ARZERRA™ 10000000101329

Ofatumumab

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 5 mL or 50 mL of colourless 20 mg/mL ofatumumab solution.

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

Excipients:

This medicinal product contains 34.8 mg sodium per 300 mg dose and 232 mg sodium per 2,000 mg dose.
For a full list of excipients, see List of Excipients.

PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent, colourless liquid. Visible particles may be present.

CLINICAL PARTICULARS

Indications

Arzerra is indicated for the treatment of chronic lymphocytic leukaemia (CLL) in patients who are refractory to fludarabine and alemtuzumab.

Dosage and Administration

Method of Administration

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

ARZERRA should be administered under the supervision of a physician experienced in the use of cancer therapy and in an environment where full resuscitation facilities are immediately available.

Premedication

Patients should be premedicated 30 mins to 2 h prior to *ARZERRA* infusion according to the following dosing schedule:

Infusion number (dosage)	Intravenous corticosteroid dose	Analgesic dose	Antihistamine dose
1 (300 mg)	Equivalent to 100 mg prednisolone	Equivalent to paracetamol (acetaminophen) 1000 mg	Equivalent to cetirizine 10 mg
2 (2000 mg)	Equivalent to 100 mg prednisolone	Equivalent to paracetamol (acetaminophen) 1000 mg	Equivalent to cetirizine 10 mg
3-8 (2000 mg)	Equivalent to 0-100 mg prednisolone [a)]	Equivalent to paracetamol (acetaminophen) 1000 mg	Equivalent to cetirizine 10 mg
9 (2000 mg)	Equivalent to 100 mg prednisolone	Equivalent to paracetamol (acetaminophen) 1000 mg	Equivalent to cetirizine 10 mg
10-12 (2000 mg)	Equivalent to 50-100 mg prednisolone [b)]	Equivalent to paracetamol (acetaminophen) 1000 mg	Equivalent to cetirizine 10 mg

[a)] If the second infusion is completed without a severe adverse drug reaction, the dose may be reduced at the discretion of the physician.

[b)] If the ninth infusion is completed without a serious adverse drug reaction, the dose may be reduced at the discretion of the physician.

Dosage

The recommended dose is 300 mg *ARZERRA* for the first infusion and 2000 mg *ARZERRA* 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/h (see Use and Handling). During infusion, the rate should be doubled every 30 minutes to a maximum of 200 mL/h (see Use and Handling).

- **Subsequent infusions**

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

- **Dose modification and reinitiation of therapy**

Infusion related ADRs may lead to slower infusion rates.

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

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

Populations

- **Paediatrics**

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. Based on available safety and efficacy data in the elderly, no dosage adjustment is required (see Pharmacokinetics: Special patient populations).

- **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 Pharmacokinetics: Special patient populations).

- **Hepatic Impairment**

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

Contraindications

Hypersensitivity to ofatumumab or to any of the excipients.

Warnings and Precautions

Infusion Reactions

Ofatumumab has been associated with infusion reactions leading to temporary interruption of treatment or withdrawal of treatment. Pre-medications attenuate infusion reactions but these may still occur, predominantly during the first infusion (see Dosage and Administration). Infusion reactions may include anaphylactic reactions, cardiac events, chills/rigors, cough, cytokine release syndrome, diarrhoea, dyspnoea, fatigue, flushing, hypertension, hypotension, nausea, pain, pyrexia, rash, and urticaria. Even with pre-medication, severe reactions, including cytokine release syndrome, have been reported following ofatumumab use. In cases of severe infusion reaction, the infusion of *ARZERRA* must be interrupted immediately and symptomatic treatment instituted (see Dosage and Administration for changes to infusion rates following infusion reactions).

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 *ARZERRA*.

Tumour Lysis Syndrome

In patients with CLL, tumour lysis syndrome (TLS) may occur with use of *ARZERRA*. Management of TLS includes correction of electrolyte abnormalities, monitoring of renal function, maintenance of fluid balance and supportive care.

Progressive Multifocal Leukoencephalopathy (PML)

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

Immunisations

The safety of, and ability to generate a primary or anamnestic response to, immunisation with live attenuated or inactivated vaccines during ofatumumab treatment, has not been studied. The response to vaccination could be impaired when B cells are depleted. The risks and benefits of vaccinating patients during *ARZERRA* therapy should be considered.

