

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Arzerra 100 mg concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of concentrate contains 20 mg of ofatumumab.

Each vial contains 100 mg of ofatumumab in 5 ml.

Ofatumumab is a human monoclonal antibody produced in a recombinant murine cell line (NS0).

Excipient(s) with known effect:

This medicinal product contains 34.8 mg sodium per 300 mg dose, 116 mg sodium per 1,000 mg dose and 232 mg sodium per 2,000 mg dose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to opalescent, colourless to pale yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Previously untreated chronic lymphocytic leukaemia (CLL):

Arzerra in combination with chlorambucil or bendamustine is indicated for the treatment of patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy.

See section 5.1 for further information.

Refractory CLL:

Arzerra is indicated for the treatment of CLL in patients who are refractory to fludarabine and alemtuzumab.

See section 5.1 for further information.

4.2 Posology and method of administration

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.

Monitoring

Patients should be closely monitored during administration of ofatumumab for the onset of infusion reactions, including cytokine release syndrome, particularly during the first infusion.

Pre-medication

Patients should always be pre-medicated 30 minutes to 2 hours prior to Arzerra infusion according to the following dosing schedules:

Previously untreated CLL:

- oral paracetamol (acetaminophen) 1,000 mg (or equivalent), plus

- oral or intravenous antihistamine (diphenhydramine 50 mg or cetirizine 10 mg or equivalent), plus
- intravenous corticosteroid (prednisolone 50 mg 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.

Refractory CLL:

- oral paracetamol (acetaminophen) 1,000 mg (or equivalent), plus
- oral or intravenous antihistamine (diphenhydramine 50 mg or cetirizine 10 mg or equivalent), plus
- intravenous corticosteroid (prednisolone 100 mg or equivalent).

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.

Prior to the ninth infusion (first monthly infusion), patients should receive the full dose of premedication agents described above. If the ninth infusion is completed without a severe ADR, the dose may be reduced to the equivalent of 50 mg prednisolone for subsequent infusions at the discretion of the physician.

Posology

Previously untreated CLL:

The recommended dose and schedule is 300 mg on day 1 followed 1 week later by 1,000 mg on day 8 (cycle 1), followed by 1,000 mg on day 1 of subsequent cycles, for a minimum of 3 cycles, until best response or a maximum of 12 cycles (every 28 days).

Best response is a clinical response that did not improve with 3 additional cycles of treatment.

First infusion

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 section 6.6).

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/h and should be increased every 30 minutes up to a maximum of 400 ml/h (see section 6.6).

Refractory CLL:

The recommended dose is 300 mg for the first infusion and 2,000 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.

First and second infusions

The initial rate of the first and second infusion of Arzerra should be 12 ml/hour. During infusion, the rate should be increased every 30 minutes to a maximum of 200 ml/hour (see section 6.6).

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 increased every 30 minutes up to a maximum of 400 ml/hour (see section 6.6).

Dose modification and reinitiation of therapy for infusion related ADRs – in patients with previously untreated CLL and refractory CLL.

Interrupt infusion for infusion related ADRs of any severity. Treatment can be resumed at the discretion of the treating physician. The following infusion rate modifications can be used as a guide:

- 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 increasing the rate every 30 minutes).
- 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 increasing the rate every 30 minutes).

Paediatric population

Arzerra is not recommended for use in children below 18 years due to insufficient data on safety and/or efficacy.

Elderly

No substantial differences were seen in safety and efficacy related to age (see section 5.1). Based on available safety and efficacy data in the elderly, no dose adjustment is required (see section 5.2).

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 section 5.2).

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 section 5.2).

Method of administration

Arzerra is for intravenous infusion and must be diluted prior to administration. For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to ofatumumab or to any of the excipients listed in see section 6.1.

4.4 Special warnings and precautions for use

Infusion reactions

Intravenous ofatumumab has been associated with infusion reactions. These reactions may result in temporary interruption or withdrawal of treatment. Pre-medications attenuate infusion reactions but these may still occur, predominantly during the first infusion. Infusion reactions may include, but are not limited to, anaphylactoid events, bronchospasm, cardiac events (eg. 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. In rare cases, these reactions may lead to death. Even with pre-medication, severe reactions, including cytokine release syndrome, have been reported following use of ofatumumab. In cases of severe infusion reaction, the infusion of Arzerra must be interrupted immediately and symptomatic treatment instituted (see section 4.2).

Infusion reactions occur more frequently on the first day of 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 ofatumumab.

Tumour lysis syndrome

In patients with CLL, tumour lysis syndrome (TLS) may occur with use of ofatumumab. Risk factors for TLS include a high tumour burden, high concentrations of circulating cells ($\geq 25,000/\text{mm}^3$), 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.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) and death has been reported in CLL patients receiving cytotoxic pharmacotherapy, including ofatumumab. A diagnosis of PML should be considered in any Arzerra patient 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.

Immunisations

The safety of, and ability to generate a primary or anamnestic response to, immunisation with live attenuated or inactivated vaccines during treatment with ofatumumab 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 ofatumumab, until B cell counts are normalised. The risks and benefits of vaccinating patients during therapy with ofatumumab should be considered.

Hepatitis B

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 those 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.

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 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 milliseconds) 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 ofatumumab. Patients who present with abdominal pain, especially early in the course of ofatumumab therapy, should be evaluated and appropriate treatment instituted.

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 ofatumumab therapy and more frequently in patients who develop cytopenias.

Sodium content

This medicinal product contains 34.8 mg sodium per 300 mg dose, 116 mg sodium per 1,000 mg dose and 232 mg sodium per 2,000 mg dose. This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Although limited formal drug-drug interaction data exist for ofatumumab, there are no known clinically significant interactions with other medicinal products. 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 ofatumumab. Therefore, the concomitant use of these agents with ofatumumab should be avoided. If the coadministration is judged unavoidable, the risks and benefits of vaccinating patients during therapy with ofatumumab should be considered (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of ofatumumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Ofatumumab should not be administered to pregnant women unless the possible benefit to the mother outweighs the possible risk to the foetus.

Women of childbearing potential have to use effective contraception during and for 12 months after the last ofatumumab treatment.

Breast-feeding

It is unknown whether ofatumumab is excreted in human milk, however human IgG is secreted in human milk. The safe use of ofatumumab in humans during lactation has not been established. The excretion of ofatumumab in milk has not been studied in animals. Published data suggest that neonatal and infant consumption of breast milk does not result in substantial absorption of these maternal

antibodies into circulation. A risk to newborns/infants cannot be excluded. Breastfeeding should be discontinued during treatment with ofatumumab and for 12 months following treatment.

Fertility

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

4.7 Effects on ability to drive and use machines

No studies on the effects of Arzerra on the ability to drive and use machines have been performed.

No detrimental effects on such activities are predicted from the pharmacology of ofatumumab. The clinical status of the patient and the ADR profile of ofatumumab should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of ofatumumab in CLL (previously untreated and relapsed or refractory) is based on data from 511 patients in clinical trials (see section 5.1). This includes 250 patients treated with ofatumumab alone (in patients with relapsed or refractory CLL) and 261 patients treated in combination with an alkylating agent (in patients with previously untreated CLL who are inappropriate for a fludarabine-based therapy).

The adverse event profile of ofatumumab in bulky fludarabine refractory CLL patients who had failed at least 2 prior therapies was consistent with the overall established safety profile from other CLL studies, as described in the tabulated list below.

Tabulated list of adverse reactions

Adverse reactions reported with ofatumumab in previously untreated and relapsed or refractory CLL patients, either alone or in combination with an alkylating agent, are listed below by MedDRA body system organ class and by frequency. Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very rare ($< 1/10,000$), not known (cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<u>MedDRA System Organ Class</u>	<u>Very common</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>
Infections and Infestations	Lower respiratory tract infection, including pneumonia, upper respiratory tract infection	Sepsis, including neutropenic sepsis and septic shock, herpes virus infection, urinary tract infection		Hepatitis B infection and reactivation
Blood and lymphatic system disorders	Neutropenia, anaemia	Febrile neutropenia, thrombocytopenia, leukopenia	Agranulocytosis, coagulopathy, red cell aplasia, lymphopenia	
Immune system disorders		Anaphylactoid reactions*, hypersensitivity*	Anaphylactic shock*	
Metabolism and nutrition disorders			Tumour lysis syndrome	
Cardiac disorders		Tachycardia*	Bradycardia*	
Vascular disorders		Hypotension*, hypertension*		
Respiratory, thoracic and mediastinal disorders		Bronchospasm*, hypoxia*, dyspnoea*, chest discomfort*, pharyngolaryngeal pain*, cough*, nasal congestion*	Pulmonary oedema*	
Gastrointestinal disorders	Nausea*	Diarrhoea*	Small intestinal obstruction	
Skin and subcutaneous tissue disorders	Rash*	Urticaria*, pruritus*, flushing*		
Musculoskeletal and connective tissue disorders		Back pain*		
General disorders and administration site conditions	Pyrexia*,	Cytokine release syndrome*, rigors*, chills*, hyperhidrosis*, fatigue*		

*These events are likely attributable to ofatumumab in the setting of an infusion reaction and typically occur after the start of infusion and within 24 hours after the completion of the infusion (see section 4.4).

