ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Arzerra 100 mg concentrate for solution for infusion
Arzerra 1000 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of concentrate contains 20 mg of ofatumumab.

Arzerra 100 mg concentrate for solution for infusion

Each vial contains 100 mg of ofatumumab in 5 ml.

Arzerra 1000 mg concentrate for solution for infusion

Each vial contains 1000 mg of ofatumumab in 50 ml.

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

Excipient with known effect

This medicinal product contains 34.8 mg sodium per 300 mg dose, 116 mg sodium per 1000 mg dose and 232 mg sodium per 2000 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 adult 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.

Relapsed CLL

Arzerra is indicated in combination with fludarabine and cyclophosphamide for the treatment of adult patients with relapsed CLL.

See section 5.1 for further information.

Refractory CLL

Arzerra is indicated for the treatment of CLL in adult 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-related reactions, including cytokine release syndrome, particularly during the first infusion.

Pre-medication

Patients should receive the following pre-medication medicinal products 30 minutes to 2 hours prior to each Arzerra infusion according to the following dosing schedules:

Premedication schedule for Arzerra

	Previously untreated CLL or relapsed CLL		**Refractory CLL**			
Infusion number	1 and 2	3 to n*	1 and 2	3 to 8	9	10 to 12
Intravenous corticosteroid (prednisolone or equivalent)	50 mg	0 to 50 mg**	100 mg	0 to 100 mg**	100 mg	50 to 100 mg***
Oral paracetamol (acetaminophen)	1000 mg					
Oral or intravenous antihistamine	Diphenhydramine 50 mg or cetirizine 10 mg (or equivalent)					
*Up to 13 infusions in previously untreated CLL; up to 7 infusions in relapsed CLL **Corticosteroid may be either reduced or omitted for subsequent infusions at the discretion of the physician, if a severe infusion-related adverse drug reaction (ADR) did not occur with the preceding infusion(s). ***Corticosteroid may be reduced for subsequent infusions at the discretion of the physician, if a severe infusion-related ADR did not occur with the preceding infusion(s).						

Posology

Previously untreated CLL
For previously untreated CLL, the recommended dosage and schedule is:

- Cycle 1: 300 mg on day 1 followed 1 week later by 1000 mg on day 8
- Subsequent cycles (until best response or a maximum of 12 cycles): 1000 mg on day 1 every 28 days.

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

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

Relapsed CLL
For relapsed CLL, the recommended dosage and schedule is:
- Cycle 1: 300 mg on day 1 followed 1 week later by 1000 mg on day 8
- Subsequent cycles (up to a maximum of 6 cycles in total): 1000 mg on day 1 every 28 days.

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

Previously untreated CLL and relapsed CLL
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). If an infusion-related ADR is observed during infusion, see below section "Dose modification and reinitiation of therapy after infusion-related ADRs".

Subsequent infusions
If the preceding infusion(s) has (have) 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). If an infusion-related ADR is observed during infusion, see below section "Dose modification and reinitiation of therapy after infusion-related ADRs".

Dose modification and reinitiation of therapy after infusion-related ADRs
In the event of a mild or moderate ADR, the infusion should be interrupted and restarted at half of the infusion rate at the time of interruption once the patient's condition is stable. If the infusion rate had not been increased from the starting rate of 12 ml/hour prior to 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, to physician discretion and to patient tolerance (not to exceed doubling the rate every 30 minutes).

In the event 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, to physician discretion and to patient tolerance (not to exceed increasing the rate every 30 minutes).

Arzerra should be permanently discontinued in patients who develop an anaphylactic reaction to the medicinal product.

Refractory CLL
The recommended dose and schedule is 12 doses administered as follows:
- 300 mg on day 1 followed 1 week later by
- 2000 mg weekly for 7 doses (infusions 2 to 8) followed 4-5 weeks later by
- 2000 mg every 28 days for 4 doses (infusions 9 to 12)

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). If an infusion-related ADR is observed during an infusion, see below section "Dose modification and reinitiation of therapy after infusion-related ADRs".

