

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

On February 22, 2008, the U.S. Food and Drug Administration granted accelerated approval for bevacizumab (Avastin®, Genentech, Inc.) to be used in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2 negative breast cancer.

The approval was based on the demonstration of an improvement in progression-free survival (PFS) in patients receiving Avastin® with paclitaxel compared to those receiving paclitaxel alone as a first-line treatment for metastatic breast cancer. No data are currently available that demonstrate an improvement in disease-related symptoms or increased overall survival with Avastin® in breast cancer.

The efficacy and safety of Avastin® as first-line treatment of patients with metastatic breast cancer was studied in a single, open-label, randomized, multicenter study (Study 7 or E2100). Patients who had not received chemotherapy for locally recurrent or metastatic breast cancer were randomized to receive either paclitaxel (N=354 patients) alone at 90 mg/m² weekly for 3 doses with one week rest (28-day cycle) or in combination with Avastin 10 mg/kg every 14 days (N=368 patients). Patients with HER2-overexpressing breast cancer were not eligible unless they had received prior therapy with Herceptin.

The addition of Avastin® to paclitaxel resulted in an improvement in PFS with no significant improvement in overall survival. The median PFS was 11.3 months (95% CI 10.5,13.3) and 5.8 months (95% CI 5.4, 8.2) months for the Avastin® plus paclitaxel arms versus the paclitaxel alone, respectively (p<0.0001, HR 0.48, 95% CI 0.39, 0.61) Partial response rates in patients with measurable disease were higher with Avastin® plus paclitaxel: 48.9% versus 22.2% (p<0.001). No complete responses were observed.

The efficacy and safety of Avastin® as a second and third line treatment of patients with metastatic breast cancer were studied in a single open-label randomized study (Study 8 or AVF2119). Patients who had received prior anthracycline and taxane therapy in the adjuvant setting or for their metastatic breast cancer were randomized to receive either capecitabine alone or in combination with Avastin®. The study enrolled 462 patients. The study failed to demonstrate a statistically significant effect on PFS or overall survival. The product labeling specifies that Avastin® is not indicated for patients with breast cancer that has progressed following anthracycline and taxane chemotherapy administered for metastatic disease.

Data collection in Trial 7 was limited to NCI-CTC grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events. A 20% increase in grade 3-5 adverse events was observed in the Avastin® plus paclitaxel arm compared to paclitaxel alone. Severe and life-threatening adverse events occurring more frequently on the Avastin®-containing arm included sensory neuropathy, hypertension, fatigue, infection without neutopenia, neutropenia, vomiting, diarrhea, bone pain, headache, proteinuria, and cerebrovascular ischemia. Fatal adverse reactions occurred in 6/363 (1.7%) of patients who received paclitaxel plus Avastin®. Causes of death were gastrointestinal perforation (2 patients), myocardial infarction (2 patients), diarrhea/abdominal pain/weakness/hypotension (2 patients).

The most serious, and sometimes fatal, Avastin® adverse events have been previously described in product labeling and include gastrointestinal perforation, wound healing complications, hemorrhage,

arterial thromboembolic events, hypertensive crisis, nephrotic syndrome, congestive heart failure, and neutropenic sepsis. The most common Avastin® adverse events previously described in product labeling include asthenia, pain, abdominal pain, headache, hypertension, diarrhea, nausea, vomiting, anorexia, stomatitis, constipation, upper respiratory infection, epistaxis, dyspnea, exfoliative dermatitis, and proteinuria.

Full prescribing information, including clinical trial information, safety, dosing, drug-drug interactions and contraindications, is available at
<http://www.fda.gov/cder/foi/label/2008/125085s91lbl.pdf>.