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**Important Drug Notification
Reports of Intraocular Inflammatory Reactions
After Intravitreal Injection with AVASTIN®**

Dear Healthcare Provider:

Genentech, Inc. would like to inform you of important safety information regarding off-label intravitreal use of AVASTIN® (bevacizumab).

As of December 8, 2008, Genentech, Inc. through its global partner F. Hoffmann-La Roche Ltd (Roche) is aware of 36¹ reports of intraocular adverse events, 32 of which are serious intraocular inflammatory reactions, all originating in Canada and following off-label intravitreal use of Avastin. These events were reported to Roche between November 4th and 20th, 2008 from four different reporting sites.

Twenty-five of these events occurred in patients who were administered aliquots from vials of AVASTIN lot B3002B028 intravitreally. Analytical release data for this lot have been reviewed by Genentech and Roche; all quality specifications established for approved intravenous use of AVASTIN were met. A review of adverse event reports occurring in patients who received intravenous AVASTIN did not reveal any unusual reporting patterns with lot B3002B028, which was not distributed in the United States.

The current production methods, formulation, single-use vial configuration, and dosages for AVASTIN were developed specifically for intravenous use in the oncology setting. Use of AVASTIN in the ophthalmology setting is not FDA approved.

Patient safety is a priority at Genentech, and we routinely monitor the safety of our products. Healthcare professionals should report any serious adverse events suspected to be associated with the use of AVASTIN or any of our other products to Genentech at 1-888-835-2555. Alternatively, report this information 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.

AVASTIN is currently approved for the first-line or second-line treatment of metastatic colorectal cancer (MCRC) in combination with intravenous 5-FU-based chemotherapy.

AVASTIN is also currently approved for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer (NSCLC) in combination with carboplatin and paclitaxel.

Additional Information on the Safety of Avastin Administered Intravenously in the Oncology Setting:

Gastrointestinal (GI) perforation: Avastin administration can result in the development of GI perforation, in some cases resulting in fatality. GI perforation, sometimes associated with intra-abdominal abscess, occurred throughout treatment with Avastin (ie, was not correlated to duration of exposure). Permanently discontinue Avastin therapy in patients with GI perforation.

Wound healing complication: Avastin administration can result in the development of wound dehiscence, in some instances resulting in fatality. Permanently discontinue Avastin therapy in patients with wound dehiscence requiring medical intervention. The appropriate interval between termination of Avastin and subsequent elective surgery has not been determined.

Hemorrhage: Severe, and in some cases fatal, pulmonary hemorrhage can occur in patients with NSCLC treated with chemotherapy and Avastin. Do not administer Avastin to patients with recent hemoptysis ($\geq 1/2$ tsp of red blood). Other serious bleeding events occurring in patients receiving Avastin across all indications include GI hemorrhage, subarachnoid hemorrhage, and hemorrhagic stroke. Permanently discontinue Avastin in patients with serious hemorrhage (i.e., requiring medical intervention) and initiate aggressive medical management.

Additional serious adverse events included non-GI fistula formation, arterial thromboembolic events, hypertensive crisis, reversible posterior leukoencephalopathy syndrome, neutropenia and infection, nephrotic syndrome, and congestive heart failure.

The most common grade 3–5 (nonhematologic) and 4–5 (hematologic) events that may have occurred in Avastin indications (first-line NSCLC, first- or -second-line MCRC) included neutropenia, fatigue, hypertension, infection, hemorrhage, asthenia, abdominal pain, pain, deep vein thrombosis, intra-abdominal thrombosis, syncope, diarrhea, constipation, leukopenia, nausea, vomiting, dehydration, ileus, neuropathy–sensory, neurologic–other, and headache.

The current Avastin package insert is enclosed. For questions regarding the use of Avastin please call our Medical Information/Communications Department at 1-800-821-8590.

Sincerely,



Hal Barron, MD
Senior Vice President, Development
Chief Medical Officer
Genentech, Inc.