

April 2011

Dear Healthcare Provider,

Avastin is indicated for the treatment of glioblastoma (GBM) in adult patients with progressive disease following prior therapy as a single agent. The effectiveness of Avastin in GBM is based on an improvement in objective response rate (ORR). There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin.

The efficacy of Avastin was demonstrated using response assessment based on both WHO radiographic criteria and by stable or decreasing corticosteroid use, which occurred in 25.9% (95% CI: 17.0%–36.1%) of the patients. Median duration of response was 4.2 months (95% CI: 3.0–5.7). Radiologic assessment was based on MRI imaging (using T1 and T2/FLAIR). MRI does not necessarily distinguish between tumor, edema, and radiation necrosis.

Avastin was evaluated in an open-label, multicenter, randomized, noncomparative study of patients with previously treated GBM. Patients received Avastin 10 mg/kg as a solution for intravenous (IV) infusion alone or Avastin plus irinotecan* every 2 weeks until disease progression or until unacceptable toxicity. Of the 85 patients randomized to the Avastin arm, the median age was 54 years, 32% were female, 81% were in first relapse, and Karnofsky performance status was 90–100 for 45% of patients and 70–80 for 55% of patients. All patients received prior radiotherapy (completed at least 8 weeks prior to receiving Avastin) and temozolomide. Patients with active brain hemorrhage were excluded.

The efficacy of Avastin was supported by an ORR of 19.6% (95% CI: 10.9%–31.3%) in a single-arm, single-institution trial with 56 patients with GBM, using the same response criteria. Median duration of response was 3.9 months (95% CI: 2.4–17.4). All patients had documented disease progression after receiving temozolomide and radiation therapy. Patients received Avastin 10 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity. The median age was 54 years, 54% were male, 98% were Caucasian, and 68% had a Karnofsky performance status of 90–100.

In patients receiving Avastin alone (N=84), the most frequently reported adverse events of any grade were infection (55%), fatigue (45%), headache (37%), hypertension (30%), epistaxis (19%), and diarrhea (21%). Of these, the incidence of grade ≥ 3 adverse events was infection (10%), fatigue (4%), headache (4%), hypertension (8%), and diarrhea (1%). Two deaths on study were possibly related to Avastin: one retroperitoneal hemorrhage and one neutropenic infection.

*Avastin is not approved for use in combination with irinotecan.

Please see accompanying full Prescribing Information, including **Boxed WARNINGS**, and pages 2 and 3 for additional important safety information.



In patients receiving Avastin alone or Avastin plus irinotecan* (N=163), the incidence of Avastin related adverse events (Grade 1–4) were bleeding/hemorrhage (40%), epistaxis (26%), CNS hemorrhage (5%), hypertension (32%), venous thromboembolic event (8%), arterial thromboembolic event (6%), wound-healing complications (6%), proteinuria (4%), gastrointestinal perforation (2%), and RPLS (1%). The incidence of grade 3–5 events in these 163 patients were bleeding/hemorrhage (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial thromboembolic event (3%), wound-healing complications (3%), proteinuria (1%), and gastrointestinal perforation (2%). Intracranial hemorrhage occurred in eight of the 163 patients; two patients had Grade 3–4 hemorrhage.

Avastin was discontinued due to adverse events in 4.8% of patients treated with Avastin alone.

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Indication

Avastin is indicated for the treatment of glioblastoma as a single agent for adult patients with progressive disease following prior therapy. The effectiveness of Avastin in glioblastoma is based on an improvement in objective response rate. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin.

Boxed WARNINGS and additional important safety information

- **Gastrointestinal (GI) perforation:** Serious and sometimes fatal GI perforation occurs at a higher incidence in Avastin-treated patients compared to controls. The incidences of GI perforation ranged from 0.3% to 2.4% across clinical studies. Discontinue Avastin in patients with GI perforation
- **Surgery and wound healing complications:** The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients. Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined. Discontinue Avastin at least 28 days prior to elective surgery and in patients with wound dehiscence requiring medical intervention
- **Hemorrhage:** Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin. Across indications, the incidence of grade ≥ 3 hemorrhagic events among patients receiving Avastin ranged from 1.2% to 4.6%. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis ($\geq 1/2$ tsp of red blood). Discontinue Avastin in patients with serious hemorrhage (ie, requiring medical intervention)
- Additional serious and sometimes fatal adverse events for which the incidence was increased in the Avastin-treated arm vs control included non-GI fistula formation ($\leq 0.3\%$), arterial thromboembolic events (grade ≥ 3 , 2.4%), and proteinuria including nephrotic syndrome ($< 1\%$). Additional serious adverse events for which the incidence was increased in the Avastin-treated arm vs control included hypertension (grade 3–4, 5%–18%) and reversible posterior leukoencephalopathy syndrome (RPLS) ($< 0.1\%$). Infusion reactions with the first dose of Avastin were uncommon ($< 3\%$), and severe reactions occurred in 0.2% of patients

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- The most common adverse reactions observed in Avastin patients at a rate >10% and at least twice the control arm rate were epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain, and exfoliative dermatitis. Across all studies, Avastin was discontinued in 8.4% to 21% of patients because of adverse reactions
- Based on animal data, Avastin may cause fetal harm and may impair fertility. Advise patients of the potential risk to the fetus during and following Avastin and the need to continue adequate contraception for at least 6 months following the last dose of Avastin. For nursing mothers, discontinue nursing or Avastin, taking into account the importance of Avastin to the mother
- In Study AVF3708g, in patients receiving Avastin alone, the most frequently reported adverse events were infection (55%), fatigue (45%), headache (37%), hypertension (30%), epistaxis (19%), and diarrhea (21%). Of these, the incidence of grade ≥ 3 adverse events was infection (10%), fatigue (4%), headache (4%), hypertension (8%), and diarrhea (1%). Two deaths were possibly related to Avastin: 1 retroperitoneal hemorrhage and 1 neutropenic infection
- In patients receiving Avastin alone or Avastin plus irinotecan,* the incidences of Avastin-related adverse events (grade 1–4) were bleeding/hemorrhage (40%), epistaxis (26%), CNS hemorrhage (5%), hypertension (32%), venous thromboembolic events (8%), arterial thromboembolic events (6%), wound healing complications (6%), proteinuria (4%), GI perforation (2%), and RPLS (1%). The incidences of grade 3–5 events in these 163 patients were bleeding/hemorrhage (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic events (7%), arterial thromboembolic events (3%), wound healing complications (3%), proteinuria (1%), and GI perforation (2%). Intracranial hemorrhage occurred in 8 of 163 patients; 2 patients had grade 3–4 hemorrhage

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We look forward to discussing these data and our single-agent Avastin indication for the treatment of adult GBM patients with progressive disease following prior therapy. Until then, if you have any questions, please call the Genentech Medical Communications Department at 1-800-821-8590.

Sincerely,



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