Subsequent infusions
If the preceding infusion(s) has (have) been completed without severe infusion-related ADRs, the subsequent 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). If an infusion-related ADR is observed during an infusion, see below section "Dose modification and reinitiation of therapy after infusion-related ADRs".

Dose modification and reinitiation of therapy after infusion-related ADRs
In the event of a mild or moderate ADR, the infusion should be interrupted and restarted at half of the infusion rate at the time of interruption, once the patient's condition is stable. If the infusion rate had not been increased from the starting rate of 12 ml/hour prior to 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, to physician discretion and to patient tolerance (not to exceed doubling the rate every 30 minutes).

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

Arzerra should be permanently discontinued in patients who develop an anaphylactic reaction to the medicinal product.

Special populations
Paediatric population
The safety and efficacy of Arzerra in children aged below 18 years have not been established. Arzerra is therefore not recommended for use in this patient population.

Elderly
No substantial differences related to age were seen in safety and efficacy (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-related reactions

Intravenous ofatumumab has been associated with infusion-related reactions. These reactions may result in temporary interruption or withdrawal of treatment. Pre-medication attenuates infusion-related reactions but these may still occur, predominantly during the first infusion. Infusion-related 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 the event of a severe infusion-related reaction, the infusion of Arzerra must be interrupted immediately and symptomatic treatment instituted (see section 4.2).

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

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

Tumour lysis syndrome

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

Progressive multifocal leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML) resulting in 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 neurological 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 Arzerra therapy 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 medicinal products 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 Arzerra 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 1000 mg dose and 232 mg sodium per 2000 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. No clinically relevant pharmacokinetic interactions were observed between ofatumumab and fludarabine, cyclophosphamide,bendamustine, 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

Women of child-bearing potential

Since ofatumumab may cause foetal B-cell depletion, effective contraception (methods that result in less than 1% pregnancy rates) has to be used during Arzerra therapy and for 12 months after the last Arzerra dose. After this period, planning of a pregnancy in relation to the underlying disease, should be evaluated by the treating physician.

Pregnancy

Ofatumumab may cause foetal B-cell depletion based on findings from animal studies and on its mechanism of action (see section 5.1).

There are no adequate and well-controlled studies in pregnant women to inform a product-associated risk. No teratogenicity or maternal toxicity were observed in an animal reproduction study with administration of ofatumumab to pregnant monkeys (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.

Administration of live vaccines to neonates and infants exposed to ofatumumab *in utero* should be avoided until B-cell recovery occurs (see sections 4.4 and 4.5).

Breast-feeding

It is unknown whether Arzerra 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. Breast-feeding should be discontinued during treatment with Arzerra 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 is based on data from 1,168 patients in clinical trials in CLL (see section 5.1). This includes 643 patients treated with ofatumumab as monotherapy (in patients with relapsed or refractory CLL) and 525 patients treated with ofatumumab in combination with chemotherapy (chlorambucil or bendamustine or fludarabine and cyclophosphamide).

Tabulated list of adverse reactions

Adverse reactions reported in patients treated with ofatumumab as monotherapy and with ofatumumab in combination with chemotherapy, are listed below by MedDRA body system organ class and by frequency, using the following convention: 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, adverse reactions are ranked in order of decreasing seriousness.

MedDRA System Organ Class	Very common	Common	Uncommon	
Infections and Infestations	Lower respiratory tract infection (including pneumonia), upper respiratory tract infection	Sepsis (including neutropenic sepsis and septic shock) herpes viral infection, urinary tract infection	Hepatitis B infection and reactivation, progressive multifocal leukoencephalopathy	
Blood and lymphatic system disorders	Neutropenia, anaemia	Febrile neutropenia, thrombocytopenia, leukopenia	Agranulocytosis, coagulopathy, red cell aplasia, lymphopenia	
Immune system disorders		Hypersensitivity*	Anaphylactic reactions (including anaphylactic shock)*	
Nervous system disorders		Headache*		
Metabolism and nutrition disorders			Tumour lysis syndrome	
Cardiac disorders		Tachycardia*	Bradycardia*	
Vascular disorders		Hypotension*, hypertension*		
Respiratory, thoracic and mediastinal disorders	Dyspnoea*, cough*	Bronchospasm*, chest discomfort*, oropharyngeal pain*, nasal congestion*	Pulmonary oedema*, hypoxia*	
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*, fatigue*	Cytokine release syndrome*, chills (including rigors)*, hyperhidrosis*		
Injury, poisoning and procedural complications		Infusion-related reaction*		
*These events are likely attributable to ofatumumab in the setting of an infusion-related 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-related reactions
Of the 1,168 patients receiving ofatumumab in clinical trials for CLL, the most frequently observed ADRs were infusion-related reactions which occurred in 711 patients (61%) at any time during treatment. The majority of infusion-related reactions were Grade 1 or Grade 2 in severity. Seven percent of patients had ≥Grade 3 infusion-related reactions at any time during treatment. Two percent of the infusion-related reactions led to discontinuation of treatment. There were no fatal infusion-related reactions (see section 4.4).

