PRODUCT INFORMATION

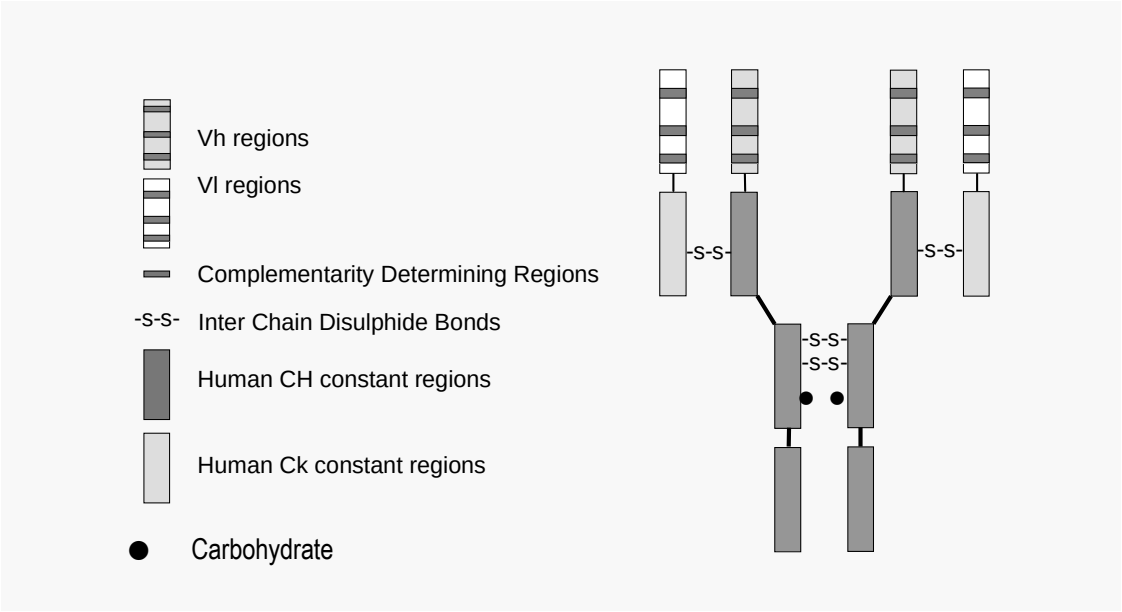
ARZERRA® CONCENTRATED injection

Ofatumumab (rmc) Concentrated Injection

NAME OF THE MEDICINE

Active ingredient: ofatumumab

Structure:



Molecular weight: approximately 149 kDa.

CAS number: 679818-59-8

Ofatumumab is a human monoclonal antibody (IgG1κ) that is generated via transgenic mouse and hybridoma technology and produced in a recombinant murine cell line (NS0).

DESCRIPTION

ARZERRA is a sterile, clear to slightly opalescent, colourless, preservative-free, concentrated solution (20 mg/mL) for intravenous infusion.

Each single-use vial of ARZERRA contains either 100 mg of ofatumumab in 5 mL of solution or 1000 mg of ofatumumab in 50 mL of solution. The excipients: arginine, sodium acetate, sodium chloride (see PRECAUTIONS – Sodium content), polysorbate 80, edetate disodium, hydrochloric acid, and water for injections.

PHARMACOLOGY

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies

ATC Code: L01XC10

Mechanism of Action

Ofatumumab is a recombinant human monoclonal antibody (IgG1) that binds specifically to 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 on B-cell tumours. The B-cell tumours include chronic lymphocytic leukaemia (CLL), that is generally associated with lower levels of CD20 expression, and non-Hodgkin's lymphomas (where > 90 % of tumours have high levels of CD20 expression).

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 and resultant lysis of tumour cells. In addition, the binding of ofatumumab induces cell death through antibody-dependent cell-mediated cytotoxicity. Ofatumumab has been shown to induce lysis in cells both with high and low CD20 expression, including cells with high expression levels of complement defence molecules.

Pharmacodynamic effects

B-cell depletion

Peripheral B cell counts decreased after the first ofatumumab infusion in patients with haematologic malignancies. In patients with refractory CLL, the median decrease in B cell counts was 22 % after the first infusion and 92 % at the eighth weekly infusion. Peripheral B cell counts remained low throughout the remainder of therapy in most patients and remained below baseline up to 15 months after the last dose in patients who responded.

In patients with previously untreated CLL, the median decreases in B-cell counts after the first cycle and prior to the sixth monthly cycle were 94 % and > 99 % for ofatumumab in combination with chlorambucil and 73 % and 97 % for chlorambucil alone. At 6 months after the last dose, the median reductions in B-cell counts were > 99 % for ofatumumab in combination with chlorambucil and 94 % for chlorambucil alone.

Immunogenicity

There is a potential for immunogenicity with therapeutic proteins such as ARZERRA. Serum samples from more than 440 patients across the CLL clinical program were tested for anti-ofatumumab antibodies during and after treatment periods ranging from 4 to 45 weeks (either by enzyme-linked immunosorbent assay or electrochemiluminescence). There was no formation of anti ofatumumab antibodies in patients with CLL after treatment with ofatumumab.

Pharmacokinetics

Absorption

Ofatumumab is administered by intravenous infusion; therefore, absorption is not applicable. Maximum ofatumumab serum concentrations were generally observed at or shortly after the end of the infusion. Pharmacokinetic data were available from 215 patients with refractory

CLL. The geometric mean C_{max} value was 61 μg/mL after the first infusion (300 mg); after the eighth weekly infusion (seventh infusion of 2000 mg), the geometric mean C_{max} value was 1391 μg/mL and geometric mean $AUC_{(0-\infty)}$ value was 463,418 μg.h/mL; after the twelfth infusion (fourth monthly infusion; 2000 mg), the geometric mean C_{max} value was 827 μg/mL and geometric mean $AUC_{(0-\infty)}$ was 203,536 μg.h/mL. 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.

Distribution

Ofatumumab has a small volume of distribution, with mean Vss values ranging from 1.7 to 8.1 L across studies, dose levels, and infusion number.

Biotransformation

Ofatumumab is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes. Classical biotransformation studies have not been performed.

