

**Health Canada Endorsed Important Safety Information on
HERCEPTIN® (trastuzumab)**



April 21, 2009

Dear Healthcare Professionals:

Subject: Association of HERCEPTIN® (trastuzumab) with Oligohydramnios

Hoffmann-La Roche Limited, in consultation with Health Canada, would like to inform prescribers of important new safety information regarding the use of HERCEPTIN® (trastuzumab) during pregnancy.

HERCEPTIN is a recombinant DNA-derived humanised monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER-2). Overexpression of HER-2 protein is observed in 25%-30% of primary breast cancers. Trastuzumab has been shown, both in in-vitro assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER-2.

HERCEPTIN is authorized for:

- The treatment of patients with early stage breast cancer, whose tumours overexpress HER-2, following surgery and after chemotherapy.
- The treatment of patients with metastatic breast cancer whose tumours substantially overexpress HER-2.

In the post-marketing setting, cases of oligohydramnios during the second and third trimesters have been reported in pregnant women receiving HERCEPTIN.

A review was recently completed of six reports of oligohydramnios that were reported between 2004 and August 2008. Four reports originated from literature articles⁽¹⁻⁴⁾. Two spontaneous reports concerned one twin pregnancy.

Literature cases (4):

- All mothers were exposed to trastuzumab and at least one other chemotherapeutic agent during pregnancy. All had also received chemotherapy prior to trastuzumab.
- The mothers gave birth to viable infants who continued to develop normally up to five years after birth despite limited post-partum complications with no long-term effects.
- In three cases, a decrease in amniotic fluid level was diagnosed seven weeks after the start of trastuzumab.
- A causal relationship to trastuzumab could not be ruled out.

Spontaneous cases (twins)

- Not enough information was provided to assess a causal relationship to trastuzumab.

Based on the information available a potential causal relationship to trastuzumab cannot be excluded.

However from the limited information about oligohydramnios in 5 women exposed to trastuzumab, we conclude that the fetal outcome is not different than in women who have not been exposed to trastuzumab.

Consistent with the product monograph, the recommendation remains that HERCEPTIN should not be used during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

If trastuzumab is administered during pregnancy, monitoring of the amniotic fluid is recommended.

The HERCEPTIN Canadian Product Monograph has been updated to include the post marketing cases of oligohydramnios and provides the following information under **Special Populations, Pregnant Women:**

“Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times the weekly human maintenance dose of 2 mg/kg HERCEPTIN and have revealed no evidence of impaired fertility or harm to the fetus. However, when assessing the risk of reproductive toxicity in humans, it is important to consider the significance of the rodent form of the HER2 receptor in normal embryonic development and the embryonic death in mutant mice lacking this receptor ⁽¹⁾. Placental transfer of HERCEPTIN during the early (days 20-50 of gestation) and late (days 120-150 of gestation) fetal development period was observed.

There are, however, no adequate and well-controlled studies in pregnant women and it is not known whether HERCEPTIN can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. In the post-marketing setting, cases of oligohydramnios during the second and third trimesters have been reported in pregnant women receiving HERCEPTIN. Because animal reproduction studies are not always predictive of human response, HERCEPTIN should not be used during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.”

The Product Monograph, Part III Consumer Information, also contains a warning for consumers that BEFORE they use HERCEPTIN they should talk to their doctor or pharmacist if they are pregnant, plan to become pregnant or are breast-feeding a child.

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 oligohydramnios or other serious or unexpected adverse reactions in patients receiving HERCEPTIN 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/form/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 HERCEPTIN, 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,

Original signed by

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

References:

1. Fanale MA *et al.* Treatment of metastatic breast cancer with trastuzumab and vinorelbine during pregnancy. *Clinical Breast Cancer*: Vol. 6 (4), 2005; 354-356.

2. Pant *et al.* Treatment of breast cancer with trastuzumab during pregnancy. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, {J-Clin-Oncol}, 20 Mar 2008: Vol. 26 (9); 1567-9.
3. Bader AA *et al.* Anhydramnios associated with administration of trastuzumab and paclitaxel for metastatic breast cancer during pregnancy. *Lancet Oncol* 2007; 8: 79–81.
4. Sekar *et al.* Trastuzumab use for metastatic breast cancer in pregnancy (Report). *Obstetrics & Gynecology*, 2007: 110 (2{2}) (Supplement); 507-510.