

1.14.2.3 Final Labeling Text

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AVASTIN safely and effectively. See full prescribing information for AVASTIN.

AVASTIN® (bevacizumab)
Solution for intravenous infusion
Initial U.S. Approval: 2004

WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND HEALING COMPLICATIONS, and HEMORRHAGE

See [full prescribing information](#) for complete boxed warning.

- **Gastrointestinal Perforation:** Occurs in up to 2.4% of Avastin-treated patients. Discontinue Avastin for gastrointestinal perforation. (5.1)
- **Surgery and Wound Healing Complications:** Discontinue in patients with wound dehiscence. Discontinue at least 28 days prior to elective surgery. Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. (5.2)
- **Hemorrhage:** Severe or fatal hemorrhage, hemoptysis, gastrointestinal bleeding, CNS hemorrhage, and vaginal bleeding are increased in Avastin- treated patients. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis. (5.3)

RECENT MAJOR CHANGES

Indications and Usage, Glioblastoma (1.4)	5/2009
Indications and Usage, Renal Cell Carcinoma (1.5)	7/2009
Dosage and Administration, Glioblastoma (2.2)	5/2009
Dosage and Administration, Renal Cell Carcinoma (2.2)	7/2009
Warnings and Precautions, Hemorrhage (5.3)	5/2009
Warnings and Precautions, Proteinuria (5.8)	7/2009

INDICATIONS AND USAGE

Avastin is a vascular endothelial growth factor-specific angiogenesis inhibitor indicated for the treatment of:

- Metastatic colorectal cancer, with intravenous 5-fluorouracil-based chemotherapy for first- or second-line treatment. (1.1)
- Non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease. (1.2)
- Metastatic breast cancer, with paclitaxel for treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer. (1.3)
 - Effectiveness based on improvement in progression-free survival. No data available demonstrating improvement in disease-related symptoms or survival with Avastin.
 - Not indicated for disease progression following anthracycline and taxane chemotherapy administered for metastatic disease.
- Glioblastoma, as a single agent for patients with progressive disease following prior therapy. (1.4)
 - Effectiveness based on improvement in objective response rate. No data available demonstrating improvement in disease-related symptoms or survival with Avastin.

- Metastatic renal cell carcinoma with interferon alfa (1.5)

DOSAGE AND ADMINISTRATION

- Do not administer as an IV push or bolus. (2.1)
- Do not initiate Avastin for 28 days following major surgery and until surgical wound is fully healed. (2.1)

Metastatic colorectal cancer (2.2)

- 5 mg/kg IV every 2 weeks with bolus-IFL
- 10 mg/kg IV every 2 weeks with FOLFOX4

Non-squamous non-small cell lung cancer (2.2)

- 15 mg/kg IV every 3 weeks with carboplatin/paclitaxel

Metastatic breast cancer (2.2)

- 10 mg/kg IV every 2 weeks with paclitaxel

Glioblastoma (2.2)

- 10 mg/kg IV every 2 weeks

Metastatic renal cell carcinoma (mRCC) (2.2)

- 10 mg/kg IV every 2 weeks with interferon alfa

DOSAGE FORMS AND STRENGTHS

- 100 mg/4 mL, single use vial (3)
- 400 mg/16 mL, single use vial (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- **Non-Gastrointestinal Fistula Formation:** Discontinue Avastin if fistula formation occurs. (5.4)
- **Arterial Thromboembolic Events** (e.g., myocardial infarction, cerebral infarction): Discontinue Avastin for severe ATE. (5.5)
- **Hypertension:** Monitor blood pressure and treat hypertension. Temporarily suspend Avastin if not medically controlled. Discontinue Avastin for hypertensive crisis or hypertensive encephalopathy. (5.6)
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** Discontinue Avastin. (5.7)
- **Proteinuria:** Monitor urine protein. Discontinue for nephrotic syndrome. Temporarily suspend Avastin for moderate proteinuria. (5.8)
- **Infusion Reactions:** Stop for severe infusion reactions. (5.9)

ADVERSE REACTIONS

Most common adverse reactions incidence (>10% and at least twice the control arm rate) are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech, Inc. at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Based on animal data, may cause fetal harm. (8.1)
- **Nursing Mothers:** Discontinue nursing or discontinue drug, taking into account the importance of the drug to the mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: July 2009

