Arzerra® 100 mg
Arzerra® 1,000 mg

1. NAME OF THE MEDICINAL PRODUCT

Arzerra® 100 mg

Arzerra® 1,000 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of concentrate contains 20 mg of ofatumumab.
Each vial contains 100 mg of ofatumumab in 5 ml, or 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 leukemia (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 pre-medication 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 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 (e.g., myocardial ischaemia/infarction, bradycardia), chills/rigors, cough, cytokine release syndrome, diarrhoea, dyspnoea, fatigue, flushing, hypertension, hypotension, nausea, pain, pulmonary oedema, pruritus, pyrexia, rash, and urticaria. 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 (≥ 25,000/mm^3), hypovolaemia, renal insufficiency, elevated pre-treatment uric acid levels and elevated lactate dehydrogenase levels. Management of TLS includes correction of electrolyte abnormalities, monitoring of renal function, maintenance of fluid balance and supportive care.

Progressive multifocal leukoencephalopathy
Progressive multifocal leukoencephalopathy (PML) and death have 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 have 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, have 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).

Tabulated list of adverse reactions
Adverse reactions reported with ofatumumab, either alone or in combination with an alkylating agent, are listed below by MedDRA body system organ class and by frequency.
Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 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.

MedDRA System Organ Class	Very common	Common	Uncommon	Rare
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 ≥ 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 ≥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.

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of Arzerra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Infusion-related Cardiac Events: Cardiac arrest.
Mucocutaneous Reactions: Stevens-Johnson syndrome, porphyria cutanea tarda.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: monoclonal antibodies, ATC code: L01XC10

This medicinal product has been authorised under a so-called 'conditional approval' scheme.
This means that further evidence on this medicinal product is awaited. The European Medicines Agency (EMA) will review new information on the medicinal product every year and this SmPC will be updated as necessary.

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/m^2 orally on days 1-7 every 28 days) or chlorambucil alone (10 mg/m^2 orally on days 1-7 every 28 days). Patients received treatment for a minimum of 3 months until best response or up to a maximum of 12 cycles. The median age was 69 years (range: 35 to 92 years), 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 Cockroft-Gault formula, was 88 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 Leukemia (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, β2M >3500 µg/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 (≤98%) (n = 177)	12.2	30.5
IGHV unmutated (>98%) (n =227)	11.7	17.3
β2M ≤3500 µg/l (n = 109)	13.8	25.5
β2M >3500 µg/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: β2M= 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 are available in the hetorgenous non-white population and patients with an ECOG performance status of PS = 2.

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

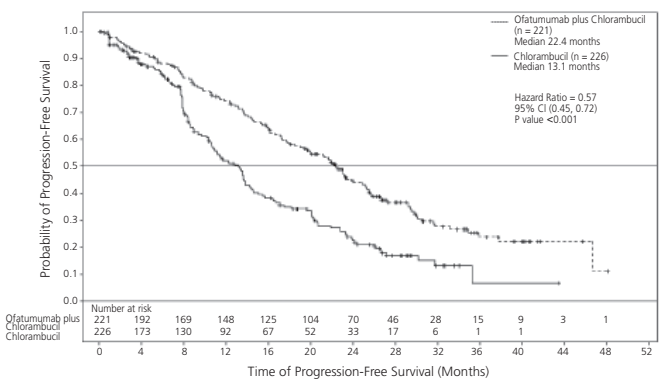

Table 2. Summary of Secondary Outcomes of Arzerra in Combination with Chlorambucil Compared with Chlorambucil in Previously Untreated CLL

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 are 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 (≤4x10⁹/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 ≤100x10⁹/l at baseline to >50% increase or >100x10⁹/l post baseline	19/50 (38)
Neutrophils <1x10⁹/l at baseline to >1.5x10⁹/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 were 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 > 5 cm) 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).
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 Leukemia (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 Vss values ranging from 1.7 to 8.1 l across studies, dose levels, and infusion number.

Biotransformation

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

Elimination

Ofatumumab is eliminated in two ways: a target-independent route like other IgG molecules and a target-mediated route which is related to binding to B cells. There was a rapid and sustained depletion of $CD20^+$ B cells after the first ofatumumab infusion, leaving a reduced number of $CD20^+$ cells available for the antibody to bind at subsequent infusions. As a result, ofatumumab clearance values were lower and $t_{½}$ values were significantly larger after later infusions than after the initial infusion; during repeated weekly infusions, ofatumumab AUC and 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 $t_{½}$ 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 $t_{½}$ values were 15.4 ml/h (range 4.1-146 ml/h) and 18.5 days (range 2.7-82.6 days) after the fourth 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)
Disodium Edetate (E386)
Hydrochloric acid (E507) (for pH-adjustment to pH 5.5)
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

The expiry date of the product is indicated on the label and packaging.

Diluted infusion

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 or 50 ml of concentrate for solution for infusion.

Arzerra 100 mg is available in a pack of 3 vials.
Arzerra 1000 mg is available in a 1 vial pack.

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 discolouration prior to dilution. Ofatumumab should be a colourless to pale yellow solution. Do not use the Arzerra concentrate if there is discolouration.

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.

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 1,000 mg 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. MANUFACTURER

Glaxo Operations (UK) Limited
Barnard Castle,
UK.

8. REGISTRATION HOLDER

Novartis Israel Ltd.,
36 Shacham St., Petach-Tikva.

9. LICENSE NUMBERS

Arzerra 100 mg 148-72-33501
Arzerra 1,000 mg 148-71-33508

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in January 2015