Infections
Of the 1,168 patients receiving ofatumumab in clinical trials for CLL, 682 patients (58%) experienced an infection. These included bacterial, viral and fungal infections. 268 (23%) of the 1,168 patients experienced ≥Grade 3 infections. 65 (6%) of the 1,168 patients experienced a fatal infection.

Neutropenia
Of the 1,168 patients receiving ofatumumab in clinical trials, 420 patients (36%) experienced an adverse event associated with a decreased neutrophil count; 129 (11%) experienced a serious adverse event associated with a decreased neutrophil count.

In the pivotal study for untreated CLL (OMB110911; ofatumumab plus chlorambucil 217 patients, chlorambucil alone 227 patients), prolonged neutropenia (defined as Grade 3 or 4 neutropenia not resolved between 24 and 42 days after last dose of study treatment) was reported in 41 patients (9%) (23 patients [11%] treated with ofatumumab and chlorambucil, 18 patients [8%] treated with chlorambucil alone). Nine patients (4%) 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). In the pivotal study (OMB110913, ofatumumab plus fludarabine and cyclophosphamide 181 patients; fludarabine and cyclophosphamide 178 patients) in relapsed CLL patients, prolonged neutropenia was reported in 38 (11%) patients (18 patients [10%] treated with ofatumumab in combination with fludarabine and cyclophosphamide compared to 20 patients [11%] in the fludarabine and cyclophosphamide arm). Thirteen (7%) patients treated with ofatumumab in combination with fludarabine and cyclophosphamide, and 5 (3%) patients treated with fludarabine and cyclophosphamide had late-onset neutropenia.

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: antineoplasic agents, 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% of 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-cell counts decreased after the first ofatumumab infusion in patients with haematological malignancies. In all patients with CLL, ofatumumab induces rapid and profound B-cell depletion, whether given as a single agent or in combination.

When ofatumumab was administered as single agent 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.

When ofatumumab was administered in combination with chlorambucil 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%. At 6 months after the last dose, the median reductions in B-cell counts were >99%..

When ofatumumab was administered in combination with fludarabine and cyclophosphamide in patients with relapsed CLL, the median decrease from baseline was 60% after the first infusion and complete depletion (100%) was reached after 4 cycles.

Immunogenicity

There is a potential for immunogenicity with therapeutic proteins such as ofatumumab. Serum samples from more than 1,000 patients across the CLL clinical programme were tested for anti-ofatumumab antibodies during and after treatment periods ranging from 8 weeks to 2 years. Formation of anti-ofatumumab antibodies was observed for less than 0.5% of patients with CLL after treatment with ofatumumab.

Clinical efficacy and safety

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 1000 mg on day 8; subsequent cycles: 1000 mg on day 1 every 28 days) in combination with chlorambucil (10 mg/m^2 orally on days 1-7 every 28 days) or chlorambucil alone (10 mg/m^2 orally on days 1-7 every 28 days). Patients received treatment for a minimum of 3 months until best response or up to a maximum of 12 cycles. The median age was 69 years (range: 35 to 92 years), 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 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 6300 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 and 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 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 leukaemia, 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 heterogeneous non-white population and in patients with an ECOG performance status of PS = 2.