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND HEALING COMPLICATIONS, and HEMORRHAGE

1 INDICATIONS AND USAGE

- 1.1 Metastatic Colorectal Cancer
- 1.2 Non-Squamous Non–Small Cell Lung Cancer
- 1.3 Metastatic Breast Cancer
- 1.4 Glioblastoma
- 1.5 Metastatic Renal Cell Carcinoma

2 DOSAGE AND ADMINISTRATION

- 2.1 Administration
- 2.2 Recommended Doses and Schedules
- 2.3 Preparation for Administration
- 2.4 Dose Modifications

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Gastrointestinal Perforations
- 5.2 Surgery and Wound Healing Complications
- 5.3 Hemorrhage
- 5.4 Non-Gastrointestinal Fistula Formation
- 5.5 Arterial Thromboembolic Events
- 5.6 Hypertension
- 5.7 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
- 5.8 Proteinuria
- 5.9 Infusion Reactions

6 ADVERSE REACTIONS

- 6.1 Clinical Trial Experience
- 6.2 Immunogenicity
- 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology
- 13.3 Reproductive and Developmental Toxicology

14 CLINICAL STUDIES

- 14.1 Metastatic Colorectal Cancer (mCRC)
- 14.2 Unresectable Non–Squamous Non–Small Cell Lung Cancer (NSCLC)
- 14.3 Metastatic Breast Cancer (MBC)
- 14.4 Glioblastoma
- 14.5 Metastatic Renal Cell Carcinoma (mRCC)

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND HEALING COMPLICATIONS, and HEMORRHAGE

Gastrointestinal Perforations

The incidence of gastrointestinal perforation, some fatal, in Avastin-treated patients ranges from 0.3 to 2.4%. Discontinue Avastin in patients with gastrointestinal perforation. [See *Dosage and Administration (2.4), Warnings and Precautions (5.1).*]

Surgery and Wound Healing Complications

The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients. Discontinue Avastin in patients with wound dehiscence. 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 at least 28 days prior to elective surgery. Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. [See *Dosage and Administration (2.4), Warnings and Precautions (5.2), and Adverse Reactions (6.1).*]

Hemorrhage

Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, central nervous systems (CNS) hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis. [See *Dosage and Administration (2.4), Warnings and Precautions (5.3), and Adverse Reactions (6.1).*]

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer (mCRC)

Avastin is indicated for the first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil-based chemotherapy.

1.2 Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Avastin is indicated for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer in combination with carboplatin and paclitaxel.

1.3 Metastatic Breast Cancer (MBC)

Avastin is indicated for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer in combination with paclitaxel.

The effectiveness of Avastin in MBC is based on an improvement in progression free survival. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin. [See *Clinical Studies (14.3).*]

Avastin is not indicated for patients with breast cancer that has progressed following anthracycline and taxane chemotherapy administered for metastatic disease.

1.4 Glioblastoma

Avastin is indicated for the treatment of glioblastoma with progressive disease following prior therapy as a single agent.

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. [See *Clinical Studies (14.4).*]

1.5 Metastatic Renal Cell Carcinoma (mRCC)

Avastin is indicated for the treatment of metastatic renal cell carcinoma in combination with interferon alfa.

2 DOSAGE AND ADMINISTRATION

2.1 Administration

Do not administer as an intravenous push or bolus. Administer only as an intravenous (IV) infusion.

- Do not initiate Avastin until at least 28 days following major surgery. Administer Avastin after the surgical incision has fully healed.
- First infusion: Administer infusion over 90 minutes.
- Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated; administer all subsequent infusions over 30 minutes if infusion over 60 minutes is tolerated.

2.2 Recommended Doses and Schedules

Patients should continue treatment until disease progression or unacceptable toxicity.

Metastatic Colorectal Cancer (mCRC)

The recommended doses are 5 mg/kg or 10 mg/kg every 2 weeks when used in combination with intravenous 5-FU-based chemotherapy.

- Administer 5 mg/kg when used in combination with bolus-IFL.
- Administer 10 mg/kg when used in combination with FOLFOX4.

Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

The recommended dose is 15 mg/kg every 3 weeks in combination with carboplatin and paclitaxel.

Metastatic Breast Cancer (MBC)

The recommended dose is 10 mg/kg every 2 weeks in combination with paclitaxel.

Glioblastoma

The recommended dose is 10 mg/kg every 2 weeks.

Metastatic Renal Cell Carcinoma (mRCC)

The recommended dose is 10 mg/kg every 2 weeks in combination with interferon alfa.

2.3 Preparation for Administration

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Withdraw necessary amount of Avastin and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. Discard any unused portion left in a vial, as the product contains no preservatives.

DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.

2.4 Dose Modifications

There are no recommended dose reductions.

Discontinue Avastin for:

- Gastrointestinal perforations (gastrointestinal perforations, fistula formation in the gastrointestinal tract, intra-abdominal abscess), fistula formation involving an internal organ [See Boxed Warning, Warnings and Precautions (5.1, 5.4).]
- Wound dehiscence and wound healing complications requiring medical intervention [See Warnings and Precautions (5.2).]
- Serious hemorrhage (i.e., requiring medical intervention) [See Boxed Warning, Warnings and Precautions (5.3).]
- Severe arterial thromboembolic events [See Warnings and Precautions (5.5).]
- Hypertensive crisis or hypertensive encephalopathy [See Warnings and Precautions (5.6).]

- Reversible posterior leukoencephalopathy syndrome (RPLS) [See Warnings and Precautions (5.7).]
- Nephrotic syndrome [See Warnings and Precautions (5.8).]

Temporarily suspend Avastin for:

- At least 4 weeks prior to elective surgery [See Warnings and Precautions (5.2).]
- Severe hypertension not controlled with medical management [See Warnings and Precautions (5.6).]
- Moderate to severe proteinuria pending further evaluation [See Warnings and Precautions (5.8).]
- Severe infusion reactions [See Warnings and Precautions (5.9).]

3 DOSAGE FORMS AND STRENGTHS

100 mg per 4 mL single-use vial

400 mg per 16 mL single-use vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Perforations

Serious and sometimes fatal gastrointestinal perforation occurs at a higher incidence in Avastin treated patients compared to controls. The incidence of gastrointestinal perforation ranged from 0.3 to 2.4% across clinical studies. [See Adverse Reactions (6.1).]

The typical presentation may include abdominal pain, nausea, emesis, constipation, and fever. Perforation can be complicated by intra-abdominal abscess and fistula formation. The majority of cases occurred within the first 50 days of initiation of Avastin.

Discontinue Avastin in patients with gastrointestinal perforation. [See Boxed Warning, Dosage and Administration (2.4).]

5.2 Surgery and Wound Healing Complications

Avastin impairs wound healing in animal models. [See Nonclinical Toxicology (13.2).] In clinical trials, administration of Avastin was not allowed until at least 28 days after surgery. In a controlled clinical trial, the incidence of wound healing complications, including serious and fatal complications, in patients with mCRC who underwent surgery during the course of Avastin treatment was 15% and in patients who did not receive Avastin, was 4%. [See Adverse Reactions (6.1).]

Avastin should not be initiated for at least 28 days following surgery and until the surgical wound is fully healed. Discontinue Avastin in patients with wound healing complications requiring medical intervention.

The appropriate interval between the last dose of Avastin and elective surgery is unknown; however, the half-life of Avastin is estimated to be 20 days. Suspend Avastin for at least 28 days prior to elective surgery. Do not administer Avastin until the wound is fully healed. [See Boxed Warning, Dosage and Administration (2.4).]

5.3 Hemorrhage

Avastin can result in two distinct patterns of bleeding: minor hemorrhage, most commonly Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin compared to patients receiving only chemotherapy. Across indications, the incidence of Grade ≥ 3

141 hemorrhagic events among patients receiving Avastin ranged from 1.2 to 4.6%. [See *Adverse*
142 *Reactions (6.1).*]

143 Serious or fatal pulmonary hemorrhage occurred in four of 13 (31%) patients with squamous cell
144 histology and two of 53 (4%) patients with non-squamous non-small cell lung cancer receiving
145 Avastin and chemotherapy compared to none of the 32 (0%) patients receiving chemotherapy alone.

