

The following is a message from the FDA's Office of Oncology Drug Products Director, Dr. Richard Pazdur:

Changes in the Avastin[®] Package Insert Regarding Warning and Dose and Administration for Non-Gastrointestinal Fistula Formation

This communication informs you of recent changes made to the Avastin[®] Injection prescription information. On March, 2007 the FDA was informed of the occurrence of two confirmed and one suspected cases of tracheoesophageal fistula in an investigator-sponsored trial using bevacizumab concurrently with chemoradiation in the treatment of limited-stage small cell lung cancer. Three cases were fatal. The trial was closed and a Dear Healthcare Provider letter was issued.

At the FDA's request, Genentech performed a search in the safety database of all events of "fistula" occurring with Avastin[®]. Results of this search serve as the basis for this safety labeling update. The occurrence of fistula associated with bevacizumab treatment is currently labeled in the Avastin[®] U.S. Package Insert under gastrointestinal perforations, along with intra-abdominal abscess formation. A new subsection is added to the "WARNINGS" section of the Avastin[®] label as follows:

"Non-Gastrointestinal Fistula Formation

Non-gastrointestinal fistula formation has been reported in patients treated with AVASTIN[®] in controlled clinical studies (with an incidence of < 0.3%) and in post-marketing experience, in some cases with fatal outcome. Fistula formation involving the following areas of the body other than the gastrointestinal tract has been reported: tracheo-esophageal, bronchopleural, biliary, vaginal and bladder. Events were reported throughout treatment with Avastin[®], with most events occurring within the first 6 months.

Permanently discontinue AVASTIN[®] in patients with fistula formation involving an internal organ." The DOSAGE AND ADMINISTRATION section has been revised to recommend Avastin[®] discontinuation in patients who develop fistula formation involving an internal organ: "AVASTIN[®] should be permanently discontinued in patients who develop gastrointestinal perforation (gastrointestinal perforation, fistula formation in the gastrointestinal tract, intra-abdominal abscess), fistula formation involving an internal organ, wound dehiscence requiring medical intervention, serious bleeding, a severe arterial thromboembolic event, nephrotic syndrome, hypertensive crisis or hypertensive encephalopathy"

Full prescribing information, including clinical trial information, safety, dosing, drug-drug interaction, contraindications is available at
<http://www.fda.gov/cder/foi/label/2007/125085s131lbl.pdf>.

Healthcare professionals should report all serious adverse events suspected to be associated with the use of any medicine and device to FDA's MedWatch Reporting System by phone at 1-800-FDA-1088, by facsimile 1-800-FDA-0178, by mail, or by using the Form 3500 at
<http://www.fda.gov/medwatch/index.html>.