Description of selected adverse reactions

Infusion reactions

The most frequently observed ADRs in patients receiving ofatumumab in clinical trials were infusion-related reactions which occurred in 68% (348/511) of patients at any time during treatment. The majority of infusion reactions were Grade 1 or Grade 2 in severity. Eight percent of patients had Grade ≥ 3 infusion reactions at any time during treatment. Two percent of the infusion reactions led to discontinuation of treatment. There were no fatal infusion reactions (see section 4.4).

Infections

Of the 511 patients receiving ofatumumab in clinical trials, 300 patients (59%) experienced an infection. These included bacterial, viral, or fungal infections. One hundred and four (20%) of the

511 patients experienced \geq Grade 3 infections. Twenty-eight (5%) of the 511 patients experienced a fatal infection.

Neutropenia

Of the 511 patients receiving ofatumumab in clinical trials, 139 patients (27%) experienced an adverse event associated with a decreased neutrophil count; 118 (23%) of the 511 patients experienced \geq Grade 3 adverse events associated with a decreased neutrophil count. Forty-two (8%) experienced a serious adverse event associated with a decreased neutrophil count.

In the pivotal study for untreated CLL (OMB110911), prolonged neutropenia (defined as Grade 3 or 4 neutropenia not resolved between 24 and 42 days of last treatment) was reported in 41 patients (23 patients treated with ofatumumab and chlorambucil, 18 patients treated with chlorambucil alone). Nine patients treated with ofatumumab and chlorambucil, and three patients treated with chlorambucil alone had late onset neutropenia, defined as Grade 3 or 4 neutropenia starting at least 42 days after the last treatment.

Cardiovascular

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 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 milliseconds) were detected. None of the patients had an increase of QTc to >500 msec. A concentration dependent increase in QTc was not detected.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: monoclonal antibodies, ATC code: L01XC10

Mechanism of action

Ofatumumab is a human monoclonal antibody (IgG1) 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 tumours. The B cell tumours include CLL (generally associated with lower levels of CD20 expression) and non-Hodgkin's lymphomas (where $> 90\%$ tumours have high levels of CD20 expression). 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 and resultant lysis of tumour cells. Ofatumumab has been shown to induce appreciable lysis of cells with high expression levels of complement defence molecules. Ofatumumab has also been shown to induce cell lysis in both high and low CD20 expressing cells and in rituximab-

resistant cells. In addition, the binding of ofatumumab allows the recruitment of natural killer cells allowing the induction of cell death through antibody-dependent cell-mediated cytotoxicity.

Pharmacodynamic effects

Peripheral B cells 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% respectively for ofatumumab in combination with chlorambucil and 73% and 97% respectively 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 ofatumumab. Serum samples from more than 440 patients across the CLL clinical program were tested for anti-ofatumumab antibodies (either by enzyme-linked immunosorbent assay or electrochemiluminescence) during and after treatment periods ranging from 4 to 45 weeks. There was no formation of anti-ofatumumab antibodies in patients with CLL after treatment with ofatumumab.

Clinical efficacy and safety

The efficacy of Arzerra has 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 relapsed or refractory CLL.

Previously untreated CLL:

Study OMB110911 (randomised, open-label, parallel-arm, multicentre) 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), with active disease and indicated for treatment. Patients 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/m² orally on days 1-7 every 28 days) or chlorambucil alone (10 mg/m² 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), 27% patients were ≥75 years of age, 63% were male and 89% were white. Median cumulative illness rating score for geriatrics (CIRS-G) was 9 and 31% of patients had a CIRS-G >10. Median creatinine clearance (CrCl), assessed with the use of the Cockcroft-Gault formula, was 70 mL/min 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. 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 median progression-free survival (PFS) as assessed by a blinded Independent Review Committee (IRC) using the International Workshop for Chronic Lymphocytic Leukaemia (IWCLL) 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 IWCLL guidelines.

Arzerra in combination with chlorambucil showed a statistically significant, 71%, improvement in median PFS compared with chlorambucil alone (HR: 0.57; 95% CI: 0.45, 0.72) (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, unmutated IGHV, $\beta 2M > 3500 \mu\text{g/l}$, and ZAP-70 expression).

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

IRC-Assessed Primary and Subgroup Analyses of PFS, Months	Chlorambucil (N=226)	Arzerra and Chlorambucil (N=221)
Median, all patients	13.1	22.4
95% CI	(10.6, 13.8)	(19.0, 25.2)
Hazard Ratio	0.57 (0.45, 0.72)	
P Value	p<0.001	
Age ≥ 75 years (n = 119)	12.2	23.8
Co-morbidity 0 or 1 (n = 126)	10.9	23.0
Co-morbidity 2 or more (n=321)	13.3	21.9
ECOG 0, 1 (n=411)	13.3	23.0
ECOG 2 (n= 35)	7.9	20.9
CIRS-G ≤ 10 (n = 310)	13.1	21.7
CIRS-G > 10 (n= 137)	12.2	23.2
CrCl < 70 mL/min (n= 214)	10.9	23.1
CrCl ≥ 70 mL/min (n= 227)	14.5	22.1
17p or 11q deletion (n = 90)	7.9	13.6
IGHV mutated ($\leq 98\%$) (n= 177)	12.2	30.5
IGHV unmutated ($> 98\%$) (n= 227)	11.7	17.3
$\beta 2M \leq 3500 \mu\text{g/l}$ (n= 109)	13.8	25.5
$\beta 2M > 3500 \mu\text{g/l}$ (n= 322)	11.6	19.6
ZAP-70 positive (n= 161)	9.7	17.7
ZAP-70 intermediate (n= 160)	13.6	25.3
ZAP-70 negative (n= 100)	13.8	25.6
IGHV mutated & ZAP-70 negative (n=60)	10.5	NR
IGHV mutated & ZAP-70 positive (n=35)	7.9	27.2
IGHV unmutated & ZAP-70 negative (n=27)	16.7	16.2
IGHV unmutated & ZAP-70 positive (n=122)	11.2	16.2

Abbreviations: $\beta 2M$ = Beta-2-microglobulin, CI= confidence interval; CIRS-G= Cumulative Illness Rating Scale for Geriatrics, CLL= Chronic Lymphocytic Leukemia, CrCl= Creatinine Clearance, ECOG= Eastern Cooperative Oncology Group, IGHV= Immunoglobulin Heavy Chain Variable Region, IRC= Independent Review Committee, N= number, NR= Not Reached, PFS= Progression-free Survival, ZAP-70= Zeta-Chain-associated protein kinase 70.

Limited data is available in the heterogeneous non-white population and patients with an ECOG performance status of PS = 2.

