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Direct HealthCare Professional Communication

Ofatumumab ▼ (Arzerra): reminder of risk of serious and fatal infusion reactions

Dear Healthcare Professional,

GlaxoSmithKline (GSK) in agreement with the European Medicines Agency and the Health Products Regulatory Authority (HPRA), (formally known as The Irish Medicines Board) would like to inform you of the following:

Summary

A fatal infusion reaction has occurred during administration of the first dose of ofatumumab to a 71-year old male with chronic lymphocytic leukaemia (CLL) and no known history of cardiac disease.

Recommendations:

- **Ofatumumab should only be administered under the supervision of a physician experienced in the use of cancer therapy and where facilities to monitor and treat infusion reactions are available**
- **Patients should receive premedication agents 30 minutes to 2 hours prior to each infusion of ofatumumab, according to the protocol in the ofatumumab summary of product characteristics (SmPC)**
- **Despite premedication, infusion reactions may still occur. In cases of severe infusion reaction, the infusion of ofatumumab must be interrupted immediately and symptomatic treatment instituted.**

Further information

Ofatumumab is indicated for the treatment of patients with CLL refractory to fludarabine and alemtuzumab. Intravenous ofatumumab has been associated with a risk of potentially fatal infusion reactions.

Healthcare professionals should inform their patients of the risk of potentially fatal infusion reactions associated with the infusion of ofatumumab. Such reactions may still occur despite premedication, especially during the first infusion.

There are no changes to the recommended premedication regimen. However, all healthcare professionals are reminded that:

- Patients should receive the following premedication agents 30 minutes to 2 hours prior to each infusion:
  - Oral paracetamol (acetaminophen) 1000 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).

Where severe infusion reactions are observed, the infusion of ofatumumab must be interrupted immediately and symptomatic treatment instituted.

Patients with a history of decreased pulmonary function may be at a high risk for pulmonary complications from severe reactions. Therefore these patients should be monitored closely during infusion of ofatumumab.

Call for reporting:
All healthcare professionals should report any suspected sides effects of ofatumumab via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

Healthcare professionals may also report any suspected adverse reactions to GlaxoSmithKline (Ireland) Ltd., Stonemasons Way, Rathfarnham, Dublin 16 (Free phone 1800 244 255, Fax 01 4938839 or e-mail ireland.drugsurveillance@gsk.com).

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

Company contact point
Further information can be obtained from:
GlaxoSmithKline (Ireland) Ltd., Stonemasons Way, Rathfarnham, Dublin 16 (Freephone 1800 244 255).

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Yours sincerely,

Dr Stephen McDonough BM, BS, MRCGP, MSc, FFPM

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Annexes

Summary of Product Characteristics - updated Sections 4.2, 4.4 and 4.8

*Changed text is **underlined**, ~~strikethrough~~ as appropriate.*

4.2 Posology and method of administration

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

Monitoring

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

Pre-medication

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

Previously untreated CLL:

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

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

Refractory CLL:

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

If the second weekly infusion is completed without a severe ADR, the dose of the corticosteroid may be reduced for infusion numbers 3 through 8, at the discretion of the physician.
Prior to the ninth infusion (first monthly infusion), patients should receive the full dose of premedication agents described above. If the ninth infusion is completed without a severe ADR, the dose may be reduced to the equivalent of 50 mg prednisolone for subsequent infusions at the discretion of the physician.

Posology

Previously untreated CLL:

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

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

First infusion
The initial rate of the first infusion of Arzerra should be 12 ml/h. During infusion, the rate should be increased every 30 minutes to a maximum of 400 ml/h (see section 6.6).

Subsequent infusions
If the first infusion has been completed without severe infusion related ADRs, the subsequent infusions can start at a rate of 25 ml/h and should be increased every 30 minutes up to a maximum of 400 ml/h (see section 6.6).

Refractory CLL:
The recommended dose is 300 mg for the first infusion and 2,000 mg for all subsequent infusions. The infusion schedule is 8 consecutive weekly infusions, followed 4-5 weeks later by 4 consecutive monthly (i.e. every 4 weeks) infusions.

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

Subsequent infusions
If the second infusion has been completed without severe infusion related ADRs, the remaining infusions can start at a rate of 25 ml/hour and should be increased every 30 minutes up to a maximum of 400 ml/hour (see section 6.6).

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

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

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

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

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

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

Renal impairment
No formal studies of Arzerra in patients with renal impairment have been performed. No dose adjustment is recommended for mild to moderate renal impairment (creatinine clearance >30 ml/min) (see section 5.2).

Hepatic impairment
No formal studies of Arzerra in patients with hepatic impairment have been performed. However, patients with hepatic impairment are unlikely to require dose modification (see section 5.2).

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

4.4 Special warnings and precautions for use

Infusion reactions
Intravenous ~~O~~**o**fatumumab has been associated with infusion reactions**. These reactions may result in** temporary interruption ~~**of treatment**~~ 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 ($\geqslant$ 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 has been reported in CLL patients receiving cytotoxic pharmacotherapy, including ofatumumab. A diagnosis of PML should be considered in any Arzerra patient who reports the new onset of or changes in pre-existing

neurologic signs and symptoms. If a diagnosis of PML is suspected Arzerra should be discontinued and referral to a neurologist should be considered.

Immunisations

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

Hepatitis B

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

HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels and, in severe cases, increase in bilirubin levels, liver failure, and death.

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

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

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

Cardiovascular

Patients with a history of cardiac disease should be monitored closely. Arzerra should be discontinued in patients who experience serious or life-threatening cardiac arrhythmias.

The effect of multiple doses of Arzerra on the QTc interval was evaluated in a pooled analysis of three open-label studies in patients with CLL (N = 85). Increases above 5 msec were observed in

the median/mean QT/QTc intervals in the pooled analysis. No large changes in the mean QTc interval (i.e., >20 milliseconds) were detected. None of the patients had an increase of QTc to >500 msec. A concentration dependent increase in QTc was not detected. It is recommended that patients have electrolytes such as potassium and magnesium measured prior to and during the administration of ofatumumab. Electrolyte abnormalities should be corrected. The effect of ofatumumab on patients with prolonged QT intervals (e.g., acquired or congenital) is unknown.

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

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

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

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

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

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.