter, multiple arm, open label, randomized	Ofatumumab added to chlorambucil (O+Chl) vs. chlorambucil monotherapy (Chl). Ofatumumab: • Cycle 1/Day 1: 300mg IV • Cycle 1/Day 8: 1000mg IV • Cycles 2 to 12: 1000mg IV, d1 q28d (1 dose at day 1 every 28 days) Chlorambucil: • Cycles 1 to 12: 10mg/m^2 po, d1-7 q28d (1 dose days 1-7 every 28 days)	Efficacy Population: 447 (221 in the O+Chl arm and 226 in the Chl arm)	69 yrs (35-92)	Male (63%)
2	Multicenter, single arm, open label, non-randomized, uncontrolled	Ofatumumab: 300 or 2000 mg [1]8 Weekly infusions, iv; followed 4 weeks later by 4 monthly infusions over 24 weeks.	Efficacy Population: 95	64 yrs (41 - 86)	Male (75%)

[1] 1st infusion, 300 mg; all subsequent infusions, 2000 mg

Previously Untreated CLL

Study 1 was a randomised, open-label, parallel-arm, multicentre study evaluating the efficacy of ARZERRA in combination with chlorambucil compared with chlorambucil alone in 447 patients with previously untreated CLL who were considered inappropriate for fludarabine-based treatment (based on investigator assessment and based on the sponsor-defined criteria of ≥65 years of age or ≥2 comorbidities or creatinine clearance <70 mL/min). Patients received either ofatumumab as monthly intravenous infusions (Cycle 1: 300 mg day 1 and 1000 mg day 8; Subsequent cycles: 1000 mg on day 1 every 28 days) in combination with chlorambucil (10 mg/m^2 orally on days 1-7 every 28 days) or chlorambucil alone (10 mg/m^2 orally on days 1-7 every 28 days).

In the overall trial population, the median age was 69 years (range: 35 to 92 years), 27% patients were ≥75 years of age, 63% were male and 89% were White. Seventy-two percent (72%) of patients had 2 or more co-morbidities and 48% of patients had a CrCl of <70 mL/min. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 were enrolled into the study, and 91% had an ECOG performance status of 0 or 1. At baseline, 75% of patients showed elevated beta-2 microglobulin (β2m) >3,500 mcg/L, and 15% and 6% of patients showed chromosome 11q and 17p deletions, respectively.

Patients received treatment for a minimum of 3 months until best response, up to a maximum of 12 cycles. Approximately 60% of patients received 3-6 cycles of ofatumumab and 30% received 7-12 cycles. The median number of cycles completed in patients was 6 (total ofatumumab dose of 6,300 mg).

The primary endpoint of this study was median progression-free survival (mPFS) as assessed by a blinded Independent Review Committee (IRC) using the International Workshop for Chronic Lymphocytic Leukemia (IWCLL) updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008). ARZERRA plus chlorambucil resulted in statistically significant improvement in IRC-assessed mPFS compared with chlorambucil alone (22.4 months vs. 13.1 months; hazard ratio: 0.57 [0.45, 0.72]) (Table 10; Figure 6).

Secondary endpoints included the overall response rate (ORR), complete response (CR) rate, and duration of response. The ORR, including CR rate, was assessed by an IRC using the 2008 IWCLL guidelines (Table 10). ORR assessed by IRC was 82% (95% CI: 76.7, 87.1) with ofatumumab plus chlorambucil compared with 69% (95% CI: 62.1, 74.6) for chlorambucil alone. Overall, 12% of patients achieved CR with ofatumumab plus chlorambucil compared with 1% for chlorambucil alone. The median duration of response for ofatumumab in combination with chlorambucil was 22.1 months (95% CI: 19.1, 24.6) compared with 12.5 months (95% CI: 10.5, 15.0) for chlorambucil alone.

Table 10 IRC-Assessed Efficacy Endpoints with ofatumumab in Combination with Chlorambucil Compared with Chlorambucil in Previously Untreated CLL (ITT Population[a])

Primary and Key Secondary Endpoints	Ofatumumab and Chlorambucil (n=221)	Chlorambucil (n=226)
IRC-assessed PFS		
Median, months	22.4	13.1
(95% CI)	(19.0, 25.2)	(10.6, 13.8)
Hazard Ratio[b] (95% CI)	0.57 (0.45, 0.72)	
Stratified log rank *P* Value	p<0.001	
Overall Response Rate[c], %	82	69
95%CI	(76.7, 87.1)	(62.1, 74.6)
P value	P<0.001	
Complete Response, %	12	1
Duration of Response		
Median, months (95% CI)	22.1 (19.1, 24.6)	12.5 (10.5, 15.0)
Hazard Ratio (95% CI)	0.55 (0.43, 0.71)	

