

**NOTICE TO HOSPITALS**  
**Health Canada Endorsed Important Safety Information on**  
**[MABCAMPATH® (alemtuzumab)]**



November 18, 2008

**To:** Hospital Chief of Staff

Please distribute to relevant Departments [Hematology, Oncology, Pharmacy, Internal Medicine, Infectious Diseases and/or other departments as required], and other involved professional staff [Surgical Oncologists] and **post this NOTICE** in your institution.

**Subject:            Infection-Related Deaths Reported with the Use of MABCAMPATH®  
                          (alemtuzumab) as Consolidation Therapy following Chemoimmunotherapy  
                          in B-Cell Chronic Lymphocytic Leukemia**

Bayer HealthCare and Genzyme, in collaboration with Health Canada, wish to inform you of important safety information regarding the use of MABCAMPATH® (alemtuzumab) as consolidation therapy following combination treatment with other chemotherapeutic or biologic agents.

MABCAMPATH is a recombinant humanized monoclonal antibody and is currently authorized for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who had been treated with alkylating agents and who have failed fludarabine therapy.

- |  |
|--|
| <ul style="list-style-type: none"><li>• <b>MABCAMPATH is not authorized for use as consolidation therapy.</b></li><li>• <b>Preliminary safety information from the CALGB10101 clinical trial conducted in the United States, reported six infection-related deaths out of 51 patients who received three chemotherapeutic agents (fludarabine + rituximab followed by consolidation therapy with MABCAMPATH).</b></li><li>• <b>The potential for an increased risk of infection-related complications may exist following treatment with multiple chemotherapeutic or biological agents.</b></li></ul> |
|--|

**Additional information on the safety concern**

The phase II CALGB10101 clinical trial is an ongoing study investigating the administration of induction chemotherapy with fludarabine + rituximab (FR) followed by MABCAMPATH for remission consolidation in previously untreated symptomatic B-CLL patients. The induction regimen in this study consisted of fludarabine 25 mg/m<sup>2</sup> intravenously (IV) on days 1-5; rituximab escalated from 50 mg/m<sup>2</sup> on day 1 to 325 mg/m<sup>2</sup> on day 3, to 375 mg/m<sup>2</sup> on day 5 (cycle 1) and then 375 mg/m<sup>2</sup> 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 subcutaneous

MABCAMPATH 3 mg on day 1, 10 mg on day 3, 30 mg on day 5, and 30 mg three times weekly thereafter for 6 weeks.

This study reported six infection-related deaths out of 51 patients who received the three chemotherapeutic agents (FR induction and consolidation with MABCAMPATH). The six fatal infections were reported as: Viral meningitis, *Listeria* meningitis, *Legionella* pneumonia, cytomegalovirus (CMV) infection, *Pneumocystis jiroveci* pneumonia (PCP), and Epstein Barr Virus (EBV) associated lymphoproliferative disorder.<sup>1</sup> Bayer HealthCare and Genzyme were also informed of an additional non-infection related fatality, believed to be Transfusion Associated Graft versus Host Disease (TAGVHD), which occurred in a non-lymphopenic patient who had received non-irradiated blood products. As of this mailing, no significant new safety information regarding this study has been received by either Bayer HealthCare or Genzyme.

The use of MABCAMPATH consolidation therapy 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 MABCAMPATH). 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 drugs without sufficient time for recovery; the risk may also be influenced by the induction regimen and/or dose or schedule of the agents used. The relative contribution of each drug to the safety outcomes in this study is not clear based on the available data.

Canadian investigators participating in oncology trials of MABCAMPATH were previously informed of the safety information from CALGB10101. Bayer HealthCare and Genzyme remain committed to the safe and appropriate development of MABCAMPATH in the treatment of B-CLL, including its potential utility in consolidation. MABCAMPATH is not authorized for use as consolidation therapy. Company sponsored clinical study events should be reported as described in the protocols.

The MABCAMPATH Canadian Product Monograph will be updated to reflect this safety information.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any occurrence of serious and/or unexpected adverse reactions in patients receiving MABCAMPATH should be reported to Bayer HealthCare, or Health Canada at the following addresses:

Bayer HealthCare  
77 Belfield Road  
Toronto ON M9W 1G6  
Tel: 1-800-265-7382  
Fax: 1-866-232-0565  
E-mail: DSI\_Canada@bayer.com

**Any suspected adverse reaction can also be reported to:**

Canada Vigilance Program  
Marketed Health Products Directorate  
HEALTH CANADA  
Address Locator: 0701C  
Ottawa, Ontario, K1A 0K9  
Tel: 613-957-0337 or Fax: 613-957-0335  
To report an Adverse Reaction, consumers and health professionals may call toll free:  
Tel: 866-234-2345  
Fax: 866-678-6789  
[CanadaVigilance@hc-sc.gc.ca](mailto:CanadaVigilance@hc-sc.gc.ca)

The AR Reporting Form and the AR Guidelines can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.

**For other inquiries related to this communication, please contact Health Canada at:**

Marketed Health Products Directorate (MHPD)  
E-mail: [MHPD\\_DPSC@hc-sc.gc.ca](mailto:MHPD_DPSC@hc-sc.gc.ca)  
Tel: 613-954-6522  
Fax: 613-952-7738

Sincerely,

***Original signed by***

Shurjeel H. Choudhri, MD FRCPC  
Senior Vice President & Head,  
Medical & Scientific Affairs

---

<sup>1</sup> Lin 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: Interim Safety Analysis of the CALGB Study 10101. *Blood* (ASH Annual Meeting Abstracts) 2007 110: Abstract 755.