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

July 14, 2008

Subject: Association of microangiopathic haemolytic anemia (MAHA) with the combined use of AVASTIN® (bevacizumab) and sunitinib malate in metastatic renal cell carcinoma.

Please distribute to relevant Departments: [e.g. Oncology, Hematology, Nephrology, Urology, Internal Medicine, Pharmacy, Laboratory Medicine and/or other departments as required] and other involved professional staff and **post this NOTICE** in your institution].

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) in combination with sunitinib malate.

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 clinical trial reports:

- In two recent clinical trials conducted in the US, combining AVASTIN (10 mg/kg IV q 2 weeks) and sunitinib malate 50 mg once daily, 7 of 19 patients (37%) with metastatic renal cell carcinoma exhibited laboratory findings consistent with microangiopathic haemolytic anemia (MAHA)
- In this group of 19 patients, grade 4 hypertension was noted in 3 of the 19 patients (16%) and Reversible Posterior Leukoencephalopathy Syndrome (RPLS) was noted in 2 of the 19 patients (11%).
- AVASTIN is not authorized for use in combination with sunitinib malate, nor for use at dosages above 5 mg/kg q 2 weeks.

MAHA is a subgroup of hemolytic anemia caused by thrombotic lesions in the microvessels and other mechanical causes and is associated with thrombocytopenia and red blood cell fragmentation. This is diagnosed by schistocytes on microscopy of the blood film together with other laboratory abnormalities such as LDH increase and reductions in serum haptoglobin.

Extended information on the safety finding

In a phase I study of the safety and maximum tolerated dose of sunitinib malate in combination with bevacizumab, patients with metastatic renal cell carcinoma (mRCC) were divided into 3 cohorts, each receiving a fixed dose of AVASTIN at 10 mg/kg every 2 weeks combined with either 25 mg, 37.5 mg, or 50 mg of sunitinib malate given per os daily in a 4 week on / 2 week off schedule. Of the 12 patients in the trial who were treated with the 50 mg dose of sunitinib, 5 were identified as having MAHA.

Two of 7 patients taking the same combination for the first-line treatment of mRCC in a phase II study were reported to have developed MAHA. This resulted in closure of this trial.

In summary, 7 of 19 patients treated with bevacizumab 10 mg/kg/2 weeks combined with sunitinib 50 mg daily developed MAHA. These 7 patients ranged in age from 41 to 76. The latency was reported in 5 patients and ranged from 14 to 196 days. Four of the cases were complicated by grade 3 to 4 hypertension and 2 of those cases also developed RPLS. In the cases that developed RPLS, there were additional events of thrombocytopenia, anemia, reticulocytosis, reductions in serum haptoglobin, modest increases in serum creatinine levels, severe hypertension and proteinuria. Hypertension and RPLS are labeled for AVASTIN and sunitinib malate.

The AVASTIN Canadian Product Monograph will be updated to reflect this new 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 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:
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/medeff/report-declaration/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 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