Abbreviations: IRC=Independent Review Committee; ITT=Intent to Treat; CI= confidence interval; CLL= Chronic Lymphocytic Leukemia, n= number, PFS= Progression-free Survival

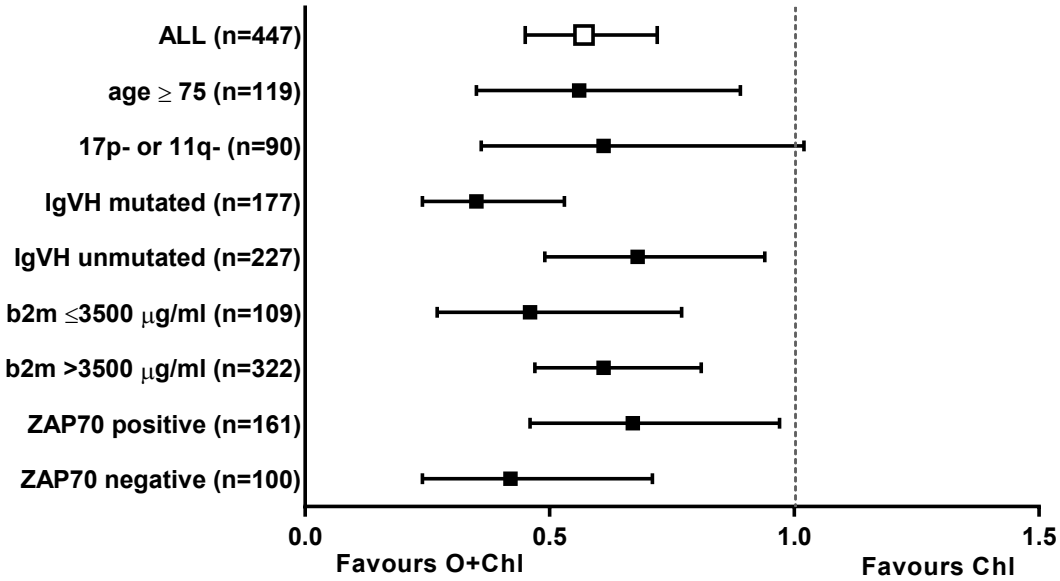
[a]Intent to treat population includes all 447 randomized patients

[b]Pike Estimator

[c]Type I error was controlled for the overall response rate by the sequential gatekeeping strategy where the primary endpoint IRC-assessed PFS was tested first at alpha=0.05 level. If the IRC-assessed PFS was statistically significantly, the pre-specified inferential secondary endpoint ORR was then tested subsequently also at alpha level of 0.05.

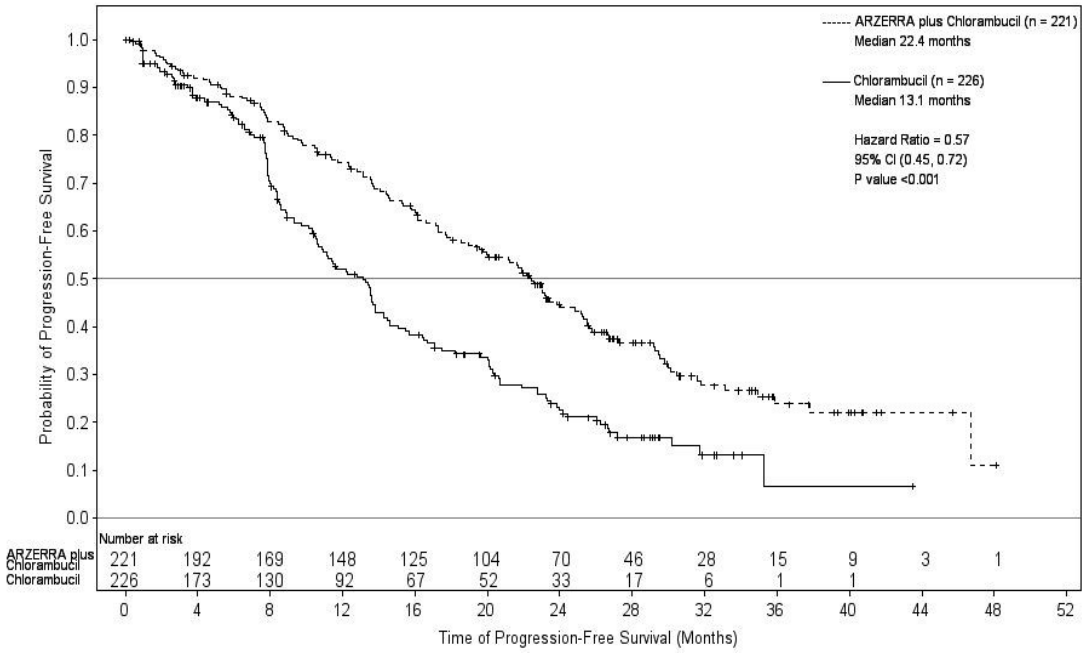
Subgroup analyses were performed to investigate the influence of key prognostic factor for CLL on PFS (Figure 5).