Elimination

Ofatumumab is eliminated in two ways: a target-independent route like other IgG molecules and a target-mediated route which is related to binding to B cells. There was a rapid and sustained depletion of CD20+ B cells after the first ofatumumab infusion, leaving a reduced number of CD20+ cells available for the antibody to bind at subsequent infusions. As a result, ofatumumab clearance values were lower and $t_{½}$ values were significantly larger after later infusions than after the initial infusion; during repeated weekly infusions, ofatumumab AUC and Cmax values increased more than the expected accumulation based on first infusion data.

Across the studies in patients with refractory CLL, the geometric mean values for CL and $t_{½}$ were 64 mL/h (range 4.3 – 1122 mL/h) and 1.3 days (range 0.2 – 6.0 days) after the first infusion, 8.5 mL/h (range 1.3 – 41.5 mL/h) and 11.5 days (range 2.3 – 30.6 days) after the fourth infusion, 11.7 mL/h (range 3.9 – 54.2 mL/h) and 13.6 days (range 2.4 – 36.0 days) after the eighth infusion, and 12.1 mL/h (range 3.0 - 233 mL/h) and 11.5 days (range 1.8 – 36.4 days) after the twelfth infusion.

In patients with previously untreated CLL receiving ofatumumab and chlorambucil, geometric mean CL and t½ values for ofatumumab were 15.4 mL/h (range 4.1-146 mL/h) and 18.5 days (range 2.7-82.6 days) after the fourth infusion.

Special Patient Populations

Elderly (greater than 65 years of age)

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.

Children and Adolescents (up to 18 years of age)

No pharmacokinetic data are available in paediatric patients.

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.

Renal Impairment

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 ranging from 26 to 287 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).

Hepatic Impairment

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.

CLINICAL TRIALS

The efficacy of ofatumumab have been evaluated in two clinical studies (OMB110911 and OMB115991) in patients with previously untreated CLL considered inappropriate for a fludarabine-based treatment, and two clinical studies (Hx-CD20-406 and Hx-CD20-402) in patients with refractory CLL.

Previously Untreated CLL

Open Label Studies

Study OMB110911

This randomised, open label, parallel-arm, multicentre study evaluated the efficacy of ARZERRA in combination with chlorambucil compared with chlorambucil alone in 447 patients with previously untreated CLL considered inappropriate for fludarabine-based treatment (e.g. due to advanced age or presence of co-morbidities). Patients received either ARZERRA 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). Patients received treatment for a minimum of 3 months until best response or up to a maximum of 12 cycles. The median age was 69 years (range: 35 to 92 years),

63% were male, and 89% were White. Approximately 60% of patients received 3-6 cycles of ARZERRA and 32% received 7-12 cycles. The median number of cycles completed in patients was 6 (total ARZERRA dose of 6,300 mg).

The primary endpoint was progression-free survival (PFS) as assessed by a blinded Independent Review Committee (IRC) using the updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008). The overall response rate (ORR) including complete response (CR) was also assessed by an IRC using the 2008 NCI-WG guidelines.

ARZERRA in combination with chlorambucil (O+Chl) showed a statistically significant longer median PFS compared with chlorambucil (Chl) alone (O+Chl: 22.4 months; Chl: 13.1 months; HR: 0.57; 95% CI: 0.45-0.72), and the risk of experiencing a PFS event was reduced by 43 % (see Table 1, Figure 1). PFS benefit with the addition of ARZERRA was observed in all patients, including those with poor-risk biological features (such as 17p or 11q deletion, IGV_H unmutated status, β_2M > 3500 μg/L, and ZAP-70 expression).

Table 1 Summary of PFS with Ofatumumab in Combination with Chlorambucil Compared with Chlorambucil in Previously Untreated CLL

IRC-Assessed Primary and Subgroup Analyses of PFS, Months	Chlorambucil (N=226)	Ofatumumab and Chlorambucil (N=221)
Median, all patients	13.1	22.4
95% CI	(10.6, 13.8)	(19.0, 25.2)
Hazard Ratio P Value	0.57 (0.45-0.72) p < 0.001	
Age ≥ 75 years (n = 119)	12.2	23.8
17p or 11q deletion (n = 90)	7.9	13.6
IGVH mutated (≤ 98 %) (n= 177)	12.2	30.5
IGVH unmutated (> 98 %) (n= 227)	11.7	17.3
β_2M ≤ 3500 μg/L (n= 109)	13.8	25.5
β_2M > 3500 μg/L (n= 322)	11.6	19.6
ZAP-70 positive (n= 161)	9.7	17.7
ZAP-70 negative (n= 100)	13.8	25.6

Abbreviations: β2M= Beta-2-microglobulin; CI= confidence interval; CLL= Chronic Lymphocytic Leukaemia; IgV_H= Immunoglobulin Heavy Chain Variable Region; IRC= Independent Review Committee; N, n = number; PFS= Progression-free Survival; ZAP-70= Zeta-Chain-associated protein kinase 70 expression