Figure 1 Kaplan-Meier estimates of IRC-assessed PFS in previously untreated CLL

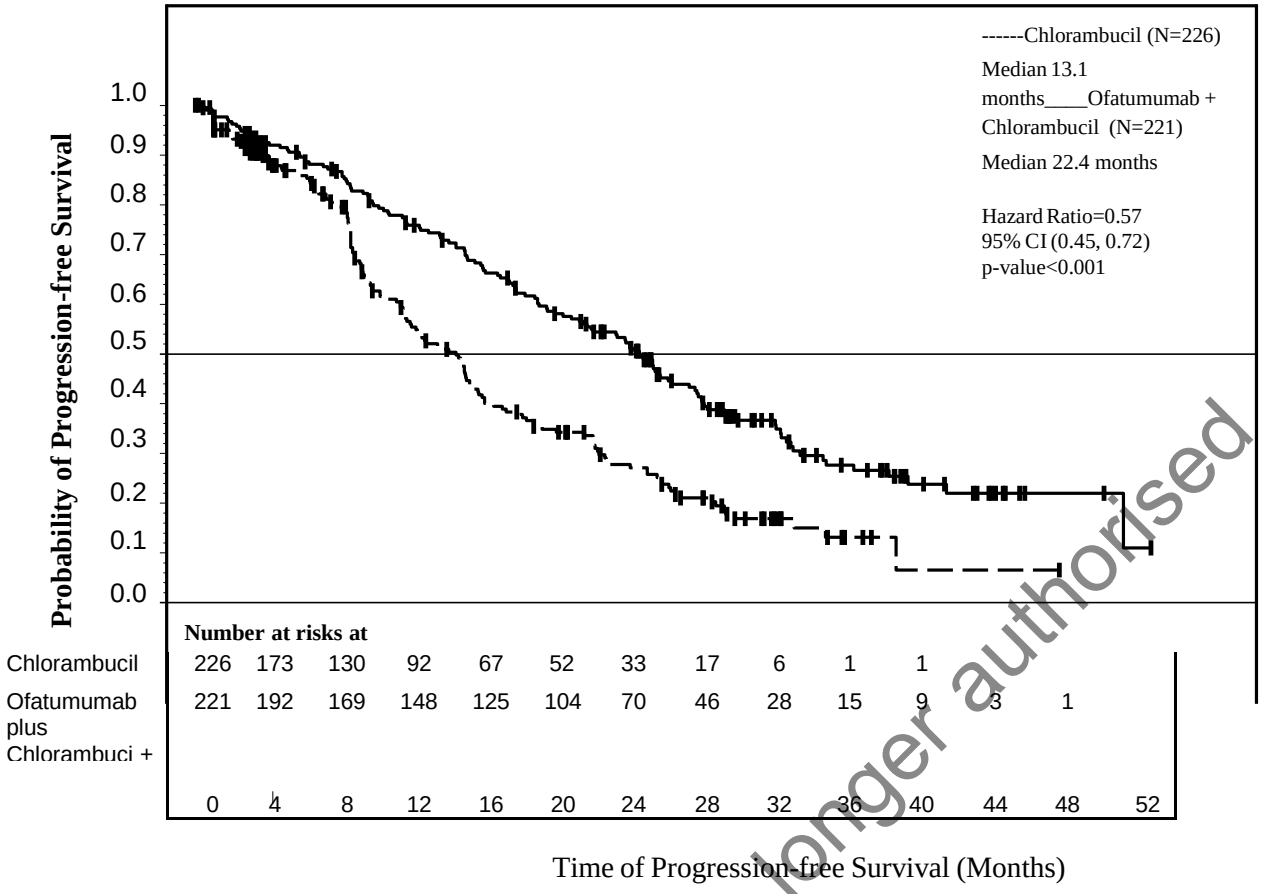


Table 2 Summary of secondary outcomes of Arzerra in combination with chlorambucil compared with chlorambucil in previously untreated CLL