Figure 5 Forest plot of Hazard Ratios and associated 95% confidence intervals for IRC-assessed PFS by subgroups – Study 1



Abbreviations: IRC=Independent Review Committee; ITT=Intent to Treat; b2M= Beta-2-microglobulin, IgV_H= Immunoglobulin Heavy Chain Variable Region, n= number, PFS= Progression-free Survival, ZAP= Zeta-Chain-associated protein kinase 70

Figure 6 Kaplan-Meier Estimates of IRC-Assessed Progression-Free Survival



Refractory CLL

Study 2 was a single-arm, multicenter trial in 223 patients with relapsed or refractory CLL (Table 9). The efficacy analysis from Study 2 is based on an analysis that included data from 95 patients with CLL, refractory to fludarabine and alemtuzumab, who were administered ofatumumab as monotherapy. The primary efficacy endpoint was objective response rate (ORR) determined using NCIWG 1996 guidelines. Patient median age was 64 years (range: 41 to 86 years), and the majority were male (75%) and Caucasian (93%).

The 95 patients that made up the final efficacy population were refractory to both fludarabine and alemtuzumab therapy (defined as failure to achieve at least a partial response with fludarabine or alemtuzumab treatment or disease progression within 6 months of the last dose of fludarabine or alemtuzumab). The majority of these patients had high risk CLL at screening by Rai stage (61% stage III/IV) or by Binet stage (59% stage C). Furthermore, 61% of these fludarabine and alemtuzumab refractory patients had an ECOG performance status of 1 or 2, and 95% had at least one lymph node >5 cm.

These patients (n=95) had received a median of 5 prior therapies, including rituximab (59%), alkylating agents (96%), and both fludarabine and alemtuzumab (100%), either as mono- or combination therapy.

Patients were to receive 12 infusions of ofatumumab over a period of 24 weeks. Dosing consisted of 8 weekly infusions of ofatumumab from week 0 to week 7, followed by 1 infusion of ofatumumab every 4 weeks from week 12 through week 24. The first infusion was 300 mg ofatumumab. All subsequent infusions were 2000 mg ofatumumab. The 95 patients classified as refractory to fludarabine and alemtuzumab all received at least 1 infusion. Forty-five (47%) received all 12 infusions, and an additional 4 (4%) received 11 infusions, 13 (14%) received 10 infusions, 9 (9%) received 9 infusions, and 24 (25%) received ≤8 infusions.

The investigator determined overall response rate was 36% (95.3% CI: 26.0, 46.0) in the fludarabine and alemtuzumab refractory group (see Table 11). No patient experienced a complete response. The median duration of response was 8.0 months (95% CI: 5.9, 8.3).

Table 11 Summary of Response to Ofatumumab in Patients with CLL Refractory to Fludarabine and Alemtuzumab

Endpoints	Fludarabine and Alemtuzumab Refractory n = 95
Overall Response Rate*	
Responders, n (%)	34 (36%)
95.3% CI (%)	26.0, 46.0
Median Duration of Response	
Months	8.0
95% CI	5.9, 8.3

*Primary endpoint - Overall response rate as determined from individual assessments of response made by clinical investigators applying the NCIWG 1996 guidelines for the diagnosis and treatment of CLL

** For final primary endpoint, the level of the corresponding two-sided confidence interval is 95.3%. All secondary and subgroup analyses were analyzed using 95% confidence intervals.

DETAILED PHARMACOLOGY

Mechanism of Action

Preclinical data reveal no special hazards for humans.

