

May 2009

Dear Healthcare Provider,

Avastin is now indicated for the treatment of glioblastoma (GBM) 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 an 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 to 100 for 45% and 70 to 80 for 55%. 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 until unacceptable toxicity. The median age was 54 years, 54% were male, 98% were Caucasian, and 68% had a Karnofsky performance status of 90 to 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 incidences of grade  $\geq 3$  adverse events were 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.

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



In patients receiving Avastin alone or Avastin plus irinotecan (N=163), the incidences 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 incidences 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%).

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

### Indication

Avastin is indicated for the treatment of GBM with progressive disease following prior therapy as a single agent. The effectiveness of Avastin in GBM is based on an improvement in ORR. 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:** The incidences of gastrointestinal perforation, some fatal, in Avastin-treated patients range from 0.3% to 2.4%. Discontinue Avastin in patients with GI perforation
- **Surgery and wound healing complications:** Avastin administration can result in the development of surgery and wound healing complications, in some instances resulting in serious and fatal complications. Do not initiate Avastin for at least 28 days after surgery or until the surgical wound is fully healed. 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, gastrointestinal bleeding, central nervous system hemorrhage, epistaxis, and vaginal bleeding, occurred up to five-fold more frequently in patients receiving Avastin. Across indications, the incidence of grade  $\geq 3$  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)

Please see accompanying full Prescribing Information and next page for **Boxed WARNINGS** and additional safety information.



## Boxed WARNINGS and additional important safety information (continued)

- Additional serious adverse events for which the incidence was increased in the Avastin-treated arm vs control included non-GI fistula formation (<0.3%), arterial thromboembolic events (grade  $\geq 3$ , 2.6%), hypertension (grade  $\geq 3$ , 5%-18%), reversible posterior leukoencephalopathy syndrome (<0.1%), and proteinuria including nephrotic syndrome (<1%). Infusion reactions with the first dose of Avastin were uncommon (<3%), and severe reactions occurred in 0.2% of patients
- 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  $\geq 3$  events was infection (10%), fatigue (4%), headache (4%), hypertension (8%), and diarrhea (1%). Two deaths were possibly related to Avastin: one retroperitoneal hemorrhage and one 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 event (8%), arterial thromboembolic event (6%), wound healing complications (6%), proteinuria (4%), GI perforation (2%), and RPLS (1%). The incidences of grade 3-5 events in these 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 GI perforation (2%). Intracranial hemorrhage occurred in 8 of 163 patients; two patients had grade 3-4 hemorrhage

Please see accompanying full Prescribing Information, including **Boxed WARNINGS**, for additional safety information.

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

Sincerely,



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Genentech, Inc.