IRC-assessed secondary outcome	Chlorambucil (N=226)	Arzerra and chlorambucil (N=221)
ORR (%) 95% CI P value	69 (62.1, 74.6) p<0.001	82 (76.7, 87.1)
CR (%) CR with MRD negativity (% of CR)	1 0	12 37
Median duration of response, all patients, months 95% CI P value	13.2 (10.8, 16.4) p<0.001	22.1 (19.1, 24.6)
Abbreviations: CI = confidence interval, CLL = chronic lymphocytic leukaemia, CR = complete response, IRC = Independent Review Committee, MRD = minimal residue disease, N = number, ORR = overall response rate		

Study OMB115991 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 1000 mg on day 8; subsequent cycles: 1000 mg on day 1 every 28 days) in combination with intravenous bendamustine 90 mg/m^2 on days 1 and 2 every 28 days. Patients received treatment 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.

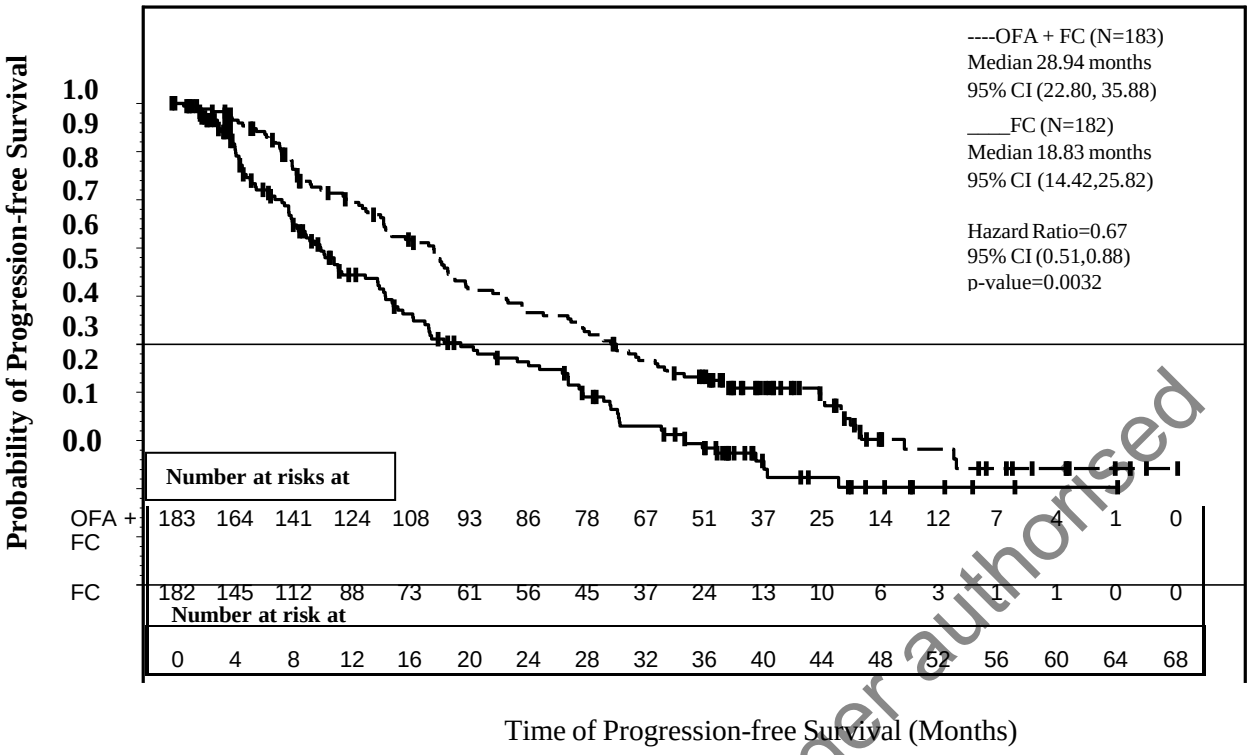
Relapsed CLL

Study OMB110913 (randomised, open-label, parallel-arm, multicentre trial) evaluated the efficacy of ofatumumab in combination with fludarabine and cyclophosphamide compared with fludarabine and cyclophosphamide in 365 patients with relapsed CLL (defined as a patient who has received at least one prior CLL therapy and previously achieved a complete or partial remission/response, but after a period of six or more months demonstrated evidence of disease progression). Baseline disease characteristics and prognostic markers were balanced between treatment arms and representative of a relapsed CLL population. Patient median age was 61 years (range: 32 to 90 years, 7% were 75 years of age or older), 60% were male and 16%, 55% and 28% of patients were Binet stage A, B and C, respectively. The majority of patients (81%) received 1-2 prior lines of treatments (of whom approximately 50% received 1 prior treatment) and 21% of patients had received prior rituximab. The median CIRS score was 7 (range: 4 to 17), 36% of patients had CrCl <70 ml/min, 93% of patients had ECOG 0 or 1. Limited data are available in the heterogeneous non-white population and in patients with an ECOG performance status of 2.

Patients received ofatumumab as intravenous infusions (cycle 1: 300 mg on day 1 and 1000 mg on day 8; subsequent cycles: 1000 mg on day 1 every 28 days). Approximately 90% of patients received 3-6 cycles of ofatumumab and 66% completed 6 cycles.