Hepatitis B

Hepatitis B (HBV) infection and reactivation, including fatal cases, can occur in patients taking ofatumumab. Patients at high risk of HBV infection should be screened before initiation of *ARZERRA*. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection during treatment with ofatumumab and for 6-12 months following the last infusion of *ARZERRA*. *ARZERRA* should be discontinued in patients who develop viral hepatitis, and appropriate treatment should be instituted. Insufficient data exist regarding the safety of administration of ofatumumab in patients with active hepatitis.

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.

Bowel obstruction

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

Laboratory monitoring

Since ofatumumab binds to all CD20-positive lymphocytes (malignant and non-malignant), complete blood counts and platelet counts should be obtained at regular intervals during *ARZERRA* therapy and more frequently in patients who develop cytopenias. Appropriate management should be considered should cytopenias occur.

Interactions

No drug-drug interaction studies have been conducted with ofatumumab.

Pregnancy and Lactation

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.

Pregnancy

There are no data from the use of ofatumumab in pregnant women. The effect on human pregnancy is unknown. Precautions should be undertaken to avoid pregnancy and adequate contraception should be used while using *ARZERRA* and for at least 6 months after the last *ARZERRA* treatment. *ARZERRA* should not be administered to pregnant women unless the possible benefit to the mother outweighs the possible risk to the foetus.

Animal studies do not indicate direct or indirect harmful effects with respect to maternal toxicity, pregnancy or embryonal/foetal development (see Pre-clinical safety data).

Lactation

The safe use of ofatumumab in humans during lactation has not been established. It is not known whether ofatumumab is secreted in human milk; however, human IgG is secreted in human milk. Published data suggest that neonatal and infant consumption of breast milk does not result in substantial absorption of these maternal antibodies into circulation. Because the effects of local gastrointestinal and limited systemic exposure to ofatumumab are unknown, caution should be exercised when *ARZERRA* is administered to a nursing woman.

Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of ofatumumab on driving performance or the ability to operate machinery. No detrimental effects on such activities are predicted from the pharmacology of ofatumumab. The clinical status of the patient and the ADR profile of *ARZERRA* should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills.

Adverse Reactions

Clinical Trial Data

The safety of ofatumumab in patients with relapsed or refactory CLL has been evaluated in two open label studies.
In study Hx-CD20-406, 154 patients were enrolled to receive an initial dose of 300 mg followed 1 week later by 2,000 mg once weekly for 7 infusions, followed 5 weeks later by 2,000 mg once every 4 weeks for 4 infusions, for a total of 12 infusions. The second study was a dose-finding study and patients in three cohorts (3 patients, 3 patients, 27 patients) received a starting dose of 100 mg, 300 mg or 500 mg, followed a week later with 3 consecutive weekly infusions of 500 mg, 1000 mg or 2000 mg of ofatumumab, respectively. The adverse reactions reported are from 181 patients who received a 2,000 mg dose (a combination of the final data from the initial dose-range finding and a planned interim analysis of study Hx-CD20-406).

Infusion reactions occurred with the greatest incidence (44%) on the first infusion day (300 mg or 500 mg), decreased to 26% with the second infusion (2000 mg) and declined further during subsequent infusions (2000 mg).

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

Very common ≥ 1 in 10

Common ≥ 1 in 100 and < 1 in 10

Uncommon ≥ 1 in 1,000 and < 1 in 100

MedDRA SOC	Very common	Common:	Uncommon
Immune System Disorders		Hypersensitivity,	Anaphylactic reactions including anaphylactic shock
Metabolism and Nutrition Disorders			Tumour lysis syndrome
Cardiac Disorders		Tachycardia	
Vascular Disorders		Hypertension, hypotension	
Respiratory, Thoracic and Mediastinal Disorders		Pharyngolaryngeal pain, dyspnoea, cough, bronchospasm, chest discomfort, nasal congestion, hypoxia	
Gastrointestinal Disorders		Nausea, small bowel obstruction, diarrhoea	
Skin and Subcutaneous Tissue Disorders	Rash	Pruritus, urticaria, flushing	
Musculoskeletal and Connective Tissue Disorders		Back pain	
General Disorders and Administration Site Conditions		Fatigue, chills, rigors, hyperhidrosis, cytokine release syndrome, pyrexia	

Post Marketing Data

No data available

Overdose

No data from clinical studies are available regarding overdose of ofatumumab.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

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. In addition, the binding of ofatumumab induces cell death through antibody-dependent cell-mediated cytotoxicity. Ofatumumab has also been shown to induce cell lysis in both high and low CD20 expressing cells and in rituximab-resistant cells.

