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

December 2, 2011

Dear Health Care Professional:

Subject: Reports of severe infectious endophthalmitis leading to blindness following use of AVASTIN® (bevacizumab) when repackaged for unauthorized intravitreal injection

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

- **AVASTIN is not formulated for intravitreal use.**
- **Three clusters of serious ocular complications, including acute ocular inflammation, endophthalmitis, and infectious endophthalmitis resulting in blindness, have been recently reported in Florida, Tennessee, and California, all associated with intravitreal injection of AVASTIN.**
- **Although these clusters continue to be investigated, it is possible that the events of blindness from streptococcal endophthalmitis in Florida were due to repackaging of AVASTIN without proper aseptic technique.**
- **The production methods, formulation and dosages for AVASTIN were specifically developed for intravenous use in the oncology setting. Use of AVASTIN in the ophthalmology setting is not authorized in Canada.**

Further Information

Recently, Roche became aware of a cluster of Streptococcal endophthalmitis involving 12 patients injected within four days of each other in the area of Miami, Florida, US. Most of these patients have reported blindness or near blindness in the injected eye as a result of this infection. Additional information issued by the FDA can be found at: http://www.fda.gov/Drugs/DrugSafety/ucm270296.htm.

Inflammatory events, such as vitritis, uveitis, and sterile endophthalmitis, have previously been reported both as individual events and in clusters (following the repackaging of a single vial in a large number of syringes). Some of these events have led to blindness. One such cluster, reported in Canada, was the object of a Health Care

Professional Communication in 2008
(http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/avastin_4_hpc-cps-eng.php).

While a causal relationship between AVASTIN and the cluster events in Florida, Tennessee, or California has not been established, the reports are subject to ongoing analysis. Roche believes it is likely that the events of infectious endophthalmitis leading to blindness reported in Miami, Florida resulted from the repackaging of AVASTIN without proper aseptic technique. This can compromise product sterility, potentially putting the patients at risk for microbial infections with the number of patients being affected depending on the number of syringes repackaged from a single vial.

The Canadian Product Monograph contains information on unauthorized intravitreal use in the boxed warning and *Warnings and Precautions*. However, based on this new information, Roche will be working with Health Canada to implement further updates.

AVASTIN Indication Information

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 indications:

- 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 glioblastoma after relapse or disease progression, following prior therapy*.

  **It should be noted that the glioblastoma indication has 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.*

AVASTIN is packaged into single-use sterile preservative free vials for intravenous use in the oncology setting; the practice of repackaging single-use AVASTIN vials for intravitreal use into multiple aliquots may be associated with the contamination of the product.

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 ocular complications or other serious or unexpected adverse reactions in patients receiving AVASTIN should be reported to Roche or Health Canada.

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 health product 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,

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