Health Canada Endorsed Important Safety Information on AVASTIN® (bevacizumab)

August 19, 2010

Dear Health Care Professional:

Subject: Association of AVASTIN® (bevacizumab) with Hypersensitivity Reactions and Infusion Reactions

Hoffmann-La Roche Limited (Roche), in consultation with Health Canada, would like to inform you of an important update to the safety information regarding the use of AVASTIN. Hypersensitivity reactions and infusion reactions have been identified as risks in patients treated with AVASTIN.

AVASTIN is a recombinant humanized monoclonal antibody that is directed against the vascular endothelial growth factor (VEGF). It is authorized for intravenous administration in the following:

- first-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with fluoropyrimidine-based chemotherapy;
- treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer in combination with carboplatin/paclitaxel chemotherapy regimen;
- treatment of patients with metastatic HER2-negative breast cancer who are ECOG Class 0-1 in combination with paclitaxel*;
- treatment of patients with glioblastoma after relapse or disease progression, following prior therapy*.

**It should be noted that the breast cancer and glioblastoma indications have been issued a marketing authorization with conditions, pending the results of confirmatory studies to verify clinical benefit. A marketing authorization with conditions is issued to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.*

- A risk of developing serious hypersensitivity reactions, including anaphylactic and anaphylactoid reactions, has been reported in up to 5% of patients receiving AVASTIN in clinical trials. Post-marketing reports have also captured cases of serious hypersensitivity and infusion reactions.
- Infusion and hypersensitivity reactions may manifest as: dyspnea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors, and nausea/vomiting.
- Patients should be closely monitored for signs and symptoms of hypersensitivity or infusion reactions during and following the administration of AVASTIN infusion.
- If a reaction occurs, the infusion should be interrupted and appropriate medical therapies should be administered.

In clinical trials, anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving AVASTIN in combination with chemotherapy than with chemotherapy alone. The incidence of these reactions in clinical trials of AVASTIN is common (up to 5% in AVASTIN-treated patients). No fatal cases with a clear causal association with AVASTIN treatment have been reported so far from clinical trials.

AVASTIN has been administered to more than 500,000 cancer patients. Although, for the overall population, the incidence of hypersensitivity was very similar between the AVASTIN and comparator groups, imbalances were noted in hypersensitivity reactions and infusion reactions reported in some clinical studies among patients treated with AVASTIN and chemotherapy. Medical assessment of all reports from the Roche safety database showed that the majority of cases were confounded by concomitant chemotherapy. Seven cases of positive rechallenge and two cases with a positive cutaneous test were identified. In light of this information, Roche considers there is sufficient evidence to confirm the causal role of AVASTIN in the occurrence of hypersensitivity reactions and infusion reactions.

Patients should be closely monitored during and after AVASTIN infusion as expected for any infusion of a therapeutic humanized monoclonal antibody. If a reaction occurs, the infusion should be interrupted and appropriate medical therapies administered. A systematic premedication specifically for AVASTIN administration, in general, is not warranted; however, use of premedication should be based on clinical judgment.

The Canadian Product Monograph (CPM) for AVASTIN has been revised to include this updated 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 case of serious hypersensitivity reactions, infusion reactions, or other serious or unexpected adverse reactions in patients receiving AVASTIN should be reported to 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

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario K1A 0K9

The Reporting Forms, postage paid labels, and Guidelines can be found on the MedEffect™ Canada Web site in the Adverse Reaction Reporting section (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php). The Reporting Form is also 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
Tel: (613) 954-6522
Fax: (613) 952-7738

To change your mailing address or fax number, contact the Market Authorization Holder (Industry).

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

Sincerely,

original signed by

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