Intravenous and subcutaneous administration to monkeys resulted in the expected depletion of peripheral and lymphoid tissue B cell counts with no associated toxicological findings. As anticipated, a reduction in the IgG humoral immune response to keyhole limpet haemocyanin was noted, but there were no effects on delayed-type hypersensitivity responses. In a few animals, increased red cell destruction occurred as a result of monkey anti-drug antibodies coating the red cells. A corresponding increase in reticulocyte counts seen in these monkeys was indicative of a regenerative response in the bone marrow.

Intravenous administration of ofatumumab to pregnant cynomolgus monkeys at 100 mg/kg once weekly from days 20 to 50 of gestation did not elicit maternal toxicity, developmental toxicity or teratogenicity.

As ofatumumab is a monoclonal antibody, genotoxicity and carcinogenicity studies have not been conducted with ofatumumab.

TOXICOLOGY

Table 12 Summary of Toxicology Findings with ofatumumab

Study ID	Species/ Dose/(mg/kg)/ Route	Study Design	Findings / Conclusion
Non-Pivotal Toxicity			
Pilot 4 day repeat dose study of ofatumumab	Monkey (cynomolgus) Doses: 1.25, 6.25, 12.5 mg/kg Route: Intravenous (infusion)	1 animal/sex/group 4 daily doses of Ofatumumab or rituximab Sampled on Days -7 to 134	Anti-ofatumumab antibodies were seen in both animals at 1.25 mg/kg. Anti-rituximab antibodies were seen in all animals at all dose levels. $CD20^+$ B cell counts fell markedly on the commencement of dosing with ofatumumab or rituximab. At 6.25 and 12.5 mg/kg, B cell counts recovered earlier in the animals dosed with rituximab. Ofatumumab NOAEL >12.5 mg/kg
Pilot 5 day repeat dose study of ofatumumab	Monkey (cynomolgus) Doses: 25/50, 50/75, 75/100, 100/150 mg/kg (Day 1/Day 5) Route: Intravenous (infusion)	1 animal/sex/group 2 intravenous infusions over a 5 day period. Single intravenous administration on Day 1. The doses were increased on Day 5. Animals were killed and necropsied on Day 22, following a 17 day post-dose observation period.	Increased spleen and thyroid weights occurred in the 100/150 mg/kg female, in the absence of any correlating findings at necropsy. Histopathological examination was not conducted, and there was only one animal per group, and so the significance of these findings is uncertain. The NOAEL > 100/ 150 mg/kg

Study ID	Species/ Dose/(mg/kg)/ Route	Study Design	Findings / Conclusion
Repeat dose Toxicity			
4 Week repeat dose study of ofatumumab	Monkey (cynomolgus) Doses: 0, 20, 100 mg/kg Route: Intravenous (infusion)	3 animals/sex/group plus 3 recovery animals/sex/group 4 weekly doses The main group animals were kept for a 2 week post-dose observation period and then killed and necropsied on Day 35. The recovery animals were retained for 26 weeks prior to termination and necropsy.	**In all ofatumumab-treated dose groups:** B cell depletion, Atrophy (minimal to moderate) of germinal centre or follicular B cells in lymphoid organs (e.g. mandibular and mesenteric lymph nodes, Peyer's Patch and spleen) ADAs were seen in 3/12 animals at 20 mg/kg and 2/12 animals at 100 mg/kg, In the 100 mg/kg group there was evidence of inhibition of specific KLH antibodies. **In all ofatumumab -treated recovery groups:** Minimal germinal centre atrophy was noted in the spleen (1 out of 2 monkeys) In the 100 mg/kg group, there was still evidence of inhibition of specific KLH antigens. The NOAEL > 100 mg/kg
7 Month repeat dose study of ofatumumab	Monkey (cynomolgus) Doses: 0, 20, 100 mg/kg Route: Intravenous (infusion)	3 animals/sex/group plus 4 recovery animals/sex/group 8 weekly doses followed by 5 monthly doses The main study animals were killed and necropsied 2 days after administration of the last dose (Day 192). Recovery animals were retained for 26 weeks prior to termination and necropsy (Day 372).	**In all ofatumumab-treated dose groups:** At 20 mg/kg: 3 found dead or humanely sacrificed, at 100 mg/kg: 2 humanely sacrificed – probable *C. jejuni* infection and/or signs of haemolytic anaemia Decreased haemoglobin, red blood cell count, haematocrit. Increased reticulocyte count. Increased lactate dehydrogenase, total bilirubin and a positive Coombs test observed in some monkeys and was due to monkey anti drug antibodies coating red cells. Peripheral blood-B cell depletion. Lymph node-B cell depletion. IgG humoral immune response inhibition. Atrophy of lymphoid organs (ie.g. submandibular and mesenteric lymph nodes, Peyer's Patch and spleen). **Additional findings at 20 mg/kg ofatumumab:** ADAs in 1/12 animals given 20 mg/kg. **In all ofatumumab-treated recovery groups:** IgG humoral immune response inhibition up to Day 372 Full recovery of the T-cell dependent antigen response was not noted The NOAEL > 100 mg/kg

