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

November 9, 2011

Dear Health Care Professional:

Subject: Higher incidence of new cases of ovarian failure observed in premenopausal women treated with AVASTIN® (bevacizumab)

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.

- In NSABP C-08, a phase III trial in adjuvant treatment of patients with Stage II and III colon cancer, a higher incidence of new cases of ovarian failure has been observed in premenopausal women treated with AVASTIN + mFOLFOX6 as compared to mFOLFOX6 alone.
- As angiogenesis is required for normal cyclical ovarian function and as inhibition of folliculogenesis has been observed in animal models, a causal role of bevacizumab in the occurrence of ovarian failure must be considered possible.
- Fertility preservation strategies and hormonal changes associated with ovarian failure should be discussed with premenopausal women prior to starting treatment with AVASTIN.

Further Information

As already described in the current Canadian Product Monograph (CPM), repeat dose safety studies in animals have shown that bevacizumab, or specific VEGF blockade, results in a dose-dependent reversible inhibition of ovarian function, which may have an adverse effect on female fertility.

NSABP C-08, a phase III trial of mFOLFOX6+/-AVASTIN as adjuvant treatment of Stage II or III colon cancer included 2687 patients, of whom 1344 were women. The incidence of new cases of ovarian failure (defined as amenorrhea lasting 3 or more months, FSH levels ≥30 mIU/mL and a negative serum β-HCG pregnancy test occurring during protocol treatment) was evaluated in 295 premenopausal women included in the study.

The incidence of new cases of ovarian failure (defined as not having ovarian failure at randomization, but developing ovarian failure during protocol treatment) was 2.6% in the mFOLFOX6 group and 39.0% in the mFOLFOX6 + AVASTIN group. In this setting, age did not seem to be a risk factor for developing ovarian failure. After

bevacizumab treatment was discontinued, ovarian function recovered in 86.2% of evaluable women in the mFOLFOX6 + AVASTIN group.

Chemotherapy alone is a known risk factor for ovarian failure in patients with cancer. In the literature, a wide range of 17 to 77% incidence has been reported.

The CPM for AVASTIN has been revised to include this updated safety 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 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.*

AVASTIN is not authorized for use in combination with mFOLFOX6 as adjuvant treatment of patients with colon cancer.

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 ovarian failure 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

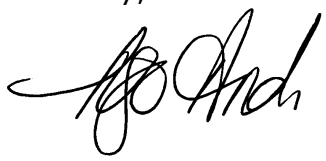
The Reporting Forms, postage paid labels, and Guidelines can be found on the MedEffect™ Canada Web site in the Adverse Reaction Reporting section (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php). The Reporting Form is also in the *Canadian Compendium of Pharmaceuticals and Specialties.*

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
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