Figure 1 Kaplan-Meier Estimates of PFS in previously untreated CLL

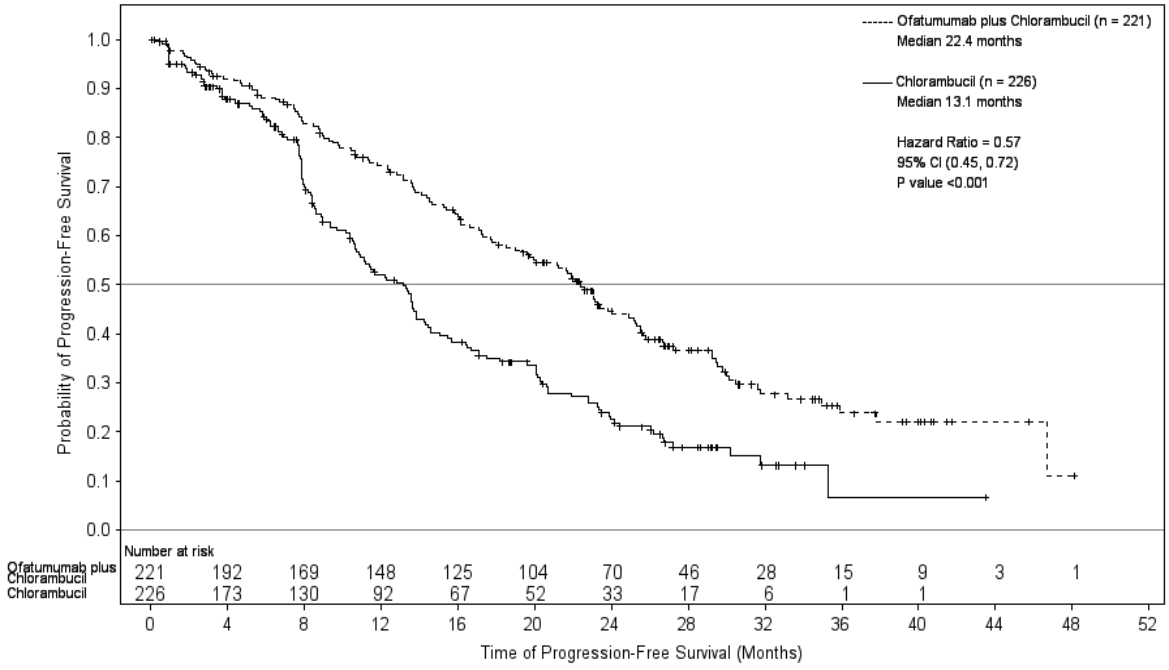


Table 2 Summary of Secondary Outcomes of Ofatumumab in Combination with Chlorambucil Compared with Chlorambucil in Previously Untreated CLL

IRC-Assessed Secondary Outcome	Chlorambucil (N=226)	Ofatumumab and Chlorambucil (N=221)
ORR (%)	69	82
95 % CI	(62.1, 74.6)	(76.7, 87.1)
p value	p < 0.001	
CR (%)	1	12
MRD Negativity in CR patients (%)	0	38
Median Duration of Response, all Patients, months	13.2	22.1
95 % CI	(10.8, 16.4)	(19.1, 24.6)
p value	p < 0.001	

Abbreviations: CI= confidence interval; CLL= Chronic Lymphocytic Leukaemia, CR= Complete Response, IRC= Independent Review Committee, MRD= Minimal Residue Disease, N= number, ORR= Overall Response Rate

Study OMB115991

This study evaluated the efficacy of ofatumumab in combination with bendamustine in 44 patients with previously untreated CLL considered inappropriate for fludarabine-based treatment. Patients received ofatumumab as monthly intravenous infusions (Cycle 1 300 mg day 1 and 1000 mg day 8, subsequent cycles: 1000 mg at day 1 every 28 days) in combination with bendamustine 90 mg/m^2 intravenous at days 1-2 every 28 days. Patients received treatment for a minimum of 3 cycles until best response or a maximum of 6 cycles. The median number of cycles completed in patients was 6 (total ofatumumab dose of 6300 mg).

The primary endpoint was ORR assessed by the investigator according to the 2008 NCI-WG guidelines.

The results of this study demonstrated that ARZERRA in combination with bendamustine is

an effective therapy providing an ORR of 95 % (95 % CI: 85, 99) and a CR of 43 %. More than half of the patients (56 %) with CR were MRD negative following the completion of study treatment.

Refractory CLL

Open Label Studies

Study Hx-CD20-406

ARZERRA was administered as a monotherapy to 223 patients with refractory CLL in this study. Patient median age was 64 years (range: 41 to 87 years), and the majority were male (73 %) and white (96 %). Patients received a median of 5 prior therapies, including rituximab (57 %). 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). Baseline cytogenetic (FISH) data were available for 209 patients. 36 patients had a normal karyotype and chromosomal aberrations were detected in 174 patients; there were 47 patients with 17p deletion, 73 patients with 11q deletion, 23 patients with trisomy 12q, and 31 patients with 13q deletion as the sole aberration.

The overall response rate was 49% in patients refractory to fludarabine and alemtuzumab (see Table 3 for a summary of the efficacy data from the study). Patients who had prior rituximab therapy, either as monotherapy or in combination with other medicinal products, responded to treatment with ARZERRA at a similar rate as those who had not had prior rituximab therapy.

Table 3 Summary of response to ARZERRA in patients with Refractory CLL

(Primary) endpoint[1]	**Patients refractory to fludarabine and alemtuzumab n = 95**
Overall response rate	
Responders, n (%)	47 (49)
95.3 % CI (%)	39, 60
Response rate	
in patients with prior rituximab therapy	
Responders, n (%)	25/56 (45)
95 % CI (%)	31, 59
in patients with chromosomal abnormality	
17p deletion	
Responders, n (%)	10/27 (37)
95 % CI (%)	19, 58
11q deletion	
Responders, n (%)	15/32 (47)
95 % CI (%)	29, 65
Median overall survival	
Months	13.9
95 % CI	9.8, 18.6
Progression-free survival	
Months	4.6
95 % CI	3.9, 6.3
Median duration of response	
Months	5.5

(Primary) endpoint[1]	Patients refractory to fludarabine and alemtuzumab n = 95
95 % CI	3.7, 7.2
Median time to next CLL therapy	
Months	8.5
95 % CI	7.2, 9.6

[1] The overall response was assessed by an Independent Response Committee using the 1996 National Cancer Institute Working Group (NCIWG) guidelines for CLL.

Improvements also were demonstrated in components of the NCI-WG response criteria. These included improvements associated with constitutional symptoms, lymphadenopathy, organomegaly, or cytopenias (see Table 4).