Study ID	Species/ Dose/(mg/kg)/ Route	Study Design	Findings / Conclusion
Cycled repeat dose study of ofatumumab	Monkey (cynomolgus) Doses: 0, 20, 100 Route: Intravenous (infusion)	3 animals/sex/group plus 3 recovery animals/sex/group Animals dosed on 4 occasions (Cycle 1: Days 1 and 14; Cycle 2: Days 148 and 162) The main study animals were killed and necropsied 6 days after administration of the last dose (Day 168). The recovery animals were kept for a further 4 month recovery period and then killed and necropsied on Day 282.	**In all ofatumumab -treated dose groups:** B cell depletion in peripheral blood. Atrophy of lymphoid organs (e.g. submandibular and mesenteric lymph nodes and spleen (also tonsils at 100 mg/kg)). Inhibition of T cell-dependent antigen response, but not in the primary response following immunisation with KLH **Additional findings at 20 mg/kg ofatumumab:** ADAs in 9/12 animals. **Additional findings at 100 mg/kg ofatumumab:** Atrophy of tonsils Positive Direct Coombs Test correlating with slight reduction in red cell parameters most likely due to formation of anti-ofatumumab antibody complexes, resulting in complement mediated haemolysis **In all ofatumumab-treated recovery groups:** Mild to moderate germinal centre atrophy of the spleen **Additional findings in 20 mg/kg ofatumumab recovery group:** Mild germinal centre atrophy in the mandibular lymph node (1/ 3 females) and in the mesenteric lymph node (1/3 females) The NOAEL > 100 mg/kg
2 Week sub-cutaneous and intravenous repeat dose bridging study of ofatumumab	Monkey (cynomolgus) Doses: 0, 20 (Subcutaneous administration), 100 (Subcutaneous administration), 100 (Intravenous infusion administration)	3 females/group plus 3 female recovery animals/group 2 doses given 2 weeks apart Six days after administration of the last dose (Day 21), the main study animals were killed and necropsied. The remaining animals were killed and necropsied on Day 258, after an 8 month recovery period.	**In all ofatumumab-treated dose groups:** B cell depletion. ADAs were seen in 3/6 animals at 20 mg/kg and 1/6 animals at 100 mg/kg subcutaneously. The NOAEL > 100 mg/kg

Study ID	Species/ Dose/(mg/kg)/ Route	Study Design	Findings / Conclusion
Reproductive and Developmental Toxicity			
Embryofetal development study of ofatumumab	Monkey (cynomolgus) Doses: 0, 20, 100 Route: Intravenous (infusion)	12 females/group 5 weekly doses from Day 20 to Day 50 of gestation (Days 20 to 100 pc). The fetuses were delivered via caesarian section and killed on Day 100±1 of gestation.	**In all ofatumumab-treated dose groups:** There was no maternal toxicity, developmental toxicity or teratogenicity. ADAs were seen in 3/24 dams and in 3/20 fetal cord blood samples, consistent with placental transfer. At the end of organogenesis (GD 48), ofatumumab exposure (AUCinf) in the pregnant animals were 212800 µ.h/mL and 1646000 µ.h/mL (geometric mean) for 20 and 100 mg/kg/day respectively. These correspond to 0.46 to 3.6 time the human exposure after 8th infusion of the MRHD of 2,000 mg (AUCinf = 463418 µ.h/mL). B cell depletion was observed in all maternal animals at both dose levels. Reduced B cell counts in cord blood and fetal spleen tissue were seen at both dose levels (decreased to approximately 12% and 15% of control values at both dose levels, respectively), which was associated, in the 100 mg/kg dose group only with significantly decreased spleen weights (decreased by approximately 15% in low-dose group and by approximately 30% in high-dose group, compared with control values), but there was no related histopathology. Although fetal spleen weights were close to the lower limit of the normal range, a compound-related effect could not be excluded. The kinetics of B-lymphocyte recovery and the potential long-term effects of perinatal B-cell depletion in offspring from ofatumumab-treated maternal monkeys have not been studied. The NOAEL > 100 mg/kg
Other Studies - Immunotoxicity			