Pharmacodynamic Effects

Peripheral B cell counts decreased after the first ofatumumab infusion in patients with haematologic malignancies. In patients with refractory CLL, the median decrease in B cell counts was 23% after the first infusion and 92% after the eighth infusion. Peripheral B cell counts remained low throughout the remainder of therapy in most patients, then gradually recovered (median decrease in B cell counts was 68% below baseline 3 months after the end of ofatumumab therapy).

Immunogenicity

There is a potential for immunogenicity with therapeutic proteins such as ofatumumab; however the formation of anti-ofatumumab antibodies may be decreased because ofatumumab is a human antibody that depletes B cells.

In the pivotal clinical study (Hx-CD20-406), no anti-ofatumumab antibodies were detected in the 46 patients who had received at least 8 infusions (33 of whom received all 12 infusions) and had sufficiently low circulating ofatumumab concentrations to allow detection.

Pharmacokinetics

Absorption

ARZERRA 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 146 patients with refractory CLL. The geometric mean C_{max} value was 63 µg/mL after the first infusion (300 mg); after the eighth weekly infusion (seventh infusion of 2000 mg), the geometric mean C_{max} value was 1482 µg/mL and geometric mean AUC(0-∞) value was 674,463 µg.h/mL; after the twelfth infusion (fourth monthly infusion; 2000 mg), the geometric mean C_{max} value was 881 µg/mL and geometric mean AUC(0-∞) was 265,707 µg.h/mL.

Distribution

Ofatumumab has a small volume of distribution, with mean Vss values ranging from 1.7 to 5.1 L across studies, dose levels, and infusion number.

Metabolism

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 CLL, the mean values for CL and $t_{½}$ were 64 mL/h (range 4.3-1122 mL/h) and 1.3 days (range 0.2-6.0 days) after the first infusion, 8.5 mL/h (range 1.3-41.5 mL/h) and 11.5 days (range 2.3-30.6 days) after the fourth infusion, 9.5 mL/h (range 2.2-23.7 mL/h) and 15.8 days (range 8.8-61.5 days) after the eighth infusion, and 10.1 mL/h (range 3.3-23.6 mL/h) and 13.9 days (range 9.0-29.2 days) after the twelfth infusion.

Special Patient Populations

- **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 86 years of age.

- **Children and Adolescents (up to 18 years of age)**

No pharmacokinetic data are available in paediatric patients.

- **Gender**

Gender had a modest effect (14-25%) on ofatumumab pharmacokinetics in a cross-study analysis, with higher C_{max} and AUC values observed in female patients (41% of the patients in this analysis were male and 59% 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 clinically significant factor on ofatumumab pharmacokinetics in a cross-study population analysis in patients with calculated creatinine clearance values ranging from 33 to 287 mL/min. No dose adjustment is recommended for mild to moderate renal impairment (creatinine clearance >30 mL/min). There are no pharmacokinetic data in patients with severe renal impairment (creatinine clearance <30 mL/min).

- **Hepatic Impairment**

No pharmacokinetic data are available in patients with hepatic impairment. IgG1 molecules such as ofatumumab are catabolised by ubiquitous proteolytic enzymes, which are not restricted to hepatic tissue; therefore, changes in hepatic function are unlikely to have any effect on the elimination of ofatumumab.

Clinical Studies

The clinical efficacy of *ARZERRA* has been demonstrated in a planned interim analysis of an ongoing study, Hx-CD20-406 (single-arm, open-label, multicentre), and one completed supportive study, Hx-CD20-402 (open-label, dose ranging, multicentre).

Hx-CD20-406

Ofatumumab was administered as a monotherapy to 154 patients with CLL. Patient median age was 63 years (range: 41 to 86 years), and the majority were male (72%) and white (97%). Patients received a median of 5 prior therapies, including ritixumab (57%). Of these 154 patients, 138 were refractory to fludarabine and alemtuzumab therapy (n=59), or were refractory to fludarabine and had bulky lymphadenopathy (defined as at least one lymph node > 5 cm) and were inappropriate for alemtuzumab therapy (bulky fludarabine refractory, n=79). Baseline cytogenetic (fluorescence in-situ hybridization (FISH)) data were available for 151 patients. Chromosomal aberrations were detected in 118 patients; there were 33 patients with 17p deletion, 50 patients with 11q deletion, 16 patients with trisomy 12q, 30 patients with a normal karyotype and 19 patients with 13q deletion as the sole aberration.