146 In clinical studies in non-small cell lung cancer where patients with CNS metastases who
147 completed radiation and surgery more than 4 weeks prior to the start of Avastin were evaluated with
148 serial CNS imaging, symptomatic Grade 2 CNS hemorrhage was documented in one of 83
149 Avastin-treated patients (rate 1.2%, 95% CI 0.06%–5.93%).

150 Intracranial hemorrhage occurred in 8 of 163 patients with previously treated glioblastoma; two
151 patients had Grade 3–4 hemorrhage.

152 Do not administer Avastin to patients with recent history of hemoptysis of $\geq 1/2$ teaspoon of red
153 blood. Discontinue Avastin in patients with hemorrhage. [See *Boxed Warning, Dosage and*
154 *Administration (2.4).*]

155 **5.4 Non-Gastrointestinal Fistula Formation**

156 Serious and sometimes fatal non-gastrointestinal fistula formation involving tracheo-esophageal,
157 bronchopleural, biliary, vaginal, renal and bladder sites occurs at a higher incidence in
158 Avastin-treated patients compared to controls. The incidence of non-gastrointestinal perforation was
159 $\leq 0.3\%$ in clinical studies. Most events occurred within the first 6 months of Avastin therapy.

160 Discontinue Avastin in patients with fistula formation involving an internal organ. [See *Dosage*
161 *and Administration (2.4).*]

162 **5.5 Arterial Thromboembolic Events**

163 Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction,
164 transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a
165 higher incidence in patients receiving Avastin compared to those in the control arm. Across
166 indications, the incidence of Grade ≥ 3 ATE in the Avastin containing arms was 2.4% compared to
167 0.7% in the control arms. Among patients receiving Avastin in combination with chemotherapy, the
168 risk of developing ATE during therapy was increased in patients with a history of arterial
169 thromboembolism, or age greater than 65 years. [See *Use in Specific Populations (8.5).*]

170 The safety of resumption of Avastin therapy after resolution of an ATE has not been studied.
171 Discontinue Avastin in patients who experience a severe ATE. [See *Dosage and Administration*
172 *(2.4).*]

173 **5.6 Hypertension**

174 The incidence of severe hypertension is increased in patients receiving Avastin as compared to
175 controls. Across clinical studies the incidence of Grade 3 or 4 hypertension ranged from 5-18%.

176 Monitor blood pressure every two to three weeks during treatment with Avastin. Treat with
177 appropriate anti-hypertensive therapy and monitor blood pressure regularly. Continue to monitor
178 blood pressure at regular intervals in patients with Avastin-induced or -exacerbated hypertension
179 after discontinuation of Avastin.

180 Temporarily suspend Avastin in patients with severe hypertension that is not controlled with
181 medical management. Discontinue Avastin in patients with hypertensive crisis or hypertensive
182 encephalopathy. [See *Dosage and Administration (2.4).*]

183 **5.7 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**

184 RPLS has been reported with an incidence of $<0.1\%$ in clinical studies. The onset of symptoms
185 occurred from 16 hours to 1 year after initiation of Avastin. RPLS is a neurological disorder which
186 can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic
187 disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging (MRI) is
188 necessary to confirm the diagnosis of RPLS.

189 Discontinue Avastin in patients developing RPLS. Symptoms usually resolve or improve within
190 days, although some patients have experienced ongoing neurologic sequelae. The safety of
191 reinitiating Avastin therapy in patients previously experiencing RPLS is not known. [See *Dosage*
192 *and Administration (2.4).*]

193 **5.8 Proteinuria**

194 The incidence and severity of proteinuria is increased in patients receiving Avastin as compared to
195 controls. Nephrotic syndrome occurred in < 1% of patients receiving Avastin in clinical trials, in
196 some instances with fatal outcome. [See *Adverse Reactions (6.1).*] In a published case series, kidney
197 biopsy of six patients with proteinuria showed findings consistent with thrombotic microangiopathy.

198 Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria
199 with serial urinalyses during Avastin therapy. Patients with a 2+ or greater urine dipstick reading
200 should undergo further assessment with a 24-hour urine collection.

