

April 2007

IMPORTANT DRUG WARNING
Regarding AVASTIN® (bevacizumab)

Dear Healthcare Provider:

Genentech, Inc. would like to inform you of important new safety information regarding AVASTIN® (bevacizumab). This information concerns **tracheoesophageal (TE) fistula** that occurred in a study combining concurrent chemotherapy and radiation plus AVASTIN in patients with limited-stage small cell lung cancer (SCLC). AVASTIN is not indicated for use in SCLC.

In an investigator-sponsored multicenter, single-arm phase II trial, patients with limited-stage SCLC received four cycles of concurrent irinotecan, carboplatin, radiation therapy, and AVASTIN followed by maintenance AVASTIN for up to 6 months. There have been two confirmed serious adverse events of TE fistula (one fatal) reported in the first 29 patients enrolled in the study. A third, fatal event (upper aerodigestive tract hemorrhage and death of unknown cause), was also reported, in which TE fistula was suspected but not confirmed. All three events occurred during the AVASTIN maintenance phase of the study in the context of persistent esophagitis. As of March 22, 2007, six cases of TE fistula have also been reported in other lung and esophageal cancer studies involving the use of AVASTIN and chemotherapy alone or with concurrent radiation treatment.

There is limited information in the published literature on the background rate of TE fistula in patients with limited-stage SCLC, but is estimated to be <1%. The incidence of TE fistula observed in this trial to date exceeds this rate. Due to the small number of patients treated in the setting of limited-stage SCLC and the non-randomized nature of this trial, it is not possible to distinguish the toxicity observed in this trial from other risk factors for the development of TE fistula, such as intra-thoracic organ sensitivity from chemotherapy and radiotherapy alone. This study has been closed to further accrual as of March 12, 2007.

A description of cases of gastrointestinal tract fistula formation in patients with colorectal cancer and other types of cancer treated with AVASTIN in clinical studies and post-marketing reports is included in the current US prescribing information (see WARNINGS: Gastrointestinal Perforation). Genentech intends to revise the AVASTIN package insert to include more detailed information regarding the incidence of all cases of fistula in patients treated with AVASTIN.

AVASTIN is currently approved for the first-line and second-line treatment of metastatic colorectal cancer in combination with intravenous 5-FU-based chemotherapy, in addition to the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer in combination with carboplatin and paclitaxel.

We have enclosed the current AVASTIN package insert for your information. Should you have any questions regarding the use of AVASTIN, please call our Medical Information/Communications Department at 1-800-821-8590.

Healthcare professionals should report any serious adverse events suspected to be associated with the use of AVASTIN to Genentech at 1-888-835-2555. Alternatively, this information may be reported to FDA's MedWatch reporting system by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), online (<https://www.accessdata.fda.gov/scripts/medwatch/>) or mailed, using the MedWatch for FDA 3500, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

Sincerely,

A handwritten signature in blue ink, appearing to read "Hal Barron", with a long horizontal flourish extending to the right.

Hal Barron, M.D., FACC
Senior Vice President, Development
Chief Medical Officer
Genentech, Inc.