Patients received 300 mg ofatumumab in the first infusion and 2000 mg ofatumumab for all subsequent infusions. The infusion schedule was 8 consecutive weekly infusions, followed 5 weeks later by a single infusion for the following 4 consecutive months. Most patients (90%) received at least 8 infusions, 69% received at least 10 infusions, and 55% received all 12 infusions.

The primary endpoint of this ongoing study was to evaluate the efficacy of ofatumumab in the subject populations, as measured by the response rate over a 24 week period. The overall response was assessed by an Independent Response Committee using the 1996 National Cancer Institute Working Group (NCIWG) guidelines for CLL.

The overall response rates were 58% in the fludarabine and alemtuzumab refractory group and 47% in the bulky fludarabine refractory group (see Table 1 for a summary of the efficacy data from the study). Additionally, a group of patients (n=16) who were intolerant/ineligible for fludarabine treatment and/or intolerant to alemtuzumab treatment and who were not included in either of the two groups above were treated with ofatumumab; the overall response rate in this group was 56% (99% CI: 24%, 85%). All responses were partial remission, with the exception of one patient in the bulky fludarabine refractory group who achieved a complete remission. Stable disease was the best response for 31% of the fludarabine and alemtuzumab refractory group and 41% in the bulky fludarabine refractory group. Progressive disease as best response was 3% in the fludarabine and alemtuzumab refractory group and 10% in the bulky fludarabine refractory group.

Table 1. Summary of response to ofatumumab in patients with CLL

Endpoint	Fludarabine and Alemtuzumab Refractory n = 59	Bulky Fludarabine Refractory n = 79
Overall Response Rate Responders, n (%) 99% CI (%)	 34 (58) 40, 74	 37 (47) 32, 62
Response rate in patients with prior rituximab therapy Responders, n (%) 95% CI (%)	 19/35 (54) 37, 71	 19/43 (44) 29, 60
Response rate in patients with chromosomal abnormality 17p deletion Responders, n (%) 95% CI (%) 11q deletion Responders, n (%) 95% CI (%)	 7/17 (41) 18, 67 15/24 (63) 41, 81	 2/14 (14) 2, 43 14/22 (64) 41, 83
Median Overall Survival Months 95% CI	 13.7 9.4, non-estimable	 15.4 10.2, 20.2
Progression-free Survival Months 95% CI	 5.7 4.5, 8.0	 5.9 4.9, 6.4
Median Duration of Response Months 95% CI	 7.1 3.7, 7.6	 5.6 3.6, 7.0
Median Time to next CLL Therapy Months 95% CI	 9.0 7.3, 10.7	 7.9 7.1, 9.3

Improvements also were demonstrated in components of the NCIWG response criteria. These included improvements associated with constitutional symptoms, lymphadenopathy, organomegaly, or cytopenias (see Table 2).

Table 2. Summary of clinical improvement with a minimum duration of 2 months in subjects with abnormalities at baseline

Efficacy Endpoint or haematological parameter[a]	Subjects With Benefit/Subjects With Abnormality at Baseline (%)	
	Fludarabine and Alemtuzumab Refractory	Bulky Fludarabine Refractory
Lymphocyte count		
≥50% decrease	31/42 (74)	44/64 (69)
Normalisation (≤4x10^9/L)	20/42 (48)	26/64 (41)
Complete Resolution of Constitutional Symptoms[b]	15/31 (48)	29/46 (63)
Lymphadenopathy[c] ≥50% Improvement Complete Resolution	 34/55 (62) 9/55 (16)	 36/74 (49) 8/74 (11)
Splenomegaly ≥50% Improvement Complete Resolution	 16/30 (53) 14/30 (47)	 26/46 (57) 16/46 (35)
Hepatomegaly		
≥50% Improvement	11/18 (61)	13/21 (62)
Complete Resolution	9/18 (50)	11/21 (52)
Haemoglobin <11 g/dL at baseline to >11 g/dL post baseline	8/26 (31)	11/42 (26)
Platelet counts <100x10^9/L at baseline to >50% increase or >100x10^9/L post baseline	12/29 (41)	17/44 (39)
Neutrophils <1x10^9/L at baseline to ≥1.5x10^9/L	1/19 (5)	5/17 (29)

[a] Excludes subject visits from date of first transfusion, treatment with erythropoietin, or treatment with growth factors. For subjects 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.