Study ID	Species/ Dose/(mg/kg)/ Route	Study Design	Findings / Conclusion
In vivo determination of inflammatory and coagulation parameters	Monkey (cynomolgus) Doses: 25, 50, 75, 100 mg/kg Route: Intravenous (infusion)	Blood samples used in this study were derived from the 5 day pilot dose-ranging toxicity study on Day 1. Serum samples were taken prior to dosing, and at 15 minutes, 30 minutes, 2 hours and 4 hours post-dose.	An increase of C3b/c (activated form of C3) was noted in all monkeys at 15 minutes post dose, but after 2 to 4 hours activation had decreased. C4b/c (activated form of C4) showed a similar increase. TAT complex levels increased in all monkeys at 15 minutes post-dose, but the increase was variable. PAP levels increased in all animals, but in 3 out of 4 animals, plasmin formation was transient. Neutrophil degranulation was observed in 3 of 4 animals, but the increase was very mild in the 25 mg/kg dose group. IL-6 levels followed a biphasic course, with the early increase possibly related to complement activation and the later increase to cellular activation. TNFα levels were below the limit of detection. These results suggest that administration of ofatumumab may be associated with cytokine release syndrome. However, the severity of this syndrome in the monkeys was limited and clinical manifestations were not observed.
Other Studies - Tissue cross-reactivity			
Human tissue cross-reactivity	Human tissue 0, 0.5, 5.0 or 20.0 μg/mL	In vitro	Specific, positive, membrane bound staining was recorded in lymphocytes in lymphoid tissue scattered in the subepithelial tissue of at least one donor. The consistency of the staining was very high and it was concluded that ofatumumab demonstrated tissue reactivity consistent with its target antigen specificity.
Key: ADA = anti-drug antibodies KLH = Keyhole Limpet Haemacyanin SC = Subcutaneous IV = Intravenous NOAEL = No observed adverse effect level			

Carcinogenesis and Mutagenesis

No genotoxicity studies were conducted. ofatumumab is a monoclonal antibody and is not expected to interact directly with DNA or other chromosomal material.

No studies to assess the potential carcinogenicity of ofatumumab have been conducted. Ofatumumab is not pharmacologically active in rodents and therefore the standard carcinogenicity bioassays are unsuitable. 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 (Table 12).

Fertility and Peri- and Post-natal Reproductive Toxicology

An embryofetal development study was conducted in cynomolgous monkeys (Table 12). No fertility or peri- and post-natal reproductive toxicology studies were performed. It is recognized that the CD20 antigen is not expressed in tissues associated with fertility, and

binding to reproductive tissues has not been observed in cross-reactivity studies. Furthermore, no specific histopathological changes were observed in the reproductive tissues (epididymus, testis and ovaries) in the repeat dose toxicology studies.

PART III: CONSUMER INFORMATION

[Pr]ARZERRA™
(ofatumumab)

This leaflet is part III of a three-part "Product Monograph" published when ARZERRA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ARZERRA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

ARZERRA (R-ZEER-ah) contains ofatumumab, which belongs to a group of medicines called monoclonal antibodies.

ARZERRA is used to treat chronic lymphocytic leukaemia (CLL). CLL is a cancer of the blood that affects a type of white blood cell called lymphocytes. The lymphocytes multiply too quickly and live too long, so there are too many of them circulating in your blood. The disease can also affect other organs in your body. The antibody in ARZERRA binds to the lymphocytes and decreases the amount of lymphocytes in the body.

What it does:

ARZERRA is used in combination with chlorambucil to treat CLL in patients who have not received previous therapy.

ARZERRA is also used as monotherapy to treat CLL in patients who have not responded to other types of chemotherapy or other treatments.

When it should not be used:

- If you have or have had progressive multifocal leukoencephalopathy (PML).
- If you are allergic (hypersensitive) to ofatumumab or to any of the other nonmedicinal ingredients of ARZERRA.

Check with your doctor if you think this may apply to you.

What the medicinal ingredient is:

The active substance in ARZERRA is ofatumumab.

What the important nonmedicinal ingredients are:

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.

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:

ARZERRA is a clear to opalescent, colourless to pale yellow concentrate solution for infusion.

