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IMPORTANT SAFETY INFORMATION

Six infection-related deaths reported after treatment with MabCampath® (alemtuzumab) following Fludarabine+Rituximab induction in patients with B-Cell Chronic Lymphocytic Leukemia (CLL)

Dear Healthcare Professional,

Summary
Following discussion with the European Medicines Agency scientific committee, the Committee for Human Medicinal Products (CHMP) and the Irish Medicines Board, Bayer Schering Pharma AG and Genzyme Europe BV are writing to inform you of six infection-related deaths reported from a trial (CALGB10101)* in which previously untreated, symptomatic B-Cell Chronic Lymphocytic Leukemia (CLL) patients were treated with fludarabine and rituximab followed by alemtuzumab for remission consolidation.

MabCampath® is approved for the treatment of patients with B-cell chronic lymphocytic leukaemia (B-CLL) for whom fludarabine combination chemotherapy is not appropriate and should not be used as consolidation therapy following induction with fludarabine + rituximab outside of a clinical trial.

Fludarabine, rituximab and MabCampath® all have known immunosuppressive properties, and it is possible that the fatal infectious complications which occurred in this trial are the result of a prolonged period of immunosuppression resulting from the sequencing of these drugs without sufficient time for recovery, as well as other factors specific to this trial.

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Further information on the safety concern

The five fatal infections were reported as: Viral meningitis, *Listeria* meningitis, *Legionella* pneumonia, cytomegalovirus (CMV) infection and *Pneumocystis jiroveci* pneumonia (PCP), all in patients who achieved a complete response (CR) after induction therapy. In addition, a case of fatal EBV associated lymphoproliferative disorder was reported in a patient who achieved a partial response (PR) after induction therapy. Bayer Schering Pharma AG and Genzyme have subsequently been informed of an additional non-infection related fatality believed to be related to Transfusion Associated Graft Versus Host Disease (TAGVHD) in a patient who had received non-irradiated blood products.

The above fatalities were presented in an abstract submitted for the 2007 American Society of Hematology (ASH) Annual Meeting on the first 51 patients who received all three agents (induction with fludarabine + rituximab & consolidation with alemtuzumab).

The induction regimen in this study consisted of fludarabine 25 mg/m^2 IV on days 1-5; rituximab escalated from 50 mg/m^2 on day 1 to 325 mg/m^2 on day 3, to 375 mg/m^2 on day 5 (cycle 1) and then 375 mg/m^2 IV on day 1 of cycles 2-6; every 28 days for up to 6 cycles. Approximately four months after the last dose of fludarabine, patients with stable or responsive disease were to receive consolidation therapy with alemtuzumab escalated to 30 mg SC on days 1, 2 and 3 of Week 1, and 30 mg three times weekly thereafter for 6 weeks.

Based on the toxicity in CR patients, the clinical trial was amended to restrict consolidation therapy with MabCampath® to patients who experienced a PR, with close monitoring for infectious and other toxicities. The authors conclude that MabCampath® cannot be safely administered as consolidation therapy to patients who achieve a CR following induction chemotherapy and that administration of MabCampath® consolidation for patients in PR following fludarabine + rituximab induction should not be pursued outside of a clinical trial due to concerns about serious infectious morbidity and mortality.

The use of MabCampath® consolidation in CLL is an area of active investigation. Moreover, the design of the CALGB10101 study did not allow for a direct assessment of the relative contribution of any one of the agents in this regimen (including alemtuzumab). Fludarabine, rituximab, and MabCampath® all have known immunosuppressive properties, and it is possible that the infectious complications which occurred in this trial are the result of a prolonged period of immunosuppression resulting from the sequencing (i.e. the interval between induction and consolidation) of these

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drugs without sufficient time for recovery, but the risk may also be influenced by the induction regimen and/or dose or schedule of the agents used.

The protocol described in the highlighted ASH abstract employs MabCampath® for use as consolidation therapy, which is not approved in the current EU SPC/labelling for MabCampath®. The benefit/risk profile of MabCampath® is unchanged when it is used, as approved, for the treatment of patients with B-CLL for whom fludarabine combination chemotherapy is not appropriate. MabCampath® should not be used as consolidation therapy outside of a clinical trial.

Further information on recommendation to healthcare professionals
The CHMP has reviewed the safety concern and considered that since the safety issue relates to off label use there is no need for changes to the product information at this time.

Call for reporting
You can assist us by monitoring the safety of MabCampath® and reporting adverse reactions to Bayer Limited or the Irish Medicines Board in the usual way.

Communication information
Should you require any further information then please contact Stephen Keating, Product Manager for Oncology and Haematology, at Bayer Limited tel. no. 01 2999313.

The CALGB10101 abstract is available on the ASH online website (http://www.hematology.org).

Yours sincerely

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* Reference:
Lin TS, Donahue KA, Lucas MS, et al.
Consolidation therapy with subcutaneous (SC) alemtuzumab results in severe infections toxicity in previously untreated CLL patients who achieve a complete response (CR) after fludarabine and rituximab (FR) induction therapy. Blood 2007;110:232a, abstract number 755