Hx-CD20-402

A dose-ranging study was conducted in 33 patients with relapsed or refractory CLL. Patient median age was 61 years (range: 27 to 82 years), the majority were male (58%), and all were white. Treatment with ofatumumab (when given as 4 once weekly infusions), led to a 48% objective response rate in the highest dose group (n=27; 1st dose: 500 mg; 2nd, 3rd and 4th dose: 2000 mg) and included 12 partial remissions and one nodular partial remission. For the highest dose group, the median time to progression was 15.6 weeks (95% CI: 15-22.6 weeks) in the full analysis population, and 23 weeks (CI: 20-31.4 weeks) in responders. The duration of response was 16 weeks (CI: 13.3 – 19.0 weeks) and the time to next CLL therapy was 52.4 weeks (CI: 36.9 – non-estimable).

Pre-clinical 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 as a result of monkey anti-drug antibodies coating the red cells. A corresponding increase in reticulocyte counts seen in these monkeys was indicative of a regenerative response in the bone marrow.

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

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

PHARMACEUTICAL PARTICULARS

List of Excipients

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

Incompatibilities

The concentrate for solution for infusion must only be mixed with 0.9% sodium chloride solution for infusion (see Instructions for Use/ Handling). It is **not recommended** that *ARZERRA* be mixed with any other drug in an infusion bag.

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.

Shelf Life

Concentrate for solution for infusion

The expiry date is indicated on the packaging.

Special Precautions for Storage

Store between 2 °C – 8 °C.

Do not freeze.

Protect from light.

Nature and Contents of Container

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

Instructions for Use/Handling

1. Before diluting *ARZERRA*

Check the *ARZERRA* concentrate for particulate matter and discoloration prior to dilution. *ARZERRA* should be a colourless solution. **Do not use** the *ARZERRA* concentrate if there is discolouration. The concentrate may contain a small amount of visible translucent-to-white, amorphous, ofatumumab particles. The filters provided as part of the extension set will remove these particles.

Do not shake the *ARZERRA* vial for this inspection.

2. How to prepare the solution for infusion

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

300 mg dose - Use 3 x 100 mg/5 mL vials (15 mL total):

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

2000 mg dose – Use 2 x 1000 mg/50 mL vials (100 mL total):

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

3. Administration

***ARZERRA* must not be administered as an i.v. push or bolus.** Administer using an i.v. infusion pump, using the extension sets provided. The in-line filter must be used during the entire infusion.

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 should be stored below 25 °C and must be used within 24 hours of 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 *ARZERRA* administration with 0.9% sodium chloride to avoid this.

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

Infusion schedule for infusions 1 and 2

Time (mins)	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 Dosage and Administration), through a peripheral line or indwelling catheter, according to the schedule below:

Infusion schedule for infusions 3 to 12

Time (mins)	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.

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

Not all presentations are available in every country.

Manufactured by:
Glaxo Operations UK Limited*, Barnard Castle, UK
*Member of the GlaxoSmithKline group of companies

GDS Version Number: 04, **Version Date:** 12 April 2011

ان هذا الدواء

- الدواء مستحضر يؤثر على صحتك و استهلاكه خلافا للتعليمات يعرضك للخطر.
- اتبع بدقة وصفة الطبيب و طريقة الاستعمال المنصوص عليها و تعليمات الصيدلانى الذى صرفها لك.
- فالطبيب و الصيدلانى هما الخبيران بالدواء و بنفعه و ضرره.
- لا تقطع مدة العلاج المحددة لك من تلقاء نفسك.
- لا تكرر صرف الدواء بدون وصفة طبية.

لا تترك الأدوية فى متناول أيدى الأطفال

مجلس وزراء الصحة العرب
و اتحاد الصيادلة العرب

THIS IS A MEDICAMENT
Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of the reach of children.

Council of Arab Health Ministers, Union of Arab Pharmacists.

GlaxoSmithKline

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