The primary endpoint of progression-free survival (PFS), as assessed by a blinded independent review committee (IRC) using the updated National Cancer Institute-sponsored Working Group (NCI-WG) guidelines (2008), was prolonged in the ofatumumab plus fludarabine-cyclophosphamide (OFA+FC) arm compared to the fludarabine-cyclophosphamide (FC) arm (28.9 months versus 18.8 months; HR: 0.67; 95% CI: 0.51-0.88, p=0.0032) resulting in a 10-month improvement in median PFS (see Figure 2). PFS based on local (investigator) assessment was consistent with the primary endpoint and resulted in a ~11-month improvement in median PFS (OFA+FC 27.2 months versus 16.8 months for FC; HR=0.66 (95% CI: 0.51, 0.85, p=0.0009).

Figure 2 Kaplan-Meier estimates of PFS in relapsed CLL



The overall response rate (ORR) was also assessed by an IRC using the 2008 NCI-WG guidelines. The ORR was higher for OFA+FC versus FC (84% versus 68%, p=0.0003). Median time to next therapy was longer for the OFA+FC arm versus FC (48.1 months versus 40.1 months; HR: 0.73; 95% CI: 0.51-1.05). Median time to progression was longer for the OFA+FC arm versus FC (42.1 months versus 26.8 months; HR: 0.63; 95% CI: 0.45-0.87).

With a median follow-up of approximately 34 months, 67 deaths (37%) in the OFA+FC arm and 69 deaths (38%) in the FC arm were reported. The overall survival results showed a HR=0.78 (56.4 months versus 45.8 months for the OFA+FC arm versus FC arm; 95% CI: 0.56-1.09; p=0.1410).

Refractory CLL

Arzerra was administered as 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 Arzerra at a similar rate to 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

	Patients with benefit/patients with abnormality at baseline (%)
Efficacy endpoint or haematological parameter[a]	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 >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).

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 Arzerra (when given as 4 once-weekly infusions), led to a 50% objective response rate in the highest dose group (1st dose: 500 mg; 2nd, 3rd and 4th dose: 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

Overall, the pharmacokinetics of ofatumumab were consistent across the indications, whether given as a single agent or in combination with fludarabine and cyclophosphamide or chlorambucil. Ofatumumab had non-linear pharmacokinetics related to its decreasing clearance over time.

Absorption

Arzerra is administered by intravenous infusion; therefore, absorption is not applicable.

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.

The main pharmacokinetic parameters of ofatumumab as a single agent or in combination are summarised in Table 5.