Table 4 Summary of clinical Improvement with a minimum duration of 2 Months in Refractory CLL patients with abnormalities at baseline

Efficacy Endpoint or Haematological Parameter[a]	Patients with benefit/Patients with abnormality at baseline (%) Patients refractory to fludarabine and alemtuzumab
Lymphocyte count	
≥ 50% decrease	49/71 (69)
Normalisation (≤ 4 x 10^9/L)	36/71 (51)
Complete resolution of constitutional symptoms[b]	21/47 (45)
Lymphadenopathy[c]	
≥ 50 % improvement	51/88 (58)
Complete resolution	17/88 (19)
Splenomegaly	
≥ 50 % improvement	27/47 (57)
Complete resolution	23/47 (49)
Hepatomegaly	
≥ 50 % improvement	14/24 (58)
Complete resolution	11/24 (46)
Haemoglobin	12/49 (24)
< 110 g/L at baseline to >110 g/L post baseline	
Platelet counts	
≤ 100 x 10^9/L at baseline to > 50 % increase from baseline or > 100 x 10^9/L post baseline	19/50 (38)
Neutrophils	
< 1 x 10^9/L at baseline to > 1.5 x 10^9/L post baseline	1/17 (6)

a Excludes patient visits from date of first transfusion, treatment with erythropoietin, or treatment with growth factors. For patients with missing baseline data, latest screening/unscheduled data was carried forward to baseline.

b Complete resolution of constitutional symptoms (fever, night sweats, fatigue, and weight loss) defined as the presence of any symptoms at baseline, followed by no symptoms present.

c Lymphadenopathy measured by sum of the products of greatest diameters (SPD) as assessed by physical examination.

Study Hx-CD20-402

This dose-ranging study was conducted in 33 patients with relapsed or refractory CLL. Patient median age was 61 years (range: 27 to 82 years), the majority were male (58%), and

all were white. Treatment with ARZERRA (when given as 4 once weekly infusions), led to a 50% objective response rate in the highest dose group (1st dose: 500 mg; 2nd, 3rd and 4th dose: 2000 mg) and included 12 partial remissions and one nodular partial remission. For the highest dose group, the median time to progression was 15.6 weeks (95% CI: 15, 22.6) in the full analysis population, and 23 weeks (CI: 20, 31.4) in responders. The duration of response was 16 weeks (CI: 13.3, 19.0) and the time to next CLL therapy was 52.4 weeks (CI: 36.9, non-estimable).

INDICATIONS

Previously Untreated CLL

ARZERRA is indicated in combination with chlorambucil or bendamustine for the treatment of patients with chronic lymphocytic leukaemia (CLL) who have not received prior therapy and are inappropriate for fludarabine-based therapy.

Refractory CLL

ARZERRA, as a single agent, is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL) refractory to fludarabine and alemtuzumab.

CONTRAINDICATIONS

ARZERRA is contraindicated in patients with hypersensitivity to the active substance ofatumumab or to any of the excipients (see DESCRIPTION).

PRECAUTIONS

Infusion-related reactions

Intravenous ARZERRA has been associated with infusion-related reactions. These reactions may result in temporary interruption or withdrawal of treatment or death. Pre-medications attenuate infusion-related reactions but these may still occur, predominantly during the first infusion (see DOSAGE AND ADMINISTRATION*).*

Infusion-related reactions may include, but are not limited to 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, pruritus, pyrexia, rash, and urticaria. Even with pre-medication, severe reactions, including cytokine release syndrome, have been reported following ARZERRA use. In the event of severe infusion-related reaction, the infusion of ARZERRA must be interrupted immediately and symptomatic treatment instituted (see DOSAGE AND ADMINISTRATION for changes to infusion rates following infusion-related reactions). If an anaphylactic reaction occurs, ARZERRA should be immediately and permanently discontinued and appropriate medical treatment should be initiated.

Infusion-related reactions occur more frequently during the first infusion and tend to decrease with subsequent 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.

Haematologic

Cytopenias

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

Tumour Lysis Syndrome

In patients with CLL, tumour lysis syndrome (TLS) may occur with use of ARZERRA. Risk factors for TLS include a high tumour burden, high concentrations of circulating cells ($\geq 25{,}000/mm^3$), hypovolaemia, renal insufficiency, elevated pre-treatment uric acid levels and elevated lactate dehydrogenase levels. Management of TLS includes correction of electrolyte abnormalities, monitoring of renal function, maintenance of fluid balance and supportive care.

Infections

ARZERRA causes a marked reduction in B lymphocytes and therefore may increase the risk of infection. In the pivotal study in CLL patients, 14 of 154 patients (9%) had serious infections that were considered drug-related. Fatal infections occurred in 16 of 154 patients (10%). Of these, 4 (3%) were considered drug-related.

Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) and death has been reported in CLL patients receiving cytotoxic pharmacotherapy, including ARZERRA. A diagnosis of PML should be considered in any patient treated with ARZERRA who reports the new onset of or changes in pre-existing neurologic signs and symptoms. If a diagnosis of PML is suspected ARZERRA should be discontinued and referral to a neurologist should be considered.

Hepatitis B Infection and/or Reactivation

Hepatitis B virus (HBV) infection and reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, has occurred in patients treated with drugs classified as CD20-directed cytolytic antibodies, including ARZERRA. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are hepatitis B core antibody (anti-HBc) positive but HBsAg negative. 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.

All patients should be screened for HBV infection by measuring HBsAg and anti-HBc before initiation of ARZERRA treatment. For patients who show evidence of prior (HBsAg negative, anti-HBc positive) hepatitis B infection, physicians with expertise in managing hepatitis B should be consulted regarding monitoring and initiation of HBV antiviral therapy. ARZERRA treatment should not be initiated in patients with evidence of current hepatitis B infection (HBsAg positive) until the infection has been adequately treated.

Patients with evidence of prior HBV infection should be monitored for clinical and laboratory signs of hepatitis or HBV reactivation during treatment with and for 6-12 months following the last infusion of ARZERRA. HBV reactivation has been reported up to 12 months following completion of therapy. Discontinuation of HBV antiviral therapy should be discussed with physicians with expertise in managing hepatitis B.

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

Immunisations

The safety of, and ability to generate a primary or anamnestic response to, immunisation with live attenuated or inactivated vaccines during ARZERRA treatment has not been studied. The response to vaccination could be impaired when B cells are depleted. Due to the risk of infection, administration of live attenuated vaccines should be avoided during and after treatment with ARZERRA, until B cell counts are normalised. The risks and benefits of vaccinating patients during ARZERRA therapy should be considered.

