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

June 2007

Subject: Association of AVASTIN® (bevacizumab) with tracheo-esophageal (TE) fistula

Dear Health Care Professional:

Hoffmann-La Roche Limited, in consultation with Health Canada, would like to inform you of important new safety information regarding the use of AVASTIN® (bevacizumab).

AVASTIN is a recombinant humanized monoclonal antibody that is directed against the vascular endothelial growth factor (VEGF). It is authorized for the first-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with fluoropyrimidine based chemotherapy.

Based on review of post market and clinical trial reports:

- **Serious adverse events, including fatal events, of tracheo-esophageal (TE) fistula have been reported in association with use of AVASTIN clinical trials of small cell lung cancer (SCLC), non small cell lung cancer (NSCLC) and esophageal cancer.**
- **AVASTIN should be permanently discontinued in patients with tracheo-esophageal (TE) fistula or any gastrointestinal fistula. There is limited information on the continued use of AVASTIN in patients with other fistulas.**
- **In cases of internal fistula not arising in the GI tract, discontinuation of AVASTIN should be considered.**

Tracheo-esophageal (TE) Fistulas

There have been two confirmed serious adverse events of TE fistula (one fatal) reported in the first 29 patients enrolled in a U.S. investigator-sponsored multicenter, single-arm phase II trial, in patients with limited-stage small cell lung cancer (SCLC) treated with four cycles of concurrent irinotecan, carboplatin, radiotherapy, and AVASTIN followed by maintenance AVASTIN for up to 6 months. A third, fatal event (upper aerodigestive tract hemorrhage and death of unknown cause), was also reported, in which TE fistula was suspected but not confirmed. All three events occurred during the AVASTIN maintenance phase (during continued treatment with AVASTIN monotherapy) of the study in the presence of persistent (≥ 4 weeks) esophagitis. This study was closed for further recruitment as of March 12, 2007. No Canadian patients were enrolled in this study.

AVASTIN is not indicated for use in SCLC or for use in combination with concurrent radiotherapy and chemotherapy for any cancer indication. To date, no cases of TE fistula have been reported in Canada.

As of March 22, 2007, six additional cases of TE fistula have also been reported world wide in other lung and esophageal cancer studies involving the use of AVASTIN and chemotherapy alone or with concurrent radiation treatment. A review of all available data from AVASTIN clinical trials and spontaneous reports revealed that the events of TE fistulas observed to date with AVASTIN were reported in patients with

SCLC, non-small cell lung cancer and esophageal cancer. In SCLC patients, it remains unknown if this cluster of events was influenced by the concurrent use of radiotherapy. TE fistulas have not to date been reported in patients with metastatic colorectal cancer, but the possibility that this is a rare adverse drug reaction associated with AVASTIN in indications other than lung or esophageal cancer cannot be excluded.

There is limited information in the published literature on the background rate of TE fistula in patients with limited-stage SCLC, but it is estimated to be <1%[1]. The incidence of TE fistula observed in the U.S. investigator-sponsored trial to date exceeds this rate. Due to the small number of patients treated in the setting of limited-stage SCLC and the non-randomized nature of this trial, it is not possible to distinguish the toxicity observed in this trial from other risk factors for the development of TE fistula, such as intra-thoracic organ sensitivity from chemotherapy and radiotherapy alone.

Other Fistulas

In AVASTIN clinical trials, gastrointestinal fistulas have been reported with the highest incidence of around 2% in patients with metastatic colorectal cancer, but were also reported less commonly in patients with other types of cancers (e.g. breast cancer, lung cancer and others). Uncommon (≥ 0.1% to < 1%) reports of other types of fistulas (e.g. bronchopleural, urogenital and biliary fistulas) were observed across various indications. Fistulas have also been reported in post-marketing experience. Although other risk factors (e.g. diagnosis of cancer, cancer progression, cancer treatments) are known to be associated with an increased risk of development of fistulas, a role for AVASTIN in increasing this risk cannot be excluded.

Events were reported at various time points during treatment ranging from one week to greater than 1 year from initiation of AVASTIN, with most events occurring within the first 6 months of therapy.

A description of cases of gastrointestinal fistula formation in patients treated with AVASTIN in clinical studies and post-marketing reports is included in the current Canadian Product Monograph (CPM, see Warnings and Precautions, Gastrointestinal Perforation). Roche intends to revise the AVASTIN prescribing information to include more detailed information regarding the incidence of all cases of fistula in patients treated with AVASTIN.

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 AVASTIN 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
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://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_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 AVASTIN, 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

Reference:

1. Burt M, Diehl W, Martini N, et al. Malignant esophagorespiratory fistula: management options and survival. The Annals of Thoracic Surgery 1991; 52 (6): 1222-1228. Discussion 1228-1229.