Table 5 Ofatumumab pharmacokinetic parameters (geometric mean)

Population (treatment)	Dosing regimen	Cycle[1]	C_{max} (µg/ml)	AUC (µg.h/ml)	CL (ml/h)	$t_{½}$ (days)
Refractory CLL (ofatumumab)	1st infusion (300 mg) 2000 mg: 8 weekly infusions followed by 4 monthly infusions	Cycle 1	61.4			
		12th dose	827	166000	12.1	11.5
Previously untreated patients (ofatumumab + chlorambucil)	1st infusion (300 mg) 1000 mg monthly infusions	Cycle 1	51.8	2620		
		Cycle 4	285	65100	15.4	18.5
Relapsed CLL (ofatumumab + FC)	1st infusion (300 mg) 1000 mg on the 8th day of cycle 1 followed by 1000 mg monthly infusions	Cycle 1	61.4	3560		
		Cycle 4	313	89100	11.2	19.9

([1]) Cycle for which the pharmacokinetic parameters are presented in this table.
C_{max} = maximum ofatumumab concentration at the end of infusion, AUC = exposure to ofatumumab over a dosing period, CL = ofatumumab clearance after multiple doses, $T_{½}$ = terminal half-life
Numbers rounded to three significant digits

Special populations

Elderly (≥65 years of age)
Age was not found to be a significant factor for ofatumumab pharmacokinetics in a cross-study population pharmacokinetic analysis of patients ranging in age from 21 to 87 years of age.

Paediatric population
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 the end of organogenesis (day 48 of gestation), the ofatumumab exposure (AUC_{inf}) corresponded to 0.46 to 3.6 times the human exposure after the eighth infusion of the maximum recommended human dose (MRHD) of 2000 mg. 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. Spleen weights decreased by approximately 15% in the low-dose group and by approximately 30% in the high-dose group, compared with control values. 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 solution
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 ºC, 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

Arzerra 100 mg concentrate for solution for infusion

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

Arzerra is available in packs of 3 vials.

Arzerra 1000 mg concentrate for solution for infusion

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

Arzerra is available in packs of 1 vial.

6.6 Special precautions for disposal and other handling

Dilution

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.

Arzerra 100 mg concentrate for solution for infusion
300 mg dose: Use 3 vials (15 ml total, 5 ml per vial)
- Withdraw and discard 15 ml from a 1000 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 1000 ml bag;
- Do not shake; mix diluted solution by gentle inversion.

Arzerra 1000 mg concentrate for solution for infusion
1000 mg dose: Use 1 vial (50 ml total, 50 ml per vial)
- Withdraw and discard 50 ml from a 1000 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 1000 ml bag;
- Do not shake; mix diluted solution by gentle inversion.

2000 mg dose: Use 2 vials (100 ml total, 50 ml per vial)
- Withdraw and discard 100 ml from a 1000 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 1000 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 and relapsed 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:

If the first infusion was completed without a severe adverse reaction, the remaining infusions of 1000 mg should be administered over 4 hours (see section 4.2), through a peripheral line or indwelling catheter, according to the schedule below. If any infusion-related adverse reactions are observed, infusion should be interrupted and restarted when the patient's condition is stable (see section 4.2 for further information).

Infusion schedule

Time after start of infusion (minutes)	Infusion 1	Subsequent infusions*
	Infusion rate (ml/hour)	Infusion rate (ml/hour)
0-30	12	25
31-60	25	50
61-90	50	100
91-120	100	200
121-150	200	400
151-180	300	400
180+	400	400
*If the previous infusion was completed without severe infusion-related ADRs. If any infusion-related ADRs are observed, infusion should be interrupted and restarted when the patient's condition is stable (see section 4.2 of the SmPC).		

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:

If the second infusion was 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. If any infusion-related adverse reactions are observed, infusion should be interrupted and restarted when the patient's condition is stable (see section 4.2 for further information).

Infusion schedule

Time after start of infusion (minutes)	Infusions 1 and 2	Infusions 3* to 12
	Infusion rate (ml/hour)	Infusion rate (ml/hour)
0-30	12	25
31- 60	25	50
61-90	50	100
91-120	100	200
121+	200	400
*If the second infusion is completed without severe infusion-related ADRs. If any infusion-related ADRs are observed, infusion should be interrupted and restarted when the patient's condition is stable (see section 4.2).		

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

Disposal

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)

Arzerra 100 mg concentrate for solution for infusion

EU/1/10/625/001

Arzerra 1000 mg concentrate for solution for infusion

EU/1/10/625/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 April 2010
Date of latest renewal: 17 February 2015

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/.