Cardiovascular

Patients with a history of cardiac disease should be monitored closely. ARZERRA should be discontinued in patients who experience serious or life-threatening cardiac arrhythmias. The effect of multiple doses of Arzerra on the QTc interval was evaluated in a pooled analysis of three open-label studies in patients with CLL (N = 85). Increases above 5 milliseconds (msec) were observed in the median/mean QT/QTc intervals in the pooled analysis. No large changes in the mean QTc interval (i.e., > 20 msec) were detected. None of the patients had an increase of QTc to >500 msec. A concentration dependent increase in QTc was not detected. It is recommended that patients have electrolytes such as potassium and magnesium measured prior to and during the administration of ofatumumab. Electrolyte abnormalities should be corrected. The effect of ofatumumab on patients with prolonged QT intervals (e.g., acquired or congenital) is unknown.

Bowel Obstruction

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

Skin Reactions

Severe mucocutaneous reactions can occur in this disease setting and have been reported in patients receiving anti-CD20 monoclonal antibody therapy, including ARZERRA. In case of such an event, treatment should be discontinued.

Laboratory Monitoring

Cytopenias, including prolonged and late-onset neutropenia, have been reported during ofatumumab therapy. Complete blood counts, including neutrophil and platelet counts should be obtained at regular intervals during ARZERRA therapy and more frequently in patients who develop cytopenias. Appropriate management should be considered should cytopenias occur.

Sodium content

ARZERRA contains 34.8 mg sodium per 300 mg dose and 232 mg sodium per 2000 mg dose. This should be taken into consideration by patients on a controlled sodium diet.

Effects on fertility

There are no data on the effects of ARZERRA on human fertility. Effects on male and female fertility have not been evaluated in animal studies.

Use in pregnancy (Category C)

There are no adequate and well controlled data for the use of ARZERRA in pregnant women. Ofatumumab may cause fetal B-cell depletion based on findings from the drug's mechanism of action (see PHARMACOLOGY).

An embryofetal study in which cynomolgus monkeys were treated during the period of organogenesis revealed no evidence of external, visceral or skeletal defects of the fetus at exposures similar to the anticipated clinical AUC. However, ofatumumab could be detected in the fetal circulation 50 days after the final dose and exposed fetuses had lower spleen weights and depleted B cells. Since ARZERRA may cause fetal B-cell depletion, precautions should be taken to avoid pregnancy, and effective contraception (methods that result in less than 1 % pregnancy rates) should be used while using ARZERRA and for at least 12 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 fetus.

Use in lactation

The safe use of ARZERRA in humans during lactation has not been established. It is not known whether ofatumumab is excreted in human breast milk. The excretion of ofatumumab in milk has not been studied in animals. However, maternal IgG is secreted in breast milk. , it is recommended that breastfeeding should be discontinued for the entire duration of treatment with ARZERRA.

Use in children and adolescents (up to 18 years of age) The safety and effectiveness of ARZERRA have not been established in the paediatric age group.

Use in the elderly (greater than 65 years of age)

No substantial differences were seen in safety and efficacy related to age (see DOSAGE AND ADMINISTRATION).

Ability to perform tasks that require judgement, motor or cognitive skills

No studies on the effects of ARZERRA on the ability to drive and use machines have been performed. No detrimental effect on such activities are predicted from the pharmacology of ARZERRA. The clinical status of the subject and the adverse event profile of ARZERRA should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills.

Carcinogenicity

The carcinogenic potential of ofatumumab has not been investigated.

Genotoxicity

As ofatumumab is a monoclonal antibody, the genotoxic potential of ofatumumab has not been investigated.

INTERACTIONS WITH OTHER MEDICINES

No clinically significant interactions were observed between Ofatumumab does not have a clinically relevant effect on the pharmacokinetics of chlorambucil or its active metabolite, phenylacetic acid mustard.

Live attenuated or inactivated vaccine efficacy may be impaired with ARZERRA. Therefore, the concomitant use of these agents with ARZERRA should be avoided. (See PRECAUTIONS – Immunisations.) If the coadministration is judged unavoidable, the risks and benefits of vaccinating patients during therapy with ARZERRA should be considered.

ADVERSE EFFECTS

Summary of the safety profile

Clinical Trial Data

Previously Untreated CLL

The safety of ARZERRA was evaluated in 2 studies conducted in patients previously untreated for CLL and considered inappropriate for fludarabine-based therapy. Study 1 was an open-label, parallel-arm, randomized study of 447 patients 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 to 7 every 28 days) or chlorambucil alone (10 mg/m^2 oral on Days 1 to 7 every 28 days). The median number of cycles completed was 6 (total dose of ARZERRA was 6,300 mg). The median age was 69 years (range: 35 to 92 years); 63% of patients were male and 89% were white.

Study 2 was an open-label, single-arm study including 44 patients with previously untreated CLL who received 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 bendamustine (90 mg/m^2 on Days 1 and 2 every 28 days). The majority of patients (89%) received all 6 cycles of ARZERRA. The median age was 63 years (range: 34 to 86 years); 66% of patients were male and 98% were white.

The data described in Table 5 include adverse reactions occurring in ≥5% of 261 patients with previously untreated CLL who received ARZERRA with either chlorambucil or bendamustine.