It is available in a pack containing 3x5 mL vials or 1x50 mL vial. Each glass vial is closed with a latex-free rubber stopper and aluminium over-seal, and contains 100 mg/1,000 mg of ofatumumab per 5 mL/50 mL of concentrate respectively.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- ARZERRA administration could result in serious, including fatal infusion-related reactions.
- ARZERRA administration could result in hepatitis (a liver disease) becoming active again. In some cases, this could result in liver failure and even death.
- Administration of ARZERRA and other similar medicines could result in a serious and fatal brain condition called progressive multifocal leukoencephalopathy (PML).
- ARZERRA administration could result in serious and/or fatal cardiovascular events.
- ARZERRA administration could result in serious and sometimes fatal infections.

BEFORE you use ARZERRA, talk to your doctor or pharmacist if:

- you have had heart problems.
- you have lung disease.
- you have had hepatitis B (a liver disease). ARZERRA administration could result in your hepatitis B becoming active again. Your doctor may treat you with a suitable anti-viral medicine to help prevent this.
- you are allergic (hypersensitive) to ofatumumab or to any of the other nonmedicinal ingredients of ARZERRA.
- you have had a reaction to an injectable medication in the past.

Check with your doctor if you think any of these may apply to you. You may need extra check-ups while you are being treated with ARZERRA.

Vaccination and ARZERRA
If you are having any vaccinations tell your doctor, or the person giving you the vaccine, that you are being treated with ARZERRA. Your response to the vaccine may be weakened and you may not be fully protected.

Infusion-related reactions
Medicines of this type (monoclonal antibodies) can cause infusion-related reactions when they are injected into your body, which are occasionally severe, and can cause death. You will be given medicines such as anti-histamines, steroids or pain relievers to help reduce any reaction. See SIDE EFFECTS AND WHAT TO DO ABOUT THEM, section.

Hepatitis B
Recurrence of hepatitis B virus infection has occurred in patients who show evidence of the virus in a blood test. It is advised that all patients be tested for hepatitis B virus infection before starting treatment with ARZERRA.

In some cases, patients who have had hepatitis B might have a repeat attack of hepatitis. Tell your doctor if you think you have had hepatitis in the past.

Infection with hepatitis B virus causes inflammation of the liver which may show as mild fever, feeling of sickness, fatigue, loss of appetite, joint and/or abdominal pain and yellowing of whites of the eyes, skin and tongue. If you experience any of these symptoms immediately contact your doctor. If you show evidence of hepatitis B virus infection (even if you have no symptoms) you may be referred to a liver disease expert for ongoing monitoring and management.

ARZERRA is not to be used in patients with active hepatitis B viral disease. Tell your doctor if you think you have hepatitis B.

Progressive multifocal leukoencephalopathy (PML)
ARZERRA and other similar medicines may cause a serious and life threatening brain condition called progressive multifocal leukoencephalopathy (PML). **Tell your doctor immediately** if you have memory loss, trouble with thinking, difficulty with walking or loss of vision. If you had these symptoms prior to treatment with ARZERRA, **tell your doctor immediately** about any changes in these symptoms.

Tumour Lysis Syndrome (TLS)
TLS can occur with the use of ARZERRA. TLS is a condition that causes sudden kidney failure and abnormal heart rhythms due to changes in blood chemistry, which may be fatal. Some patients with TLS in its early stages have no symptoms. The symptoms of TLS include the production of less urine than normal and muscle spasms. Patients with TLS usually have a high level of potassium, phosphate and uric acid and low calcium levels in their blood. Your doctor will be performing blood tests for this and other side effects.

Infections
Patients receiving ARZERRA may develop infections. Some of the infections may be serious. Call your healthcare provider right away if you feel sick or get any of the following symptoms, which may be early signs of a serious infection:

- Fever or chills
- Difficulty breathing
- Cough
- Cold or flu-like symptoms that do not go away
- Feel weak or generally unwell

Cytopenias
A decrease in number of one or more types of blood cells (cytopenias) can occur with patients taking ARZERRA. Your doctor will be carefully monitoring the effects of treatment and your progress by examining you and by taking blood samples on a regular basis.

Bowel obstruction
Bowel problems, including blockage in the intestines (bowel obstruction) have been reported during the use of ARZERRA. If you have persistent stomach pain, see your doctor immediately.

Other medicines and ARZERRA
Tell your doctor if you are taking any other medicines, if you've taken any recently, or if you start taking any new ones. This includes herbal medicines and other medicines you can obtain without a prescription.

Pregnancy and breast-feeding
ARZERRA is not usually recommended for use during pregnancy. There is limited information about the safety of ARZERRA in pregnant women.