Figure 1. Kaplan-Meier Estimates of IRC-Assessed PFS

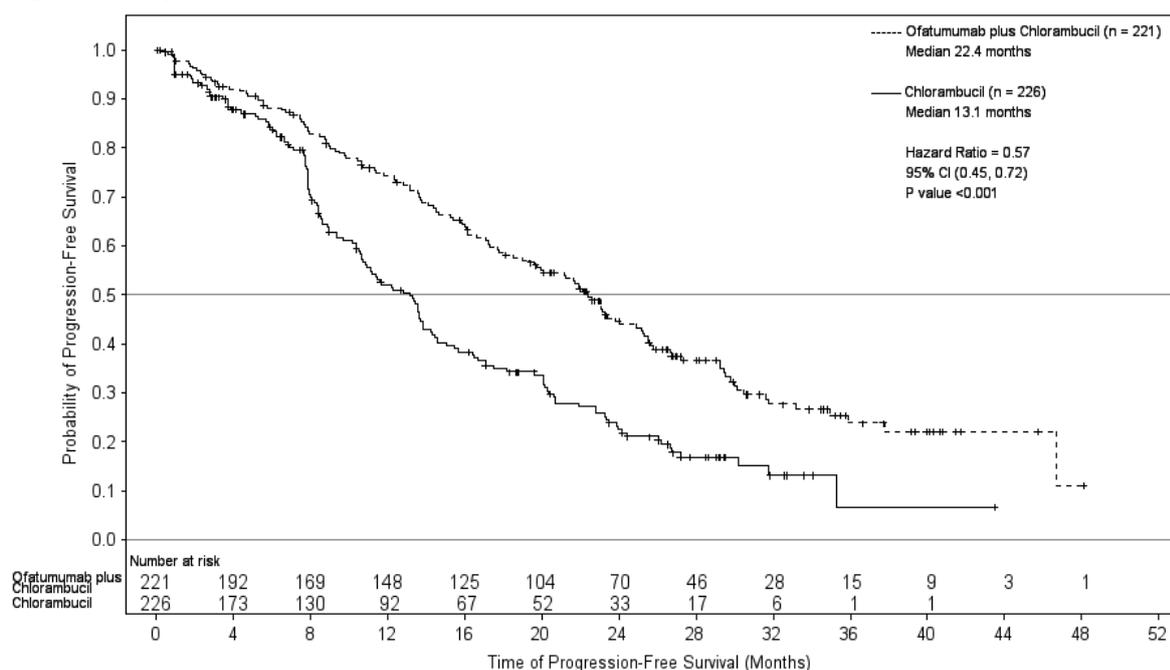


Table 2. Summary of Secondary Outcomes of Arzerra in Combination with Chlorambucil Compared with Chlorambucil in Previously Untreated CLL

IRC-Assessed Secondary Outcome	Chlorambucil (N=226)	Arzerra 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
CR with MRD Negativity (% of CR)	0	37
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 Leukemia, CR= Complete Response, IRC= Independent Review Committee, MRD= Minimal Residue Disease, N= number, ORR= Overall Response Rate

Study OMB115991 evaluated the efficacy of Arzerra in combination with bendamustine in 44 patients with previously untreated CLL considered inappropriate for fludarabine-based treatment. Patients 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 intravenous bendamustine 90 mg/m² on days 1 and 2 every 28 days. Patients received treatment for a minimum of 3 cycles and patients with stable disease or response after 3 cycles continued treatment for a further 3 cycles for a maximum of 6 cycles. The median number of cycles completed in patients was 6 (total Arzerra dose of 6300 mg).

The primary endpoint was ORR assessed by the investigator according to the 2008 IWCLL 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.

No data comparing Arzerra in combination with bendamustine or with chlorambucil versus a rituximab based regimen such as rituximab with chlorambucil is available. Thus, the benefit of such a new combination over a rituximab based regimen is unknown.

Refractory CLL:

Arzerra was administered as a monotherapy to 223 patients with refractory CLL (study Hx-CD20-406). 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 ORR 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 ofatumumab 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
Response rate 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	9.9, 18.6
Progression-free survival	
Months	4.6
95% CI	3.9, 6.3
Median duration of response	
Months	5.5
95% CI	3.7, 7.2
Median time to next CLL therapy	
Months	8.5
95% CI	7.2, 9.9
¹ The overall response was assessed by an Independent Response Committee using the 1996 NCI-WG 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 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 (≤4x10 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 <11 g/dl at baseline to >11 g/dl post baseline	12/49 (24)
Platelet counts ≤100x10 ⁹ /l at baseline to >50% increase or >100x10 ⁹ /l post baseline	19/50 (38)
Neutrophils <1x10 ⁹ /l at baseline to >1.5x10 ⁹ /l	1/17 (6)
^a Excludes patients 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, 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.	

Arzerra was also given to a group of patients (n=112) with bulky lymphadenopathy (defined as at least one lymph node > 5cm) who were also refractory to fludarabine. The ORR in this group was 43% (95.3% CI: 33, 53). The median progression-free survival was 5.5 months (95% CI: 4.6, 6.4) and the median overall survival was 17.4 months (95% CI: 15.0, 24.0). The response rate in patients with prior rituximab therapy was 38% (95% CI: 23, 61). These patients also experienced comparable clinical improvement, in terms of the efficacy endpoints and haematological parameters detailed above, to patients refractory to both fludarabine and alemtuzumab.

Additionally a group of patients (n=16) who were intolerant/ineligible for fludarabine treatment and/or intolerant to alemtuzumab treatment were treated with Arzerra. The overall response rate in this group was 63% (95.3% CI: 35, 85).

An open-label, two arm, randomised study (OMB114242) was conducted in patients with bulky fludarabine refractory CLL who had failed at least 2 prior therapies (n=122) comparing Arzerra monotherapy (n=79) to physicians' choice (PC) of therapy (n=43). There was no statistically significant difference in the primary endpoint of IRC assessed PFS (5.4 vs. 3.6 months, HR=0.79, p=0.27). The PFS in the monotherapy Arzerra arm was comparable to the results seen with Arzerra monotherapy in study Hx-CD20-406.

A dose-ranging study (Hx-CD20-402) 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 ofatumumab (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: 2,000 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) in responders. The duration of response was 16 weeks (CI: 13.3, 19) and the time to next CLL therapy was 52.4 weeks (CI: 36.9 – non-estimable).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Arzerra in all subsets of the paediatric population in Chronic Lymphocytic Leukaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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 2,000 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; 2,000 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 1,000 mg infusion on day 8, and the 1,000 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 V_{ss} 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 $t_{1/2}$ values were significantly larger after later infusions than after the initial infusion; during repeated weekly infusions, ofatumumab AUC and C_{max} values increased more than the expected accumulation based on first infusion data.

Across the studies in patients with relapsed or refractory CLL, the geometric mean values for CL and $t_{1/2}$ were 64 ml/h (range 4.3-1,122 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 $t_{1/2}$ 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 infusion.

Elderly (greater than or equal to 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

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.

5.3 Preclinical safety data

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 presumably 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 or foetal toxicity or teratogenicity. At day 100 of gestation, depletion of B-cells relating to the pharmacological activity of ofatumumab were observed in foetal cord blood and foetal splenic tissues. Pre- and post-natal development studies have not been performed. Post-natal recovery has therefore not been demonstrated.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Arginine
Sodium acetate (E262)
Sodium chloride
Polysorbate 80 (E433)
Edetate disodium (E386)

Hydrochloric acid (E507) (for pH-adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Vial

3 years.

Diluted infusion

Chemical and physical in-use stability has been demonstrated for 48 hours at ambient conditions (less than 25°C).

From a microbiological point of view, the medicinal 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 2-8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

Do not freeze.

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

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear Type I glass vial with a latex-free bromobutyl rubber stopper and aluminium over-seal, containing 5 ml of concentrate for solution for infusion.

Arzerra is available in packs of 3 vials.

6.6 Special precautions for disposal and other handling

Arzerra concentrate for solution for infusion does not contain a preservative; therefore dilution should be carried out under aseptic conditions. The diluted solution for infusion must be used within 24 hours of preparation. Any unused solution remaining after this time should be discarded.

- Before diluting Arzerra

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

Do not shake the ofatumumab vial for this inspection.

- How to dilute the solution for infusion

The Arzerra concentrate must be diluted in sodium chloride 9 mg/ml (0.9%) solution for injection prior to administration, using aseptic technique.

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

- withdraw and discard 15 ml from a 1,000 ml bag of sodium chloride 9 mg/ml (0.9%) solution for injection;
- withdraw 5 ml of ofatumumab from each of 3 vials and inject into the 1,000 ml bag;
- do not shake, mix diluted solution by gentle inversion.

• How to administer the diluted solution

Arzerra must not be administered as an intravenous push or bolus. Administer using an intravenous infusion pump.

The infusion must be completed within 24 hours after preparation. Discard any unused solution after this time.

Arzerra must not be mixed with, or administered as an infusion with other medicinal products or intravenous solutions. Flush line before and after ofatumumab administration with sodium chloride 9 mg/ml (0.9%) solution for injection to avoid this.