Table 5 Incidence of adverse reactions occurring in ≥ 5 % of patients with previously untreated CLL

Adverse Reaction	ARZERRA plus Alkylator[a] (N = 261)		ARZERRA plus Chlorambucil[b] (N = 217)		Chlorambucil[b] (N = 227)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Neutropenia	31	28	27	26	18	15
Nausea[c]	25	<1	21	<1	25	0
Rash[c]	25	3	25	3	10	<1
Pyrexia[c]	22	1	21	1	10	2
Diarrhoea[c]	17	0	18	0	15	1
Fatigue	16	1	16	1	18	1
Cough[c]	15	0	16	0	11	0
Pruritus[c]	13	<1	12	<1	5	0
Vomiting[c]	12	<1	12	<1	11	0
Dyspnoea[c]	11	1	12	1	5	<1
Headache	10	<1	9	<1	3	0
Urticaria[c]	10	2	10	1	<1	<1
Chills[c]	9	<1	9	<1	<1	0
Infusion-related reaction	9	1	9	<1	0	0
Back pain[c]	7	<1	6	<1	6	<1
Hypotension[c]	6	<1	6	<1	<1	0
Erythema[c]	5	0	5	0	<1	0
Flushing[c]	5	0	5	0	<1	0
Hyperhidrosis[c]	5	0	6	0	2	<1

a **Safety data integration of Studies 1 and 2: ARZERRA plus either chlorambucil or bendamustine.**

b **Safety data from Study 1.**

c **These events are likely attributable to ARZERRA in the setting of an infusion reaction and typically occur after the start of the infusion and within 24 hours after completion of the infusion (see PRECAUTIONS).**

Refractory CLL

The safety of ARZERRA in patients with refractory CLL has been evaluated in two open label studies. In study Hx-CD20-406, 223 patients were enrolled to receive 12 infusions of ARZERRA administered as 300 mg initial dose (Dose 1), followed 1 week later by 2,000 mg weekly for 7 doses (Doses 2 through 8), followed 4 weeks later by 2,000 mg every 4 weeks for 4 doses (Doses 9 through 12).The second study (Hx-CD20-402) was a dose-finding study and patients in three cohorts (3 patients, 3 patients, 27 patients) received a starting dose of 100 mg, 300 mg or 500 mg, followed a week later with 3 consecutive weekly infusions of 500 mg, 1000 mg or 2000 mg of ARZERRA, respectively.

The data in Table 6 are derived from 223 patients in study Hx-CD20-406. All patients received 2,000 mg weekly from the second dose onward. 90% of patients received at least 8 infusions of ARZERRA and 51% received all 12 infusions. The median age was 64 years (range: 41 to 87 years), 73% were male, and 96% were white.

Table 6 Incidence of all adverse reactions occurring in ≥ 5 % of patients, in the double refractory subset and in the bulky fludarabine refractory subset. Adverse events of note occurring in < 5 % are also included

Body System/Adverse Event	Total (n=223)		DR (n = 95)		BFR (n = 112)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Infections and infestations						
Pneumonia[a]	21	13	22	14	18	13
Upper respiratory tract infection	10	0	4	0	15	0
Bronchitis	12	<1	15	1	11	0
Sepsis[b]	9	9	13	13	6	5
Urinary tract infection[d]	8	1	5	2	10	<1
Nasopharyngitis	9	0	11	0	9	0
Herpes zoster	5	<1	6	1	5	<1
Sinusitis	7	2	7	2	6	2
Blood and lymphatic system disorders						
Neutropenia	17	13	20	16	12	9
Anaemia	17	5	17	7	18	4
Febrile neutropenia	3	3	3	2	3	3
Thrombocytopenia	4	4	7	6	3	2
Leukopenia	<1	<1	1	0	0	0
Agranulocytosis	<1	<1	0	0	<1	<1
Coagulopathy	<1	0	0	0	0	0
Red cell aplasia	<1	0	2	0	0	0
Lymphopenia	<1	<1	0	0	<1	<1
Psychiatric disorders						
Insomnia	7	0	7	0	6	0
Nervous system disorders						
Headache	6	0	8	0	4	0
Cardiovascular disorders						
Hypertension	4	0	6	0	3	0
Hypotension	6	0	7	0	5	0
Tachycardia	5	<1	6	1	4	0
Flushing	3	0	3	0	4	0
Respiratory, thoracic and mediastinal disorders						
Cough	23	0	24	0	21	0
Dyspnoea	15	2	20	4	11	0
Bronchospasm	3	<1	2	1	3	<1
Hypoxia	2	0	4	0	0	0
Oropharyngeal pain	4	0	5	0	3	0
Gastrointestinal disorders						
Diarrhoea	17	<1	17	0	14	<1
Nausea	13	0	14	0	13	0
Small bowel obstruction	<1	<1	1	1	<1	<1
Immune system disorders						
Cytokine release syndrome	4	<1	5	0	4	<1
Anaphylactoid reactions[e]	<1	0	0	0	2	0
Hypersensitivity[f]	5	<1	11	1	<1	<1
Metabolism and nutrition disorders	<1	<1	0	0	<1	<1

Body System/Adverse Event	Total (n=223)		DR (n = 95)		BFR (n = 112)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Tumour lysis syndrome						
Skin and subcutaneous tissue disorders						
Rash[c]	15	<1	20	2	8	0
Urticaria	7	0	5	0	8	0
Hyperhidrosis	7	0	6	0	7	0
Pruritus	4	0	4	0	4	0
Musculoskeletal and connective tissue disorders						
Back pain	10	<1	14	1	6	0
Muscle spasms	6	0	4	0	6	0
General disorders and administration site conditions	21	2	23	4	16	<1
Pyrexia	16	0	13	0	20	0
Fatigue	11	<1	9	1	13	0
Oedema peripheral	13	0	14	0	12	0
Chills	2	0	4	0	<1	0
Chest discomfort						

DR: Double refractory BFR: Bulky fludarabine refractory

a Pneumonia includes pneumonia, lung infection, lobar pneumonia, and bronchopneumonia.

b Sepsis includes sepsis, neutropenic sepsis, bacteraemia, and septic shock.

c Rash includes rash, rash generalized, rash papular, and rash vesicular.

d Urinary tract infection includes urinary tract infection, bacterial pyelonephritis, cystitis

e Anaphylactoid reactions includes anaphylactic reaction (including anaphylactic shock) and anaphylactoid reaction

f Hypersensitivity includes hypersensitivity and drug hypersensitivity

Description of selected adverse reactions

Infusion-related reactions

In the pivotal study (Hx-CD20-406), infusion reactions occurred in 43% of patients on the day of the first infusion (300 mg), 31% on the day of the second infusion (2,000 mg), and less frequently during subsequent infusions (see PRECAUTIONS).

Infections

Of the 223 patients enrolled in the pivotal study, a total of 162 patients (73%) experienced bacterial, viral, or fungal infections. 64 patients (29%) experienced ≥ Grade 3 infections, of which 21 (9%) were fatal. The proportion of fatal infections in the indicated fludarabine- and alemtuzumab-refractory group was 14%.

