Roche

Pharmaceuticals

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

November 10, 2006

Subject: **Reports of Bowel Obstruction and Gastrointestinal Perforation with RITUXAN® (rituximab)**

Dear Health Care Professional:

Hoffmann-La Roche Limited, following discussions with Health Canada, would like to inform you of new safety information regarding the use of RITUXAN®.

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).

Based on post-market and clinical study data:

- **Reports of abdominal pain, bowel obstruction, and perforation, in some cases leading to death, have been observed in patients receiving RITUXAN®. The majority of reports, including all deaths, have occurred in patients receiving RITUXAN® in combination with chemotherapy for the NHL indication.**
- **A causal relationship between RITUXAN® and these events has not been established.**
- **In post-marketing reports of patients with NHL, the mean time to onset of symptoms was 6 days from the start of therapy (range 1 day to 77 days) for documented gastrointestinal perforation.**
- **Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.**

Hoffmann-La Roche Limited/Limitée

Regulatory Affairs Department
2455 Meadowpine Boulevard,
Mississauga, Ontario L5N 6L7
www.rochecanada.com

Tel.: (905) 542-5555
Fax: (905) 542-5678

Information from the pharmacovigilance database for RITUXAN® indicates that 47 cases of bowel obstruction (9 deaths), and 37 cases of gastrointestinal perforation (4 deaths), have been reported in RITUXAN® patients, based on an approximately 730,000 cumulative patient exposure. The reports originate from both spontaneous sources and clinical studies and the majority of these cases were reported for the NHL indication.

Interpretation of the data from most of the 47 cases of bowel obstruction was difficult due to multiple risk factors, including gastrointestinal lymphoma, various other gastrointestinal disorders, and concomitant treatments, such as chemotherapy, steroids, and radiation therapy.

The site of gastrointestinal perforation in the cases of NHL included both the upper and lower gastrointestinal tract. Common risk factors in these reports included a history of gastrointestinal lymphoma at the time of the event and documented concomitant medications, including chemotherapy and prednisolone. Despite these confounding factors, a contributory role of RITUXAN® in causing gastrointestinal perforation in patients diagnosed with NHL has not been excluded. In addition, a pooled analysis of clinical trials in patients with NHL has indicated a higher incidence of gastrointestinal perforation in the arms treated with RITUXAN/chemotherapy compared to the arms treated with chemotherapy alone (0.38% vs 0.15%).

There have been 2 reports of bowel obstruction (1 death) and 2 reports of gastrointestinal perforation originating from Canada.

The Canadian Product Monograph (CPM) for RITUXAN® has been updated to include information on bowel obstruction and gastrointestinal perforation. The CPM can be found at the following link: http://www.rochecanada.com/pdf/rituxanHPE.pdf.

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 occurrences of serious and/or unexpected adverse reactions in patients receiving RITUXAN® should be reported to Hoffmann-La Roche Canada Ltd. 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
cadrmp@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: please refer to contact information.
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