



National Institutes of Health  
National Cancer Institute  
Bethesda, Maryland 20892

**DATE:** February 11, 2011

**FROM:** Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI

**SUBJECT:** Trastuzumab (Herceptin®) Investigator Notification: **Fatal Embryo-Fetal Toxicity (Severe oligohydramnios)**

**TO:** Investigators Using Trastuzumab (NSC 688097)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. A Dear Healthcare Professional notification which describes severe oligohydramnios in children, whose mothers were exposed to trastuzumab during pregnancy while participating in Genentech-sponsored clinical studies utilizing the investigational agent trastuzumab, was recently distributed to investigators.

The following must be completed by all investigators using Trastuzumab under IND 6667:

- Send a copy of the IND Safety Report to your Institutional Review Board (IRB) according to your local IRB's policies and procedures.
- File a copy of the IND Safety Report in your protocol file.

If your study is not covered under IND 6667, it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with Trastuzumab, there does not appear to be a change in the risk-benefit ratio for Trastuzumab studies; therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The Dear Healthcare Professional Letter that describes the following adverse event is attached:

Based on post-marketing adverse events reports, the U.S. product label for trastuzumab has been updated to include information regarding the sequelae of severe oligohydramnios in pregnant women exposed to trastuzumab.

Attachment: Dear Healthcare Professional Letter



## IMPORTANT DRUG WARNING

### **SUBJECT: Fatal Embryo-Fetal Toxicity due to Herceptin Exposure During Pregnancy**

Dear U.S. Healthcare Professional:

Genentech, Inc. would like to inform you of important new safety information regarding Herceptin (trastuzumab). Based on post-marketing adverse event reports, cases of oligohydramnios or oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death have been reported in children whose mothers were exposed to Herceptin during pregnancy. These cases resulted from severe oligohydramnios, a known and labeled adverse reaction of Herceptin for which fetal malformation and death were not previously reported.

The following sections of the U.S. product label for Herceptin have been updated to include information regarding the sequelae of severe oligohydramnios in pregnant women exposed to Herceptin:

#### BOXED WARNING

##### Embryo-Fetal Toxicity

Exposure to Herceptin during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. [see *Warnings and Precautions (5.3)*, *Use in Specific Populations (8.1)*]

#### Warnings and Precautions

##### Embryo-Fetal Toxicity

Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise women of the potential hazard to the fetus resulting from Herceptin exposure during pregnancy and provide contraception counseling to women of childbearing potential. [see *Use in Specific Populations (8.1)*, *Patient Counseling Information (17)*].

## Use in Specific Populations (8.1)

### Pregnancy

Pregnancy Category D [see *Warnings and Precautions (5.3)*, *Nonclinical Toxicology (13.2)*]

Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing reports use of Herceptin during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

These case reports described oligohydramnios in pregnant women who received Herceptin either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after Herceptin was stopped. In one case, Herceptin therapy resumed after the amniotic fluid index improved, and oligohydramnios recurred.

Monitor women exposed to Herceptin during pregnancy for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care. The efficacy of IV hydration in management of oligohydramnios due to Herceptin exposure is not known.

Advise women of the potential hazard to the fetus resulting from Herceptin exposure during pregnancy. Encourage pregnant women with breast cancer who are using Herceptin to enroll in MoTHER - the Herceptin Pregnancy Registry: phone 1-800-690-6720. [see *Patient Counseling Information (17)*].

No teratogenic effects were observed in offspring from reproduction studies in cynomolgus monkeys at doses up to 25 times the recommended weekly human dose of 2 mg/kg trastuzumab. In mutant mice lacking HER2, embryos died in early gestation. Trastuzumab exposure was reported at delivery in offspring of cynomolgus monkeys treated during the early (Days 20-50 of gestation) or late (Days 120-150 of gestation) fetal development periods, at levels of 15 to 28% of the maternal blood levels.

### Patient Counseling Information

- Advise pregnant women and women of childbearing potential that Herceptin exposure can result in fetal harm [see *Warnings and Precautions (5.3)* and *Use in Specific Populations (8.1)*].

- Advise women of childbearing potential to use effective contraceptive methods during treatment and for a minimum of six months following Herceptin [see *Warnings and Precautions* (5.3)].
- Advise nursing mothers treated with Herceptin to discontinue nursing or discontinue Herceptin, taking into account the importance of the drug to the mother [see *Use in Specific Populations* (8.3)].
- Encourage women who are exposed to Herceptin during pregnancy to enroll in MoTHER - the Herceptin Pregnancy Registry [see *Pregnancy* (8.1)].