Previously untreated CLL:

For the first infusion, administer over 4.5 hours (see section 4.2), through a peripheral line or indwelling catheter, according to the schedule below:

Infusion 1: schedule

Time (minutes)	ml/hour
0 – 30	12
31 – 60	25
61 – 90	50
91 – 120	100
121 – 150	200
151 – 180	300
180 +	400

If the first infusion has been completed without a severe adverse reaction, the remaining infusions (2-13) of 1,000mg should be administered over 4 hours (see section 4.2), through a peripheral line or indwelling catheter, according to the schedule below:

Infusions 2 to 13: schedule

Time (minutes)	ml/hour
0 – 30	25
31 – 60	50
61 – 90	100
91 – 120	200
121 +	400

Refractory CLL:

For the first and second infusion, administer over 6.5 hours (see section 4.2), through a peripheral line or indwelling catheter, according to the schedule below:

Infusions 1 and 2: schedule

Time (minutes)	ml/hour
0 – 30	12
31 – 60	25
61 – 90	50
91 – 120	100
121 +	200

If the second infusion has been completed without a severe adverse reaction, the remaining infusions (3-12) should be administered over 4 hours (see section 4.2), through a peripheral line or indwelling catheter, according to the schedule below:

Infusions 3 to 12: schedule

Time (minutes)	ml/hour
0 – 30	25
31 – 60	50
61 – 90	100
91 – 120	200
121 +	400

If any adverse reactions are observed, infusion rates should be reduced (see section 4.2).

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/625/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19/04/2010

Date of last renewal: 16/01/2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.ema.europa.eu/>.

1. NAME OF THE MEDICINAL PRODUCT

Arzerra 1,000 mg concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of concentrate contains 20 mg of ofatumumab.

Each vial contains 1,000 mg of ofatumumab in 50 ml.

Ofatumumab is a human monoclonal antibody produced in a recombinant murine cell line (NS0).

Excipient(s) with known effect:

This medicinal product contains 34.8 mg sodium per 300 mg dose, 116 mg sodium per 1,000 mg dose and 232 mg sodium per 2,000 mg dose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to opalescent, colourless to pale yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Previously untreated chronic lymphocytic leukaemia (CLL):

Arzerra in combination with chlorambucil or bendamustine is indicated for the treatment of patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy.

See section 5.1 for further information.

Refractory CLL:

Arzerra is indicated for the treatment of CLL in patients who are refractory to fludarabine and alemtuzumab.

See section 5.1 for further information.

4.2 Posology and method of administration

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.

Monitoring

Patients should be closely monitored during administration of ofatumumab for the onset of infusion reactions, including cytokine release syndrome, particularly during the first infusion.

Pre-medication

Patients should always be pre-medicated 30 minutes to 2 hours prior to Arzerra infusion according to the following dosing schedules:

Previously untreated CLL:

- oral paracetamol (acetaminophen) 1,000 mg (or equivalent), plus

- oral or intravenous antihistamine (diphenhydramine 50 mg or cetirizine 10 mg or equivalent), plus
- intravenous corticosteroid (prednisolone 50 mg 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.

Refractory CLL:

- oral paracetamol (acetaminophen) 1,000 mg (or equivalent), plus
- oral or intravenous antihistamine (diphenhydramine 50 mg or cetirizine 10 mg or equivalent), plus
- intravenous corticosteroid (prednisolone 100 mg or equivalent).

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.

Prior to the ninth infusion (first monthly infusion), patients should receive the full dose of premedication agents described above. If the ninth infusion is completed without a severe ADR, the dose may be reduced to the equivalent of 50 mg prednisolone for subsequent infusions, at the discretion of the physician.

Posology

Previously untreated CLL:

The recommended dose and schedule is 300 mg on day 1 followed 1 week later by 1,000 mg on day 8 (cycle 1), followed by 1,000 mg on day 1 of subsequent cycles, for a minimum of 3 cycles, until best response or a maximum of 12 cycles (every 28 days).

Best response is a clinical response that did not improve with 3 additional cycles of treatment.

First infusion

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 section 6.6).

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/h and should be increased every 30 minutes up to a maximum of 400 ml/h (see section 6.6).

Refractory CLL:

The recommended dose is 300 mg for the first infusion and 2,000 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.

First and second infusions

The initial rate of the first and second infusion of Arzerra should be 12 ml/hour. During infusion, the rate should be increased every 30 minutes to a maximum of 200 ml/hour (see section 6.6).

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 increased every 30 minutes up to a maximum of 400 ml/hour (see section 6.6).

Dose modification and reinitiation of therapy for infusion related ADRs – in patients with previously untreated CLL and refractory CLL.

Interrupt infusion for infusion related ADRs of any severity. Treatment can be resumed at the discretion of the treating physician. The following infusion rate modifications can be used as a guide:

- 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 increasing the rate every 30 minutes).
- 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 increasing the rate every 30 minutes).

Paediatric population

Arzerra is not recommended for use in children below 18 years due to insufficient data on safety and/or efficacy.

Elderly

No substantial differences were seen in safety and efficacy related to age (see section 5.1). Based on available safety and efficacy data in the elderly, no dose adjustment is required (see section 5.2).

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 section 5.2).

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 section 5.2).

Method of administration

Arzerra is for intravenous infusion and must be diluted prior to administration. For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to ofatumumab or to any of the excipients listed in see section 6.1.

4.4 Special warnings and precautions for use

Infusion reactions

Intravenous ofatumumab has been associated with infusion reactions. These reactions may result in temporary interruption or withdrawal of treatment. Pre-medications attenuate infusion reactions but these may still occur, predominantly during the first infusion. Infusion reactions may include, but are not limited to, anaphylactoid events, bronchospasm, cardiac events (eg. 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. In rare cases, these reactions may lead to death. Even with pre-medication, severe reactions, including cytokine release syndrome, have been reported following use of ofatumumab. In cases of severe infusion reaction, the infusion of Arzerra must be interrupted immediately and symptomatic treatment instituted (see section 4.2).

Infusion reactions occur more frequently on the first day of 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 ofatumumab.

Tumour lysis syndrome

In patients with CLL, tumour lysis syndrome (TLS) may occur with use of ofatumumab. Risk factors for TLS include a high tumour burden, high concentrations of circulating cells ($\geq 25,000/\text{mm}^3$), 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.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) and death has been reported in CLL patients receiving cytotoxic pharmacotherapy, including ofatumumab. A diagnosis of PML should be considered in any Arzerra patient 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.

Immunisations

The safety of, and ability to generate a primary or anamnestic response to, immunisation with live attenuated or inactivated vaccines during treatment with ofatumumab 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 ofatumumab, until B cell counts are normalised. The risks and benefits of vaccinating patients during therapy with ofatumumab should be considered.

Hepatitis B

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 those 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.

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 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 milliseconds) 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 ofatumumab. Patients who present with abdominal pain, especially early in the course of ofatumumab therapy, should be evaluated and appropriate treatment instituted.

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 ofatumumab therapy and more frequently in patients who develop cytopenias.

Sodium content

This medicinal product contains 34.8 mg sodium per 300 mg dose, 116 mg sodium per 1,000 mg dose and 232 mg sodium per 2,000 mg dose. This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Although limited formal drug-drug interaction data exist for ofatumumab, there are no known clinically significant interactions with other medicinal products. 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 ofatumumab. Therefore, the concomitant use of these agents with ofatumumab should be avoided. If the coadministration is judged unavoidable, the risks and benefits of vaccinating patients during therapy with ofatumumab should be considered (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of ofatumumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Ofatumumab should not be administered to pregnant women unless the possible benefit to the mother outweighs the possible risk to the foetus.

Women of childbearing potential have to use effective contraception during and for 12 months after the last ofatumumab treatment.

Breast-feeding

It is unknown whether ofatumumab is excreted in human milk, however human IgG is secreted in human milk. The safe use of ofatumumab in humans during lactation has not been established. The excretion of ofatumumab in milk has not been studied in animals. Published data suggest that neonatal and infant consumption of breast milk does not result in substantial absorption of these maternal antibodies into circulation. A risk to newborns/infants cannot be excluded. Breastfeeding should be discontinued during treatment with ofatumumab and for 12 months following treatment.

Fertility

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

4.7 Effects on ability to drive and use machines

No studies on the effects of Arzerra on the ability to drive and use machines have been performed.

