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

October 21, 2009

Dear Healthcare Professional

Subject: **Association of RITUXAN® (rituximab) with Progressive Multifocal Leukoencephalopathy (PML)**

Hoffmann-La Roche Limited, in consultation with Health Canada, would like to inform healthcare professionals of important new safety information regarding the use RITUXAN® (rituximab) and progressive multifocal leukoencephalopathy (PML).

RITUXAN is authorized for the treatment of B-cell non-Hodgkin's Lymphoma (NHL), previously untreated B-cell chronic lymphocytic leukemia (B-CLL), stage B or C, and rheumatoid arthritis (RA) in combination with methotrexate to reduce signs and symptoms in adult patients with moderately to severely active RA who have had an inadequate response or intolerance to one or more tumour necrosis factor (TNF) inhibitor therapies**.**

Based upon recent post-marketing safety reports:

- A third case of progressive multifocal leukoencephalopathy (PML) has been reported in a patient with rheumatoid arthritis treated with RITUXAN.
- This is the first case of PML in a patient with rheumatoid arthritis receiving RITUXAN who has not been previously treated with other potent biologic immuno modulating therapies.
- While the potential mechanism of RITUXAN in the development of PML is unclear, a contributory role is possible. Available information to date suggests that patients with RA who receive RITUXAN may have an increased risk of PML.
- Physicians should consider PML in any patient being treated with RITUXAN who presents with new onset neurologic manifestations (i.e. cognitive impairment, motor deficit, speech and vision impairment) and should be immediately referred for neurological consultation).

Previously, 2 fatal cases of confirmed PML were reported in patients with rheumatoid arthritis treated with RITUXAN. These cases involved a 51 year-old woman and a 73 year-old woman with possible risk factors for the development of PML, including oropharyngeal malignancy treated with chemotherapy and radiation therapy and/or long standing lymphopenia prior to and during RITUXAN treatment.

The latest case occurred in a 73-year old woman with a diagnosis of seronegative rheumatoid arthritis of 3 years. Concomitant and/or prior treatments for rheumatoid arthritis included leflunomide, hydroxychloroquine, and prednisone. Other medical history included hypertension, hypothyroidism, osteoporosis, recurrent bronchitis and a cerebrovascular accident. She received one course of RITUXAN (1000 mg given two weeks apart). She developed dysesthesias and ataxia 4 to 6 months following treatment with RITUXAN. PML was diagnosed based on clinical symptoms, MRI findings, and detection of JC viral DNA in the CSF by PCR.

The overall reporting incidence of PML in patients with rheumatoid arthritis receiving RITUXAN is rare (3 reports in approximately 100,000 rheumatoid arthritis patients that have been exposed). While the potential mechanism of RITUXAN in the development of PML is unclear, a contributory role is possible. Based on the information to date, physicians treating patients with RA should consider that RITUXAN may increase the risk of PML.

Physicians should consider PML in any patient being treated with RITUXAN who presents with new onset neurologic manifestations. Consultation with a neurologist, brain MRI, and lumbar puncture (for JC virus PCR) should be considered as clinically indicated. In patients who develop PML, RITUXAN should be discontinued.

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. JC virus resides in latent form in 40-80% of healthy adults. 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 diseases, including RA. There are no known interventions that can reliably prevent or adequately treat PML.

The Canadian Product Monograph (CPM) includes information on PML and is being further updated to include additional guidance on PML. The CPM can be at found at: http://www.rochecanada.com

Managing marketed health product-related adverse reactions depends on healthcare 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 case of serious PML or other serious or unexpected adverse reactions in patients receiving RITUXAN should be reported to Hoffmann-La Roche 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:

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: 1-866-234-2345
Fax: 1-866-678-6789
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*.

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

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