- Tell your doctor if you are pregnant or planning to become pregnant. Your doctor will weigh the benefit to you against the risk to your baby of taking ARZERRA while you're pregnant.
- Use a reliable method of contraception to avoid becoming pregnant while you're being treated with ARZERRA, and for at least 6 months after your last infusion with ARZERRA.
- If you do become pregnant during treatment with ARZERRA, tell your doctor.

It is not known whether the ingredients of ARZERRA can pass into human milk. If you are breast-feeding, you must check with your doctor before you take ARZERRA.

Driving and using machines
ARZERRA is unlikely to affect your ability to drive or use machines.

INTERACTIONS WITH THIS MEDICATION

No formal drug interaction studies have been conducted with ARZERRA (ofatumumab).

PROPER USE OF THIS MEDICATION

If you have any questions about how to use ARZERRA, ask the doctor who is giving you the infusion.

Usual dose:
The usual dose of ARZERRA for the first infusion is 300 mg. This dose will be increased, usually to either 1,000 mg or 2,000 mg, for the remaining infusions.

How it is given
ARZERRA is given into a vein (intravenously) as an infusion (a drip) over several hours.

You may have a course of up to 12 infusions. Depending on whether you are being treated with ARZERRA as monotherapy or in combination with chlorambucil you will be given:

- An infusion once a week for 8 weeks, followed by a four week gap. The remaining infusions will then be given once a month for four months; or
- Two infusions eight days apart, followed by a gap of approximately 3 weeks. The remaining infusions (up to 11) will then be given every 28 days.

Medicines given before each infusion
Before each infusion of ARZERRA, you will be given medicines that help to reduce infusion reactions. These may include anti-histamines, steroids and pain relievers. You will be checked closely and if you do have any reactions these will be treated.

Overdose:

No data are available regarding overdosage with ARZERRA.

In case of overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Contact your physician immediately if you miss a dose of ARZERRA. Your physician will decide when you should receive your next dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, ARZERRA can cause side effects, although not everybody gets them.

Infusion-related reactions

Medicines of this type (monoclonal antibodies) can cause infusion-related reactions, which are occasionally severe, and can cause death. They are more likely during the first two infusions.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	Infusion-related reaction: • feeling sick (nausea) • high temperature • skin rash		✓	
Very Common	• infections of the lungs or airways (respiratory tract) such as pneumonia • infections of the ear, nose or throat		✓	
Very Common	Blood Tests: • low levels of white blood cells (neutropenia) • low levels of red blood cells (anaemia)		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Common	Infusion-related reaction: • allergic reactions, sometimes severe with swelling of face or mouth causing difficulty in breathing (anaphylactoid reactions, including anaphylactic shock) • collapse • difficulty in breathing, shortness of breath, chest tightness, cough • low blood pressure (can cause light-headedness when you stand up) • flushing • excessive sweating • shaking or shivering • rapid heart beat • diarrhoea • back pain • high blood pressure • itchy, bumpy rash (hives) • throat pain or irritation • lack of energy • blocked nose.		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Common	• fever due to an infection and low levels of white blood cells • blood infections • urinary tract infections • shingles •cold sores • blockage in the gut (intestine), which may feel like stomach pain. If you have persistent stomach pain, see your doctor as soon as possible.		✓	
Common	Blood Tests: • low levels of platelets in the blood (cells that help blood to clot)		✓	
Uncommon	Tumour Lysis Syndrome: increase in potassium, phosphate and uric acid in the blood that can cause kidney problems Symptoms of this condition include: • producing less urine than normal • muscle spasms		✓	
Uncommon	Blood Tests: • problems with blood clotting • the bone marrow failing to produce enough red or white blood cells		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Infusion-related reaction: • Fluid in the lungs (pulmonary oedema) causing breathlessness • Slow heart beat		✓	
Rare	Infection or reactivation of Hepatitis B. Symptoms of hepatitis include worsening fatigue or yellow discolouration of the skin or eyes.		✓	

This is not a complete list of side effects. For any unexpected effects while taking ARZERRA, contact your doctor or oncology pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children.

Do not use ofatumumab after the expiry date which is stated on the carton and vial label. The expiry date refers to the last day of that month.

Store and transport refrigerated (2°C – 8°C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

Store the diluted infusion solution between 2°C and 8°C and use within 24 hours. Any unused infusion solution should be discarded 24 hours after it was prepared.

Medicines should not be disposed of via wastewater or household waste. Your doctor or nurse will dispose of any medicine that is no longer required. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

www.novartis.ca or by contacting the sponsor,

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