No detrimental effects on such activities are predicted from the pharmacology of ofatumumab. The clinical status of the patient and the ADR profile of ofatumumab should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of ofatumumab in CLL (previously untreated and relapsed or refractory) is based on data from 511 patients in clinical trials (see section 5.1). This includes 250 patients treated with ofatumumab alone (in patients with relapsed or refractory CLL) and 261 patients treated in combination with an alkylating agent (in patients with previously untreated CLL who are inappropriate for a fludarabine-based therapy).

The adverse event profile of ofatumumab in bulky fludarabine refractory CLL patients who had failed at least 2 prior therapies was consistent with the overall established safety profile from other CLL studies, as described in the tabulated list below.

Tabulated list of adverse reactions

Adverse reactions reported with ofatumumab in previously untreated and relapsed or refractory CLL patients, either alone or in combination with an alkylating agent, are listed below by MedDRA body system organ class and by frequency. Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very rare ($< 1/10,000$), not known (cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<u>MedDRA System Organ Class</u>	<u>Very common</u>	<u>Common</u>	<u>Uncommon</u>	<u>Rare</u>
Infections and Infestations	Lower respiratory tract infection, including pneumonia, upper respiratory tract infection	Sepsis, including neutropenic sepsis and septic shock, herpes virus infection, urinary tract infection		Hepatitis B infection and reactivation
Blood and lymphatic system disorders	Neutropenia, anaemia	Febrile neutropenia, thrombocytopenia, leukopenia	Agranulocytosis, coagulopathy, red cell aplasia, lymphopenia	
Immune system disorders		Anaphylactoid reactions*, hypersensitivity*	Anaphylactic shock*	
Metabolism and nutrition disorders			Tumour lysis syndrome	
Cardiac disorders		Tachycardia*	Bradycardia*	
Vascular disorders		Hypotension*, hypertension*		
Respiratory, thoracic and mediastinal disorders		Bronchospasm*, hypoxia*, dyspnoea*, chest discomfort*, pharyngolaryngeal pain*, cough*, nasal congestion*	Pulmonary oedema*	
Gastrointestinal disorders	Nausea*	Diarrhoea*	Small intestinal obstruction	
Skin and subcutaneous tissue disorders	Rash*	Urticaria*, pruritus*, flushing*		
Musculoskeletal and connective tissue disorders		Back pain*		
General disorders and administration site conditions	Pyrexia*	Cytokine release syndrome*, rigors*, chills*, hyperhidrosis*, fatigue*		

*These events are likely attributable to ofatumumab in the setting of an infusion reaction and typically occur after the start of infusion and within 24 hours after the completion of the infusion (see section 4.4).

Description of selected adverse reactions

Infusion reactions

The most frequently observed ADRs in patients receiving Arzerra in clinical trials were infusion-related reactions which occurred in 68% (348/511) of patients at any time during treatment. The majority of infusion reactions were Grade 1 or Grade 2 in severity. Eight percent of patients had Grade ≥ 3 infusion reactions at any time during treatment. Two percent of the infusion reactions led to discontinuation of treatment. There were no fatal infusion reactions(see section 4.4).

Infections

Of the 511 patients receiving ofatumumab in clinical trials, 300 patients (59%) experienced an

infection. These included bacterial, viral, or fungal infections. One-hundred and four (20%) of the 511 patients experienced \geq Grade 3 infections. Twenty-eight (5%) of the 511 patients experienced a fatal infection.

Neutropenia

Of the 511 patients receiving ofatumumab in clinical trials, 139 patients (27%) experienced an adverse event associated with a decreased neutrophil count; 118 (23%) of the 511 patients experienced \geq Grade 3 adverse events associated with a decreased neutrophil count. Forty-two (8%) experienced a serious adverse event associated with a decreased neutrophil count.

In the pivotal study for untreated CLL (OMB110911), prolonged neutropenia (defined as Grade 3 or 4 neutropenia not resolved between 24 and 42 days of last treatment) was reported in 41 patients (23 patients treated with ofatumumab and chlorambucil, 18 patients treated with chlorambucil alone). Nine patients treated with ofatumumab and chlorambucil, and three patients treated with chlorambucil alone had late onset neutropenia, defined as Grade 3 or 4 neutropenia starting at least 42 days after the last treatment.

Cardiovascular

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 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 milliseconds) were detected. None of the patients had an increase of QTc to >500 msec. A concentration dependent increase in QTc was not detected.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: monoclonal antibodies, ATC code: L01XC10

Mechanism of action

Ofatumumab is a human monoclonal antibody (IgG1) 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 tumours. The B cell tumours include CLL (generally associated with lower levels of CD20 expression) and non-Hodgkin's lymphomas (where $> 90\%$ tumours have high levels of CD20 expression). 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 and resultant lysis of tumour cells. Ofatumumab has been shown to induce appreciable lysis of cells with high expression levels of complement defence molecules. Ofatumumab has also been shown to induce cell lysis in both high and low CD20 expressing cells and in rituximab-

resistant cells. In addition, the binding of ofatumumab allows the recruitment of natural killer cells allowing the induction of cell death through antibody-dependent cell-mediated cytotoxicity.

Pharmacodynamic effects

Peripheral B cells 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% respectively for ofatumumab in combination with chlorambucil and 73% and 97% respectively 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 ofatumumab. Serum samples from more than 440 patients across the CLL clinical program were tested for anti-ofatumumab antibodies (either by enzyme-linked immunosorbent assay or electrochemiluminescence) during and after treatment periods ranging from 4 to 45 weeks. There was no formation of anti-ofatumumab antibodies in patients with CLL after treatment with Arzerra.

Clinical efficacy and safety

The efficacy of Arzerra has 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 relapsed or refractory CLL.

Previously untreated CLL:

Study OMB110911 (randomised, open-label, parallel-arm, multicentre) 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), with active disease and indicated for treatment. Patients 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/m² orally on days 1-7 every 28 days) or chlorambucil alone (10 mg/m² 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), 27% patients were ≥75 years of age, 63% were male and 89% were white. Median Cumulative Illness Rating Score for Geriatrics (CIRS-G) was 9, and 31% of patients had a CIRS-G >10. Median creatinine clearance (CrCl), assessed with the use of the Cockcroft-Gault formula, was 70 mL/min, 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. 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 median progression-free survival (PFS) as assessed by a blinded Independent Review Committee (IRC) using the International Workshop for Chronic Lymphocytic Leukaemia (IWCLL) 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 IWCLL guidelines.

Arzerra in combination with chlorambucil showed a statistically significant, 71%, improvement in median PFS compared with chlorambucil alone (HR: 0.57; 95% CI: 0.45, 0.72) (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, unmutated IGHV, $\beta 2M > 3500 \mu\text{g/l}$, and ZAP-70 expression).

Table 1. Summary of Median PFS with Arzerra in Combination with Chlorambucil Compared with Chlorambucil in Previously Untreated CLL

IRC-Assessed Primary and Subgroup Analyses of PFS, Months	Chlorambucil (N=226)	Arzerra and Chlorambucil (N=221)
Median, all patients	13.1	22.4
95% CI	(10.6, 13.8)	(19.0, 25.2)
Hazard Ratio	0.57 (0.45, 0.72)	
P Value	p<0.001	
Age ≥ 75 years (n = 119)	12.2	23.8
Co-morbidity 0 or 1 (n = 126)	10.9	23.0
Co-morbidity 2 or more (n= 321)	13.3	21.9
ECOG 0, 1 (n= 411)	13.3	23.0
ECOG 2 (n= 35)	7.9	20.9
CIRS-G ≤ 10 (n = 310)	13.1	21.7
CIRS-G > 10 (n= 137)	12.2	23.2
CrCl < 70 mL/min (n= 214)	10.9	23.1
CrCl ≥ 70 mL/min (n= 227)	14.5	22.1
17p or 11q deletion (n = 90)	7.9	13.6
IGHV mutated ($\leq 98\%$) (n= 177)	12.2	30.5
IGHV unmutated ($> 98\%$) (n= 227)	11.7	17.3
$\beta 2M \leq 3500 \mu\text{g/l}$ (n= 109)	13.8	25.5
$\beta 2M > 3500 \mu\text{g/l}$ (n= 322)	11.6	19.6
ZAP-70 positive (n= 161)	9.7	17.7
ZAP-70 intermediate (n= 160)	13.6	25.3
ZAP-70 negative (n= 100)	13.8	25.6
IGHV mutated & ZAP-70 negative (n=60)	10.5	NR
IGHV mutated & ZAP-70 positive (n=35)	7.9	27.2
IGHV unmutated & ZAP-70 negative (n=27)	16.7	16.2
IGHV unmutated & ZAP-70 positive (n=122)	11.2	16.2

Abbreviations: $\beta 2M$ = Beta-2-microglobulin, CI= confidence interval, CIRS-G= Cumulative Illness Rating Scale for Geriatrics, CLL= Chronic Lymphocytic Leukemia, CrCl= Creatinine Clearance, ECOG= Eastern Cooperative Oncology Group, IGHV= Immunoglobulin Heavy Chain Variable Region, IRC= Independent Review Committee, N= number, NR= Not Reached, PFS= Progression-free Survival, ZAP-70= Zeta-Chain-associated protein kinase 70.