Herceptin can cause oligohydramnios. Severe oligohydramnios can result in pulmonary hypoplasia by causing intrauterine mechanical compression of the fetus and prevention of intrauterine expansion and contraction of fetal lungs, which results in decreased amniotic fluid hydrostatic pressure in the developing alveoli.

Provide contraceptive counseling on methods of contraception to all women of child-bearing potential undergoing Herceptin treatment. Women on active breast cancer treatment can become amenorrheic. Despite amenorrhea, ovulation can occur. Given the overlap in symptoms of anti-cancer treatment and pregnancy, pregnancy may not be recognized in the first trimester.

A woman who chooses to continue Herceptin during pregnancy should do so in close consultation with an oncologist and obstetrician. In all women who are exposed to Herceptin during pregnancy, monitor the pregnancy closely with serial ultrasound measurements. Inform the patient of the risks of oligohydramnios and its sequelae, including fatal fetal pulmonary hypoplasia.

Our primary concern is the safety and well-being of patients who receive Herceptin treatment. Genentech maintains a pregnancy registry for women who become pregnant and are exposed to Herceptin during the 6 months prior to conception or at any time during pregnancy (MoTHER - the Herceptin Pregnancy Registry: 1-800-690-6720). Serious adverse events suspected to be associated with the use of Herceptin should be reported to Genentech at 1-888-835-2555. Alternatively, such information may be reported to FDA's MedWatch reporting system, either on-line at <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>, by telephone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), or by mail using the MedWatch Form FDA 3500 (FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville MD 20852-9787).

A copy of the current Herceptin Prescribing Information is enclosed. We encourage you to review the full prescribing information and discuss this important new safety information with your patients.

Sincerely,



---

Mona Shing, M.D.  
Senior Medical Director, Herceptin  
Genentech

The following safety information is excerpted from the Herceptin Prescribing Information enclosed with this letter.

#### **INDICATIONS AND USAGE**

Herceptin is a HER2/neu receptor antagonist indicated for the treatment of HER2 overexpressing breast cancer.

In the adjuvant breast cancer setting, Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel; with docetaxel and carboplatin; and as a single agent following multi-modality anthracycline based therapy.

In the metastatic breast cancer setting, Herceptin is indicated in combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer, and as a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

In the metastatic gastric cancer setting, Herceptin is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease.

#### **BOXED WARNING**

##### **Cardiomyopathy**

Herceptin administration can result in sub-clinical and clinical cardiac failure manifesting as CHF and decreased LVEF. The incidence and severity of left ventricular cardiac dysfunction was highest in patients who received Herceptin concurrently with anthracycline-containing chemotherapy regimens.

Evaluate left ventricular function in all patients prior to and during treatment with Herceptin. Discontinue Herceptin treatment in patients receiving adjuvant therapy and strongly consider discontinuation of Herceptin treatment in patients with metastatic breast cancer for clinically significant decrease in left ventricular function. [see *Warnings and Precautions (5.1) and Dosage and Administration (2.2)*]

### **Infusion Reactions; Pulmonary Toxicity**

Herceptin administration can result in serious infusion reactions and pulmonary toxicity. Fatal infusion reactions have been reported. In most cases, symptoms occurred during or within 24 hours of administration of Herceptin. Herceptin infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinue Herceptin for infusion reactions manifesting as anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. [see *Warnings and Precautions (5.2, 5.4)*]

### **Embryo-Fetal Toxicity**

Exposure to Herceptin during pregnancy can result in oligohydramnios or oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. [see *Warnings and Precautions (5.3), Use in Specific Populations (8.1)*]

## **ADVERSE REACTIONS**

### **Adjuvant Breast Cancer**

Adverse reactions ( $\geq 2\%$  higher incidence with Herceptin-containing treatment compared with control treatment) are fatigue, infection, neutropenia, anemia, myalgia, dyspnea, rash/desquamation, headache, diarrhea, and nausea.

### **Metastatic Breast Cancer**

Adverse reactions ( $\geq 15\%$  incidence with Herceptin monotherapy or  $\geq 5\%$  with Herceptin/ paclitaxel) are nausea, fever, infection, rash, increased cough, vomiting, diarrhea, headache, and anemia.

### **Metastatic Gastric Cancer**

Adverse reactions ( $\geq 10\%$  incidence with  $\geq 5\%$  difference between the Herceptin and chemotherapy arms) were neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. The most common adverse reactions which resulted in discontinuation of treatment on the Herceptin-containing arm in the absence of disease progression were infection, diarrhea, and febrile neutropenia.

For any questions regarding the use of Herceptin, please refer to the Herceptin Product Information at [www.gene.com](http://www.gene.com) or call our Medical Communications Department at 1-800-821-8590.