Health Canada Endorsed Important Safety Information on ACTEMRA™ (tocilizumab)

September 13, 2010

Subject: ACTEMRA™ (tocilizumab) and the Risk of Fatal Anaphylaxis

Dear Health Care Professional,

Hoffmann-La Roche Limited, in consultation with Health Canada, would like to inform you of important new safety information regarding ACTEMRA™ (tocilizumab) and anaphylaxis. Roche is issuing this letter to ensure that you have the most recent information available when considering ACTEMRA as a treatment option for its approved uses.

ACTEMRA is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass with a H2L2 polypeptide structure. It is authorized for intravenous use to reduce the signs and symptoms of moderately to severely active rheumatoid arthritis in adult patients who have inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs) and/or tumour necrosis factor (TNF) antagonists.

Roche would like to inform you of the following;

- A case of fatal anaphylaxis has been reported in a patient with rheumatoid arthritis treated with ACTEMRA. No Canadian cases of anaphylactic reaction have been reported.
- As hypersensitivity reactions can occur with the administration of ACTEMRA, patients need to be closely monitored throughout the infusion for signs and symptoms of hypersensitivity.
- If a hypersensitivity reaction is suspected, infusion is to be stopped immediately and appropriate treatment should be administered.
- ACTEMRA should not be administered to patients with a known hypersensitivity to tocilizumab or any non-medicinal ingredient in ACTEMRA.

A post-marketing case of fatal anaphylaxis has been reported in an elderly patient with a prolonged history of rheumatoid arthritis who was treated with ACTEMRA. Prior treatments included methotrexate, sulfasalazine, azathioprine, etanercept, rituximab and abatacept. Concomitant medications included prednisone and leflunomide. Other medical history included hypertension for which the patient was being treated with a beta blocker and ACE inhibitor.

During the fourth infusion of 4 mg/kg ACTEMRA, the patient experienced lightheadedness resulting in discontinuation of the infusion. A decrease in systolic blood pressure below 90mm

Hg was noted, and medical management at the infusion center was followed by an emergency room evaluation. Two weeks later, the patient received a fifth infusion of ACTEMRA after pre-medication with steroids and antihistamines. Moments after the start of the infusion, the patient experienced dizziness and hypotension. Despite prompt medical intervention, the patient became apneic and unresponsive. The patient died within 24 hours of the anaphylactic event.

This is the first reported case of fatal anaphylaxis in a patient treated with ACTEMRA. Clinically significant hypersensitivity reactions associated with ACTEMRA requiring treatment discontinuation have been reported in 0.3% of all patients receiving tocilizumab in clinical trials. These reactions were generally observed during the second to fifth infusion of ACTEMRA.

The diagnosis of hypersensitivity or anaphylaxis should be considered in any patient experiencing an infusion reaction during or following ACTEMRA administration. If an anaphylactic or other serious hypersensitivity reaction occurs, administration of ACTEMRA should be stopped immediately. **Appropriate medical management should be initiated, and ACTEMRA should be permanently discontinued.**

We encourage you to review this additional important safety information with your patients.

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 case of serious hypersensitivity reactions, anaphylactic reactions or other serious or unexpected adverse reactions in patients receiving ACTEMRA 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:
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

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/pubs/medeff/_guide/2010-guid-dir_indust_hppc-cpsp/2010-temp-mod_dhcpl-aps_hp-ps-eng.php.

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 ACTEMRA, 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,

original signed by

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