Limited data is available in the heterogeneous non-white population and patients with an ECOG performance status of PS = 2.

Figure 1. Kaplan-Meier Estimates of IRC-Assessed PFS

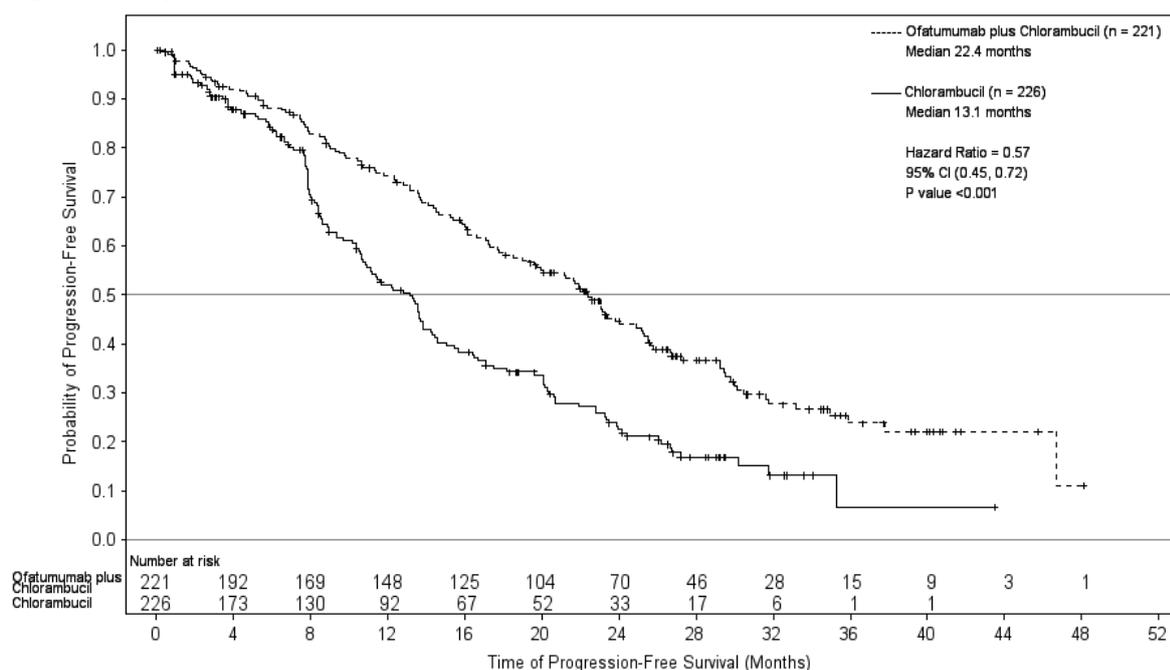


Table 2. Summary of Secondary Outcomes of Arzerra in Combination with Chlorambucil Compared with Chlorambucil in Previously Untreated CLL

IRC-Assessed Secondary Outcome	Chlorambucil (N=226)	Arzerra 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
CR with MRD Negativity (% of CR)	0	37
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 Leukemia, CR= Complete Response, IRC= Independent Review Committee, MRD= Minimal Residue Disease, N= number, ORR= Overall Response Rate

Study OMB115991 evaluated the efficacy of Arzerra in combination with bendamustine in 44 patients with previously untreated CLL considered inappropriate for fludarabine-based treatment. Patients 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 intravenous bendamustine 90 mg/m² at days 1 and 2 every 28 days. Patients received treatment for a minimum of 3 cycles and patients with stable disease or response after 3 cycles continued treatment for a further 3 cycles for a maximum of 6 cycles. The median number of cycles completed in patients was 6 (total dose of Arzerra was 6300 mg).

The primary endpoint was ORR assessed by the investigator according to the 2008 IWCLL 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.

No data comparing Arzerra in combination with bendamustine or with chlorambucil versus a rituximab based regimen such as rituximab with chlorambucil is available. Thus, the benefit of such a new combination over a rituximab based regimen is unknown.

Refractory CLL:

Arzerra was administered as a monotherapy to 223 patients with refractory CLL (study Hx-CD20-406). 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 ORR 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 ofatumumab 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 (%) 95.3% CI (%)	47 (49) 39, 60
Response rate in patients with prior rituximab therapy Responders, n (%) 95% CI (%)	25/56 (45) 31, 59
Response rate in patients with chromosomal abnormality 17p deletion Responders, n (%) 95% CI (%) 11q deletion Responders, n (%) 95% CI (%)	10/27 (37) 19, 58 15/32 (47) 29, 65
Median overall survival Months 95% CI	13.9 9.9, 18.6
Progression-free survival Months 95% CI	4.6 3.9, 6.3
Median duration of response Months 95% CI	5.5 3.7, 7.2
Median time to next CLL therapy Months 95% CI	8.5 7.2, 9.9
¹ The overall response was assessed by an Independent Response Committee using the 1996 NCI-WG 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 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 (≤4x10 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 <11 g/dl at baseline to >11 g/dl post baseline	12/49 (24)
Platelet counts ≤100x10 ⁹ /l at baseline to >50% increase or >100x10 ⁹ /l post baseline	19/50 (38)
Neutrophils <1x10 ⁹ /l at baseline to >1.5x10 ⁹ /l	1/17 (6)
^a Excludes patients 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, 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.	

Arzerra was also given to a group of patients (n=112) with bulky lymphadenopathy (defined as at least one lymph node > 5cm) who were also refractory to fludarabine. The ORR in this group was 43% (95.3% CI: 33, 53). The median progression-free survival was 5.5 months (95% CI: 4.6, 6.4) and the median overall survival was 17.4 months (95% CI: 15.0, 24.0). The response rate in patients with prior rituximab therapy was 38% (95% CI: 23, 61). These patients also experienced comparable clinical improvement, in terms of the efficacy endpoints and haematological parameters detailed above, to patients refractory to both fludarabine and alemtuzumab.

Additionally a group of patients (n=16) who were intolerant/ineligible for fludarabine treatment and/or intolerant to alemtuzumab treatment were treated with Arzerra. The overall response rate in this group was 63% (95.3% CI: 35, 85).

An open-label, two arm, randomised study (OMB114242) was conducted in patients with bulky fludarabine refractory CLL who had failed at least 2 prior therapies (n=122) comparing Arzerra monotherapy (n=79) to physicians' choice (PC) of therapy (n=43). There was no statistically significant difference in the primary endpoint of IRC assessed PFS (5.4 vs. 3.6 months, HR=0.79, p=0.27). The PFS in the monotherapy Arzerra arm was comparable to the results seen with Arzerra monotherapy in study Hx-CD20-406.

A dose-ranging study (Hx-CD20-402) 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 ofatumumab (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: 2,000 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) in responders. The duration of response was 16 weeks (CI: 13, 19) and the time to next CLL therapy was 52.4 weeks (CI: 36.9 – non-estimable).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Arzerra in all subsets of the paediatric population in Chronic Lymphocytic Leukaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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 2,000 mg), the geometric mean C_{max} value was 1,391 µg/ml and geometric mean $AUC_{(0-\infty)}$ value was 463,418 µg.h/ml; after the twelfth infusion (fourth monthly infusion; 2,000 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 1,000 mg infusion on day 8, and the 1,000 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 V_{ss} 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 $t_{1/2}$ values were significantly larger after later infusions than after the initial infusion; during repeated weekly infusions, ofatumumab AUC and C_{max} values increased more than the expected accumulation based on first infusion data.

