



**Health Canada Endorsed Important Safety Information on
RITUXAN[®] (rituximab)**

August 8, 2007

Subject: Reports of Progressive Multifocal Leukoencephalopathy (PML) following RITUXAN use in Systemic Lupus Erythematosus and Vasculitis (off-label use)

Dear Health Care Professional:

Hoffmann-La Roche Limited, in consultation with Health Canada, would like to inform you of important new safety data that have implications for the use of RITUXAN (rituximab).

RITUXAN is a recombinant chimeric anti-CD20 monoclonal antibody indicated for the treatment of B-cell non-Hodgkin's Lymphoma (NHL) and Rheumatoid Arthritis (RA). It is estimated that over one million patients have been administered RITUXAN worldwide.

Based upon review of recent post marketing and clinical safety reports:

- **Cases of fatal Progressive Multifocal Leukoencephalopathy (PML) have been reported following off-label use of RITUXAN for the treatment of certain autoimmune diseases, including Systemic Lupus Erythematosus (SLE) and vasculitis. The patients with autoimmune diseases had a history of prior or concurrent immunosuppressive therapy and were diagnosed with PML within 12 months of their last infusion of RITUXAN. PML has also been reported in patients with autoimmune disease not treated with RITUXAN.**
- **No cases of PML have been reported in patients with RA.**
- **Physicians treating patients with autoimmune diseases should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.**
- **The efficacy and safety of RITUXAN for the treatment of autoimmune diseases other than rheumatoid arthritis has not been established.**

Progressive multifocal leukoencephalopathy (PML) is a rare, progressive, demyelinating disease of the central nervous system that usually leads to death or severe disability. PML is caused by activation of the JC virus, a polyomavirus that resides in latent form in up to 80% of healthy adults. JC virus usually remains latent, typically only causing PML in immunocompromised patients. The factors leading to activation of the latent infection are not fully understood.

PML has been reported in HIV positive patients, immunosuppressed cancer patients, transplantation patients and patients with autoimmune disease including SLE. Abnormalities in T cells have been described as



important for activation of JC virus and PML. Very rare (<1/10,000) cases of PML have been described in NHL patients receiving chemotherapy alone or receiving RITUXAN; in the majority of cases this occurred in combination with chemotherapy or as part of hematopoietic stem cell transplant.

JC virus infection with resultant PML and death has been reported in 2 patients with SLE treated with RITUXAN. Both of these patients had longstanding SLE with multiple courses of immunosuppressant use prior to receiving RITUXAN. These patients were diagnosed with PML within 12 months of their last infusion of RITUXAN. JC virus infection with resultant PML has also been reported in 1 patient with ANCA-negative Vasculitis/Cyroglobulinemia (Hepatitis C negative). The patient received immunosuppressive (including cytotoxic) therapy prior to receiving RITUXAN, and continued to receive immunosuppressive therapy in combination with RITUXAN. PML was diagnosed within 12 months of the first exposure to RITUXAN and the patient is currently undergoing treatment.

PML has been reported in patients with SLE and also in patients with Vasculitis receiving other immunosuppressants without concomitant RITUXAN. A causal relationship between RITUXAN and PML has not been established. The overall incidence of PML in patients with SLE or Vasculitis is not known. There have been no reports of PML in patients with autoimmune diseases receiving RITUXAN in Canada. We continue to follow this closely and any new information will be promptly communicated.

Physicians treating patients with autoimmune diseases or lymphoid malignancies should consider the diagnosis of PML in any patient presenting with new onset neurologic manifestations. Consultation with a neurologist, brain MRI and lumbar puncture may be considered as clinically indicated. There is no currently accepted screening test for PML.

In patients who develop PML, RITUXAN should be discontinued and reductions or discontinuation in concomitant immunosuppressive therapy and appropriate treatment should be considered. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs.

The Canadian Product Monograph (CPM) has been revised to include information on PML. The CPM can be found at the following link: <http://tinyurl.com/2tqk85>. 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 RITUXAN should be reported to Hoffmann-La Roche Limited, or Health Canada at the following addresses:



Hoffmann-La Roche Limited
Drug Safety Department
2455 Meadowpine Boulevard
Mississauga, Ontario, L5N 6L7
or call toll free at: 1-888-762-4388
or Fax at: 905-542-5864
or email to: mississauga.drug_safety@roche.com

Any suspected adverse reaction can also be reported to:

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
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

cadrmpp@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*.

http://hc-sc.gc.ca/dhp-mps/medeff/report-declaration/form/ar-ei_form_e.html

http://hc-sc.gc.ca/dhp-mps/medeff/report-declaration/guide/ar-ei_guide_ldir_e.html

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

Marketed Health Products Directorate (MHPD)

E-mail: mhpd_dpssc@hc-sc.gc.ca

Tel: (613) 954-6522

Fax: (613) 952-7738

Should you have any questions or require additional information regarding the use of RITUXAN, please contact the Drug Information Department at Hoffmann-La Roche Limited at 1-888-762-4388 from 8:30 a.m. to 4:30 p.m. Monday to Friday Eastern Standard Time.

Sincerely,

A handwritten signature in black ink, appearing to read "L. Biondi".

Lorenzo Biondi
Vice President, Medical and Regulatory Affairs
Hoffmann-La Roche Limited