Neutropenia

Of 154 patients with normal neutrophil counts at baseline who were part of the pivotal study, 44 (29%) developed ≥ Grade 3 neutropenia. Twenty two (14%) developed Grade 4 neutropenia. Some patients experienced new onset Grade 4 neutropenia > 2 weeks in duration.

Post marketing data

Adverse reactions are listed below by MedDRA body system organ class and by frequency. The frequency categories used are:

Very common	≥ 1 in 10
Common	≥ 1 in 100 and < 1 in 10
Uncommon	≥ 1 in 1,000 and < 1 in 100
Rare	≥ 1/10,000 and < 1/1,000

Infections and Infestations

Rare Hepatitis B (infection and reactivation) (see PRECAUTIONS)

Cardiac

Rare Bradycardia (in setting of an infusion reaction – see PRECAUTIONS)

Respiratory, Thoracic and Mediastinal Disorders

Rare Pulmonary oedema (in setting of an infusion reaction – see PRECAUTIONS)

DOSAGE AND ADMINISTRATION

Method of Administration

ARZERRA is for intravenous infusion and must be diluted prior to administration (see Use and Handling).

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 infusion. (See PRECAUTIONS – Infusions reactions.)

Premedication

Patients should receive oral paracetamol (or equivalent) plus oral or intravenous antihistamine plus intravenous corticosteroid premedication agents half an hour to 2 hours (30 – 120 minutes) prior to each infusion (see Table 7).

Table 7 Premedication schedule for Arzerra infusions (all indications)

	Infusion number	IV cortico-steroid	Oral paracetamol	Oral or IV anti-histamine
Previously untreated CLL	1 and 2	7.5 mg dexamethasone OR equivalent	paracetamol 1000 mg	diphenhydramine 50 mg OR cetirizine 10 mg OR equivalent
	3 to 13	7.5 mg dexamethasone* OR equivalent		
Refractory CLL	1 and 2	15 mg dexamethasone OR equivalent	paracetamol 1000 mg	diphenhydramine 50 mg OR cetirizine 10 mg OR equivalent
	3 to 8	15 mg dexamethasone** OR equivalent		
	9	15 mg dexamethasone OR equivalent		

	Infusion number	IV cortico-steroid	Oral paracetamol	Oral or IV anti-histamine
	10 to 12	15 mg dexamethasone *** OR equivalent		

*Following the first and second infusion, if the patient does not experience a severe adverse drug reaction (ADR), pre-medication with a corticosteroid for subsequent infusions may either be reduced or omitted, at the discretion of the physician.

**If the second weekly infusion is completed without a severe ADR, the dose of the corticosteroid may be reduced for infusion numbers 3 through 8, at the discretion of the physician.

***If the ninth infusion is completed without a severe ADR, the dose may be reduced to the equivalent of 7.5 mg dexamethasone at the discretion of the physician.

Dosage

Previously Untreated CLL

The recommended dosage and schedule is 300 mg on day 1 followed 1 week later by 1000 mg on day 8 (cycle 1), followed by 1000 mg on day 1 of subsequent cycles until best response or a maximum of 12 cycles (every 28 days).

First infusion

The initial rate of the first infusion of ARZERRA should be 12 mL/hour. During infusion, the rate should be doubled every 30 minutes to a maximum of 400 mL/hour (see DOSAGE AND ADMINISTRATION - Use and Handling).

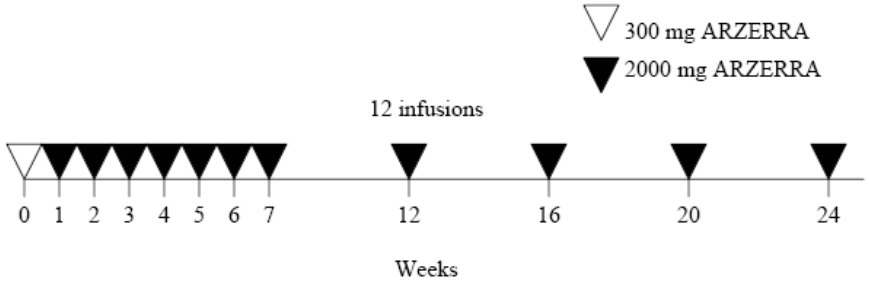
Subsequent infusions

If the first infusion has been completed without severe infusion related ADRs, the subsequent infusions can start at a rate of 25 mL/hour and should be doubled every 30 minutes up to a maximum of 400 mL/hour (see DOSAGE AND ADMINISTRATION - Use and Handling).

Refractory CLL

The recommended dose is 300 mg for the first infusion and 2000 mg for all subsequent infusions. The infusion schedule is 8 consecutive weekly infusions, followed 4-5 weeks later by 4 consecutive monthly (i.e. every 4 weeks) infusions (See Figure 2).

Figure 2 Infusion schedule for ARZERRA



First and second infusions

The initial rate of the first and second infusion of ARZERRA diluted solution should be 12 mL/hour. During infusion, the rate should be doubled every 30 minutes to a maximum of 200 mL/hour (see DOSAGE AND ADMINISTRATION - Use and Handling).

Subsequent infusions

If the second infusion has been completed without severe infusion related ADRs, the remaining infusions can start at a rate of 25 mL/hour and should be doubled every 30 minutes up to a maximum of 400 mL/hour (see Use and Handling).

Dose modification and reinitiation of therapy – in patients with previously untreated CLL and refractory CLL

Infusion related ADRs may lead to slower infusion rates.

Mild or moderate ADR

In case of a mild or moderate ADR, the infusion should be interrupted and restarted at half of the infusion rate at the time of interruption, when the patient's condition is stable. If the infusion rate had not been increased from the starting rate of 12 mL/hour prior to interrupting 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 standard procedures, according to physician discretion and patient tolerance (not to exceed doubling the rate every 30 minutes).

Severe ADR

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

Life threatening ADR

- In case of a life-threatening ADR, do not resume the infusion.