Across the studies in patients with relapsed or refractory CLL, the geometric mean values for CL and $t_{1/2}$ were 64 ml/h (range 4.3-1,122 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 $t_{1/2}$ 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 infusion.

Elderly (greater than or equal to 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

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.

5.3 Preclinical safety data

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 presumably 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 or foetal toxicity or teratogenicity. At day 100 of gestation, depletion of B-cells relating to the pharmacological activity of ofatumumab were observed in foetal cord blood and foetal splenic tissues. Pre- and post-natal development studies have not been performed. Post-natal recovery has therefore not been demonstrated.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Arginine
Sodium acetate (E262)
Sodium chloride
Polysorbate 80 (E433)
Edetate disodium (E386)

Hydrochloric acid (E507) (for pH-adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Vial

3 years.

Diluted infusion

Chemical and physical in-use stability has been demonstrated for 48 hours at ambient conditions (less than 25°C).

From a microbiological point of view, the medicinal 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 2-8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

Do not freeze.

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

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear Type I glass vial with a latex-free bromobutyl rubber stopper and aluminium over-seal, containing 50 ml of concentrate for solution for infusion.

Arzerra is available in 1 vial packs.

6.6 Special precautions for disposal and other handling

Arzerra concentrate for solution for infusion does not contain a preservative; therefore dilution should be carried out under aseptic conditions. The diluted solution for infusion must be used within 24 hours of preparation. Any unused solution remaining after this time should be discarded.

- Before diluting Arzerra

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

Do not shake the ofatumumab vial for this inspection.

- How to dilute the solution for infusion

The Arzerra concentrate must be diluted in sodium chloride 9 mg/ml (0.9%) solution for injection prior to administration, using aseptic technique.

1,000 mg dose - Use 1 vial (50 ml total, 50 ml per vial):

- withdraw and discard 50 ml from a 1,000 ml bag of sodium chloride 9 mg/ml (0.9%) solution for injection;
- withdraw 50 ml of ofatumumab from the vial and inject into the 1,000 ml bag;
- do not shake, mix diluted solution by gentle inversion.

2,000 mg dose - Use 2 vials (100 ml total, 50 ml per vial):

- withdraw and discard 100 ml from a 1,000 ml bag of sodium chloride 9 mg/ml (0.9%) solution for injection;
- withdraw 50 ml of ofatumumab from each of 2 vials and inject into the 1,000 ml bag;
- do not shake, mix diluted solution by gentle inversion.

- How to administer the diluted solution

Arzerra must not be administered as an intravenous push or bolus. Administer using an intravenous infusion pump.

The infusion must be completed within 24 hours after preparation. Discard any unused solution after this time.

Arzerra must not be mixed with, or administered as an infusion with other medicinal products or intravenous solutions. Flush line before and after ofatumumab administration with sodium chloride 9 mg/ml (0.9%) solution for injection to avoid this.

Previously untreated CLL:

For the first infusion, administer over 4.5 hours (see section 4.2), through a peripheral line or indwelling catheter, according to the schedule below:

Infusion 1: schedule

Time (minutes)	ml/hour
0 – 30	12
31 – 60	25
61 – 90	50
91 – 120	100
121 – 150	200
151 – 180	300
180 +	400

If the first infusion has been completed without a severe adverse reaction, the remaining infusions (2-13) of 1,000mg should be administered over 4 hours (see section 4.2), through a peripheral line or indwelling catheter, according to the schedule below:

Infusions 2 to 13: schedule

Time (minutes)	ml/hour
0 – 30	25
31 – 60	50
61 – 90	100
91 – 120	200
121 +	400

Refractory CLL:

For the first and second infusion, administer over 6.5 hours (see section 4.2), through a peripheral line or indwelling catheter, according to the schedule below:

Infusions 1 and 2: schedule

Time (minutes)	ml/hour
0 – 30	12
31 – 60	25
61 – 90	50
91 – 120	100
121 +	200

If the second infusion has been completed without a severe adverse reaction, the remaining infusions (3-12) should be administered over 4 hours (see section 4.2), through a peripheral line or indwelling catheter, according to the schedule below:

Infusions 3 to 12: schedule

Time (minutes)	ml/hour
0 – 30	25
31 – 60	50
61 – 90	100
91 – 120	200
121 +	400

If any adverse reactions are observed, infusion rates should be reduced (see section 4.2).

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/625/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19/04/2010

Date of last renewal: 16/01/2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.ema.europa.eu/>.

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR
BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY
AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO
THE SAFE AND EFFECTIVE USE OF THE MEDICINAL
PRODUCT**

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Lonza Biologics plc
228 Bath Road
Slough, Berks SL1 4DX
United Kingdom

Lonza Biologics, Inc.
101 International Drive
Portsmouth, NH 03801-2815
United States

Name and address of the manufacturer responsible for batch release

Glaxo Operations UK Ltd.
Harmire Road
Barnard Castle
Durham, DL12 8DT
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.
- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
To further investigate the relation between chromosomal abnormalities and PFS and OS in CLL studies Hx-CD20-406, Hx-CD20-407, OMB110911 and OMB110913. Furthermore, the impact on ORR, PFS and OS of other biomarkers should be further investigated through expression of CD 38 in study Hx-CD20-406; expression of CD 38 and IGHV mutation status in study Hx-CD20-407 and expression of ZAP-70 and IGHV-mutation status in studies OMB110911 and OMB110913.	30/11/2015

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Arzerra 100 mg concentrate for solution for infusion
Ofatumumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains 20 mg ofatumumab.
Each vial contains 100 mg ofatumumab in 5 ml.

3. LIST OF EXCIPIENTS

Arginine, sodium acetate (E262), sodium chloride, polysorbate 80 (E433), edetate disodium (E386), hydrochloric acid (E507), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion.

100 mg/5 ml

3 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/625/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Arzerra 100 mg sterile concentrate
Ofatumumab
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg/5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Arzerra 1,000 mg concentrate for solution for infusion
Ofatumumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains 20 mg ofatumumab.
Each vial contains 1,000 mg ofatumumab in 50 ml.

3. LIST OF EXCIPIENTS

Arginine, sodium acetate (E262), sodium chloride, polysorbate 80 (E433), edetate disodium (E386), hydrochloric acid (E507), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion.

1,000 mg/50 ml

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/625/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Arzerra 1,000 mg sterile concentrate
Ofatumumab
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1,000 mg/50 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Arzerra 100 mg concentrate for solution for infusion Arzerra 1,000 mg concentrate for solution for infusion

Ofatumumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Arzerra is and what it is used for
2. What you need to know before you use Arzerra
3. How to use Arzerra
4. Possible side effects
5. How to store Arzerra
6. Contents of the pack and other information

1. What Arzerra is and what it is used for

Arzerra 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 which 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 recognises a substance on the surface of lymphocytes and causes the lymphocyte to die.

2. What you need to know before you use Arzerra

Do not use Arzerra:

- **if you are allergic** (*hypersensitive*) to ofatumumab or to any of the other ingredients of Arzerra (*listed in Section 6 'Contents of the pack and other information'*)
- ➔ **Check with your doctor** if you think this may apply to you.

Warnings and precautions

Talk to your doctor or nurse before using Arzerra:

- if you have had **heart problems**,
 - if you have **lung disease**,
- ➔ **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.
- ➔ **Your doctor may test the amount of salts in your blood**, such as magnesium and potassium (*electrolytes*) before and during your treatment with Arzerra. Your doctor may treat you for salt imbalances.

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.

Hepatitis B

You should be tested for Hepatitis B (a liver disease) before starting Arzerra treatment. If you have had Hepatitis B, Arzerra could cause your hepatitis B to become active again. Your doctor may treat you with a suitable anti-viral medicine to help prevent this.

If you have or have had Hepatitis B, **tell your doctor before you are given Arzerra.**

Infusion reactions

Medicines of this type (*monoclonal antibodies*) can cause infusion reactions when they are injected into the body. You will be given medicines such as anti-histamines, steroids or pain relievers to help reduce any reaction. See also *Section 4, 'Possible side effects'*.

If you think you have had a similar reaction before, **tell your doctor before you are given Arzerra.**

Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML), a serious and life threatening brain condition, has been reported with medicines like Arzerra. **Tell your doctor immediately** if you have memory loss, trouble 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.

