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

October 24, 2006

Subject: **Association of AVASTIN® (bevacizumab) with hypertensive encephalopathy and reversible posterior leukoencephalopathy syndrome (RPLS).**

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 AVASTIN.

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:

- **Rare cases of hypertensive encephalopathy have been reported in AVASTIN patients. AVASTIN should be permanently discontinued in patients who develop hypertensive encephalopathy.**
- **There have been rare reports of patients treated with AVASTIN developing Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a rare neurologic disorder, which can present with seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension.**
- **RPLS may be reversible if recognized and treated promptly. In patients developing RPLS, treatment of specific symptoms, including control of hypertension, if present, is recommended along with discontinuation of AVASTIN.**

The majority of these reports were for the treatment of conditions other than metastatic carcinoma of the colon or rectum.

Hypertensive Encephalopathy
Hypertensive encephalopathy is a complication of malignant hypertension. Signs and symptoms may include severe hypertension associated with headache, nausea, vomiting, convulsions, or confusion. Hypertensive encephalopathy may be reversible if treated by progressively reducing blood pressure to near normal ranges within several hours.

A total of three (3) confirmed cases of hypertensive encephalopathy have been reported in AVASTIN clinical studies (with an incidence of <0.1 %) and in post-marketing experience worldwide, based on patients' exposure of approximately 67,000. In all cases reported, patients had a medical history of hypertension, and markedly increased blood pressure (≥ 200 mmHg systolic). One (1) case resulted in a fatal outcome. No cases have been reported in Canada.

RPLS
RPLS can occur with or without associated hypertension and symptoms may include headache, seizure, confusion, cortical blindness, and other visual and neurologic disturbances. It may develop in patients who have renal insufficiency, hypertension, or who are immunosuppressed. RPLS has also been associated with the use of other medications, such as immunosuppressives or drugs used in cancer treatment.[1,2]

In patients receiving AVASTIN, a total of four (4) confirmed and ten (10) suspected cases of RPLS have been reported in clinical studies (with an incidence of <0.1 %) and post-marketing experience worldwide, based on patients' exposure of approximately 67,000. Two (2) of these reports have been recently published in the literature.[3] One (1) suspected case originated in Canada. The onset of symptoms has been reported to occur from 16 hours to 1 year after initiation of AVASTIN.

RPLS may be reversible if recognised and treated promptly. Detection and treatment of RPLS depends on rapid recognition of the neurologic signs and symptoms of RPLS. The symptoms of RPLS may be difficult to differentiate from those of uncontrolled hypertension, therefore neurological examination should be carried out in a patient presenting with the above signs and symptoms. Brain imaging, particularly MRI, confirms the diagnosis of RPLS. In patients developing RPLS, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of AVASTIN. Signs and symptoms of RPLS usually resolve within days, although neurologic sequelae may remain. The safety of reinitiating therapy with AVASTIN in patients previously experiencing RPLS is unknown.

The Canadian Product Monograph (CPM) for AVASTIN has been revised to include the above updated safety information. The CPM can be accessed at the following web address:
http://www.rochecanada.com/pdf/avastinHPE.pdf

Managing marketed health product related adverse reactions depends on health care professional and consumers reporting them. Reporting rates determined on the basis of spontaneous 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 Canada 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

References:

1. Stott VL. Hurell MA, Anderson TJ. Reversible Posterior Leukoencephalopathy Syndrome: A Misnomer Reviewed. Internal Med J, 2005;25:83-90.

2. Hinchey *et al*, A reversible posterior leukoencephalopathy syndrome. N Engl J Med, Feb 22, 1996., vol 334:494-500.

3. Glusker P, Recht L, Lane B, Ozcan C, Wong SJ, Hari P, Barron H. Reversible posterior leukoencephalopathy syndrome and bevacizumab [Letters to the editor]. N Engl J Med 2006;354:980-982.