Therapy should be permanently discontinued in patients who develop an anaphylactic reaction to ARZERRA (see PRECAUTIONS – Infused-related reactions).

Special populations

Use in children and adolescents (up to 18 years of age)The safety and effectiveness of ARZERRA have not been established in the paediatric age group.

Use in the elderly (greater than 65 years of age)

No substantial differences were seen in safety and efficacy related to age (See Clinical Trials). Based on available safety and efficacy data in the elderly, no dosage adjustment is required (see PHARMACOLOGY - Pharmacokinetics: Special patient populations).

Renal Impairment

No formal studies of ARZERRA in patients with renal impairment have been performed. However, patients with renal impairment are unlikely to require dose modification (see PHARMACOLOGY - Pharmacokinetics: Special patient populations).

Hepatic Impairment

No formal studies of ARZERRA in patients with hepatic impairment have been performed. However, patients with hepatic impairment are unlikely to require dose modification (see PHARMACOLOGY - Pharmacokinetics: Special patient populations).

Use and handling

ARZERRA concentrate should be diluted using aseptic practices. ARZERRA does not contain a preservative and is for single use in one patient only. Therefore it is recommended that the diluted solution be used as soon as possible after preparation. The diluted solution for infusion must be stored at 2°C to 8°C and used within 24 hours of preparation. Any unused solution remaining after this time should be discarded.

1. **Before diluting ARZERRA**

   Check the ARZERRA concentrate for particulate matter and discoloration prior to dilution. ARZERRA should be a colourless to pale yellow solution. **Do not use** the ARZERRA concentrate if there is discolouration.

   Do not shake the ARZERRA vial for this inspection.

2. **How to dilute the solution for infusion**

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

   300 mg dose - Use 3 x 5 mL vials (15 mL total, 5 mL per vial):

   - Withdraw and discard 15 mL from a 1000 mL bag of 0.9% sodium chloride for infusion
   - Withdraw 5 mL of ARZERRA from each of 3 vials (15 mL total) and inject into the 1000 mL bag
   - ***Do not shake***, mix diluted solution ***by gentle inversion***.

1000 mg dose – Use 1 x 50 mL vial (50 mL total, 50 mL per vial):

- Withdraw and discard 50 mL from a 1000 mL bag of 0.9 % sodium chloride for infusion
- Withdraw 50 mL of ARZERRA from the vial (50 mL total) and inject into the 1000 mL bag
- ***Do not shake***, mix diluted solution ***by gentle inversion***.

2000 mg dose with 5 mL vials– Use 20 x 5 mL vials (100 mL total, 5 mL per vial):

- Withdraw and discard 100 mL from a 1000 mL bag of 0.9 % sodium chloride for infusion
- Withdraw 5 mL of ARZERRA from each of 20 vials (100 mL total) and inject into the 1000 mL bag
- ***Do not shake***, mix diluted solution ***by gentle inversion***.

2000 mg dose with 50 mL vials– Use 2 x 50 mL vials (100 mL total, 50 mL per vial):

- Withdraw and discard 100 mL from a 1000 mL bag of 0.9 % sodium chloride for infusion
- Withdraw 50 mL of ARZERRA from each of 2 vials (100 mL total) and inject into the 1000 mL bag
- ***Do not shake***, mix diluted solution ***by gentle inversion***.

3. How to administer the diluted solution

ARZERRA must not be administered as an i.v. push or bolus. Administer using an i.v. infusion pump and an i.v. administration set.

Compatibility of ARZERRA has been established with the following dosing components:

1. Polyolefin saline bags
2. PVC and PVC lined with polyethylene administration sets

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.

a. Previously Untreated CLL

For the first infusion, administer over 4.5 hours (see Dosage and Administration), through a peripheral line or indwelling catheter, according to Table 8.

Table 8 Infusion schedule - previously untreated CLL

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

If the first infusion has been completed without a severe adverse reaction, the remaining infusions (2-13) of 1000 mg should be administered over 4 hours (see DOSAGE AND ADMINISTRATION), through a peripheral line or indwelling catheter, according to the schedule below:

Refractory CLL

For the first and second infusion, administer over 6.5 hours (see DOSAGE AND ADMINISTRATION), through a peripheral line or indwelling catheter, according to Table 9.

Table 9 Infusion schedule – refractory CLL

Time (minutes)	Infusion rate (mL/hour)	
	Infusions 1 and 2	Infusions 3 to 12
0 – 30	12	25
31 – 60	25	50
61 – 90	50	100
91 – 120	100	200
121 +	200	400

If the second infusion has been completed without a severe adverse reaction, the remaining infusions (3-12) should be administered over 4 hours (SEE DOSAGE AND ADMINISTRATION), through a peripheral line or indwelling catheter, according to the schedule below:

If any adverse reactions are observed, infusion rates should be reduced (see Dose modification and reinitiation of therapy).

Any unused product or waste material should be disposed of in accordance with local requirements.

OVERDOSAGE

Symptoms and Signs

No case of overdose has been reported.

Treatment

Further management should be as clinically indicated or as recommended by the Poison Information Centre on telephone number 13 11 26 (local call in all areas).

PRESENTATION AND STORAGE CONDITIONS

Presentations

ARZERRA is supplied as 100 mg/5 mL and 1000 mg/50 mL vials (ofatumumab 20 mg/mL).

ARZERRA is presented in either 10 mL or 60 mL clear Type I glass vials with a latex-free rubber stopper and aluminium over-seal, containing 5 mL or 50 mL of concentrated solution for infusion. The drug is supplied in a single use vial without a preservative. ARZERRA is available in either packs of 3 vials (100 mg/5 mL) or 1 vial (1000 mg/50 mL).

Storage conditions

Concentrated Injection

Store at 2°C - 8°C. (Refrigerate. Do not freeze.) Protect from light.

Protect from light.

Diluted Infusion Storage

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C.Incompatibilities

The concentrate for solution for infusion must only be mixed with 0.9% sodium chloride solution for infusion *(see Use and Handling).*

Do not mix ARZERRA is with any other drug in an infusion bag.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription only medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

21 January 2011

DATE OF MOST RECENT AMENDMENT

16 March 2018

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