Children and adolescents

It is not known if Arzerra works in children and adolescents. Therefore Arzerra is not recommended for use in children and adolescents.

Other medicines and Arzerra

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. This includes herbal medicines and other medicines you can obtain without a prescription.

Pregnancy, breast-feeding and fertility

Arzerra is not usually recommended for use during pregnancy. There is no 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 up 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 12 months** after your last treatment.
- **If you do become pregnant during treatment with Arzerra**, tell your doctor

It is not known whether the ingredients in Arzerra pass into human milk. **Breast-feeding is not recommended** during treatment with Arzerra and **for 12 months** after the last time you were treated with Arzerra.

Driving and using machines

Arzerra is unlikely to affect your ability to drive or use machines

Arzerra contains sodium

Arzerra contains 34.8 mg sodium in each 300 mg dose, 116 mg sodium in each 1,000 mg dose and 232 mg sodium in each 2,000 mg dose. You need to take this into account if you are on a controlled sodium diet.

3. How to use Arzerra

If you have any questions on the use of Arzerra, ask the doctor who is giving you the infusion.

The usual dose

The usual dose of Arzerra for the first infusion is 300 mg. This dose will be increased, usually to 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.

If you have not been previously treated for CLL you will have a maximum of 13 infusions. You will be given an infusion followed by a second infusion 7 days later. The remaining infusions will then be given once a month for up to 11 months.

If you have been previously treated for CLL you will usually have a course of 12 infusions. You will be given an infusion once a week for eight weeks. This is followed by a four- to five-week gap. The remaining infusions will then be given once a month for four months.

Medicines given before each infusion

Before each infusion of Arzerra, you will be given **pre-medication** - medicines which help to reduce any 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.

4. Possible side effects

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

Infusion reactions

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

Very common symptoms of an infusion reaction (may affect more than 1 in 10 people):

- feeling sick (*nausea*)
- high temperature
- skin rash

Common symptoms of an infusion reaction (may affect up to 1 in 10 people):

- allergic reactions, sometimes severe with swelling of face or mouth causing difficulty in breathing (*anaphylactoid reactions*)
- 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.

Uncommon symptoms of an infusion reaction (may affect up to 1 in 100 people):

- fluid in the lungs (*pulmonary oedema*) causing breathlessness
- slow heart beat.

Tell your doctor or a nurse immediately if you get any of these symptoms.

Very common side effects

These may affect **more than 1 in 10 people**:

- infections of the lungs or airways (*respiratory tract*) such as pneumonia
- infections of the ear, nose or throat.

Very common side effects that may show up in your blood tests:

- low levels of white blood cells (*neutropenia*)
- low levels of red blood cells (*anaemia*).

Common side effects

These may affect **up to 1 in 10 people**:

- a fever due to an infection and low levels of white blood cells
- blood infections
- urinary tract infections
- shingles
- cold sores.

Common side effects that may show up in your blood tests:

- low levels of platelets in the blood (cells that help blood to clot).

Uncommon side effects

These may affect **up to 1 in 100 people**:

- blockage in the gut (*intestine*), which may feel like stomach pain.
- ➔ If you have persistent stomach pain, **see your doctor as soon as possible.**
- increase in potassium, phosphate and uric acid in the blood that can cause kidney problems (*tumour lysis syndrome*)

The symptoms of this condition include:

- producing less urine than normal
- muscle spasms.
- ➔ If you notice these symptoms, **contact your doctor as soon as possible.**

Uncommon side effects that may show up in your blood tests:

- problems with blood clotting
- the bone marrow failing to produce enough red or white blood cells

Rare side effects

These may affect **up to 1 in 1000 people**:

- Infection or reactivation of hepatitis B virus

If you get side effects

- ➔ **Tell your doctor or nurse** if any of the side effects you experience become severe or troublesome, or if you notice any side effects not listed in this leaflet.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Arzerra

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date shown 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.

6. Contents of the pack and other information

What Arzerra contains

- The active substance is ofatumumab. One ml of concentrate contains 20 mg of ofatumumab.
- The other ingredients are arginine, sodium acetate (E262), sodium chloride, polysorbate 80 (E433), edetate disodium (E386), hydrochloric acid (E507) (for pH-adjustment), water for injections..

What Arzerra looks like and contents of the pack

Arzerra is a colourless to pale yellow concentrate for solution for infusion.

Arzerra 100 mg is available in a pack containing 3 vials. Each glass vial is closed with a latex-free rubber stopper and aluminium over-seal, and contains 5 ml of concentrate (100 mg of ofatumumab).

Arzerra 1,000 mg is available in a pack containing 1 vial. Each glass vial is closed with a latex-free rubber stopper and aluminium over-seal, and contains 50 ml of concentrate (1,000 mg of ofatumumab).

Marketing Authorisation Holder

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Manufacturer

Glaxo Operations UK Limited (Trading as Glaxo Wellcome Operations), Harmire Road, Barnard Castle, County Durham, DL12 8DT, United Kingdom.

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This leaflet was last approved in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.ema.europa.eu/>.

The following information is intended for medical or healthcare professionals only:

1) Before diluting Arzerra

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

Do not shake the ofatumumab vial for this inspection.

2) How to dilute the solution for infusion

The Arzerra concentrate must be diluted in sodium chloride 9 mg/ml (0.9%) solution for injection prior to administration, using aseptic technique.

300 mg dose - Use 3 x 100 mg/5 ml vials (15 ml total, 5 ml per vial):

- withdraw and discard 15 ml from a 1,000 ml bag of sodium chloride 9 mg/ml (0.9%) solution for injection
- withdraw 5 ml of ofatumumab from each of 3 x 100 mg vials and inject into the 1,000 ml bag
- **do not shake**, mix diluted solution **by gentle inversion**.

1,000 mg dose – Use 1 x 1,000 mg/50 ml vial (50 ml total, 50 ml per vial):

- withdraw and discard 50 ml from a 1,000 ml bag of sodium chloride 9 mg/ml (0.9%) solution for injection
- withdraw 50 ml of ofatumumab from the 1,000 mg vial and inject into the 1,000 ml bag
- **do not shake**, mix diluted solution **by gentle inversion**.

2,000 mg dose – Use 2 x 1,000 mg/50 ml vials (100 ml total, 50 ml per vial):

- withdraw and discard 100 ml from a 1,000 ml bag of sodium chloride 9 mg/ml (0.9%) solution for injection
- withdraw 50 ml of ofatumumab from each of 2 x 1,000 mg vials and inject into the 1,000 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 intravenous push or bolus. Administer using an intravenous infusion pump.

The infusion must be completed within 24 hours after preparation. Discard any unused solution after this time.

Arzerra must not be mixed with, or administered as an infusion with other medicinal products or intravenous solutions. Flush line before and after ofatumumab administration with sodium chloride 9 mg/ml (0.9%) solution for injection to avoid this.

Previously untreated CLL:

For the first infusion, administer over 4.5 hours (see section 4.2 of the SmPC), through a peripheral line or indwelling catheter, according to the schedule below:

Infusion 1: schedule

Time (minutes)	ml/hour
0 – 30	12
31 – 60	25
61 – 90	50
91 – 120	100
121 – 150	200
151 – 180	300
180 +	400

If the first infusion has been completed without a severe adverse reaction, the remaining infusions (2-13) of 1,000mg should be administered over 4 hours (see section 4.2 of the SmPC), through a peripheral line or indwelling catheter, according to the schedule below:

Infusions 2 to 13: schedule

Time (minutes)	ml/hour
0 – 30	25
31 – 60	50
61 – 90	100
91 – 120	200
121 +	400

Refractory CLL:

For the first and second infusion, administer over 6.5 hours (see section 4.2 of the SmPC), through a peripheral line or indwelling catheter, according to the schedule below:

Infusions 1 and 2: schedule

Time (minutes)	ml/hour
0 – 30	12
31 – 60	25
61 – 90	50
91 – 120	100
121 +	200

If the second infusion has been completed without a severe adverse reaction, the remaining infusions (3-12) should be administered over 4 hours (see section 4.2 of the SmPC), through a peripheral line or indwelling catheter, according to the schedule below:

Infusions 3 to 12: schedule

Time (minutes)	ml/hour
0 – 30	25
31 – 60	50
61 – 90	100
91 – 120	200
121 +	400

If any adverse reactions are observed, infusion rates should be reduced, according to section 4.2 of the Summary of Product Characteristics.

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