201 Suspend Avastin administration for ≥ 2 grams of proteinuria/24 hours and resume when
202 proteinuria is < 2 gm/24 hours. Discontinue Avastin in patients with nephrotic syndrome. Data from
203 a postmarketing safety study showed poor correlation between UPCR (Urine Protein/Creatinine
204 Ratio) and 24 hour urine protein (Pearson Correlation 0.39 (95% CI 0.17, 0.57). [See *Use in Specific*
205 *Populations (8.5).*] The safety of continued Avastin treatment in patients with moderate to severe
206 proteinuria has not been evaluated. [See *Dosage and Administration (2.4).*]

207 **5.9 Infusion Reactions**

208 Infusion reactions reported in the clinical trials and post-marketing experience include
209 hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen
210 desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. In clinical
211 studies, infusion reactions with the first dose of Avastin were uncommon (< 3%) and severe
212 reactions occurred in 0.2% of patients.

213 Stop infusion if a severe infusion reaction occurs and administer appropriate medical therapy.
214 [See *Dosage and Administration (2.4).*]

216 **6 ADVERSE REACTIONS**

217 The following serious adverse reactions are discussed in greater detail in other sections of the
218 label:

- 219 • Gastrointestinal Perforations [See *Boxed Warning, Dosage and Administration (2.4), Warnings*
220 *and Precautions (5.1).*]
- 221 • Surgery and Wound Healing Complications [See *Boxed Warning, Dosage and Administration*
222 *(2.4), Warnings and Precautions (5.2).*]
- 223 • Hemorrhage [See *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions*
224 *(5.3).*]
- 225 • Non-Gastrointestinal Fistula Formation [See *Dosage and Administration (2.4), Warnings and*
226 *Precautions (5.4).*]
- 227 • Arterial Thromboembolic Events [See *Dosage and Administration (2.4), Warnings and*
228 *Precautions (5.5).*]
- 229 • Hypertensive Crisis [See *Dosage and Administration (2.4), Warnings and Precautions (5.6).*]
- 230 • Reversible Posterior Leukoencephalopathy Syndrome [See *Dosage and Administration (2.4),*
231 *Warnings and Precautions (5.7).*]
- 232 • Proteinuria [See *Dosage and Administration (2.4), Warnings and Precautions (5.8).*]

233
234 The most common adverse reactions observed in Avastin patients at a rate > 10% and at least
235 twice the control arm rate, are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration,
236 dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis.

237 Across all studies, Avastin was discontinued in 8.4 to 21% of patients because of adverse
238 reactions.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data below reflect exposure to Avastin in 2661 patients with mCRC, non-squamous NSCLC, MBC, glioblastoma, or mRCC in controlled (Studies 1, 2, 4, 5, 6 and 9) or uncontrolled, single arm (Study 7) trials treated at the recommended dose and schedule for a median of 8 to 16 doses of Avastin. [See *Clinical Studies (14)*.] The population was aged 21-88 years (median 59), 46.0% male and 84.1% white. The population included 1089 first- and second-line mCRC patients who received a median of 11 doses of Avastin, 480 first-line metastatic NSCLC patients who received a median of 8 doses of Avastin, 592 MBC patients who had not received chemotherapy for metastatic disease received a median of 8 doses of Avastin, 163 glioblastoma patients who received a median of 9 doses of Avastin, and 337 mRCC patients who received a median of 16 doses of Avastin.

Surgery and Wound Healing Complications

The incidence of post-operative wound healing and/or bleeding complications was increased in patients with mCRC receiving Avastin as compared to patients receiving only chemotherapy. Among patients requiring surgery on or within 60 days of receiving study treatment, wound healing and/or bleeding complications occurred in 15% (6/39) of patients receiving bolus-IFL plus Avastin as compared to 4% (1/25) of patients who received bolus-IFL alone.

In Study 7, events of post-operative wound healing complications (craniotomy site wound dehiscence and cerebrospinal fluid leak) occurred in patients with previously treated glioblastoma: 3/84 patients in the Avastin alone arm and 1/79 patients in the Avastin plus irinotecan arm. [See *Boxed Warning, Dosage and Administration (2.4)*, *Warnings and Precautions (5.2)*.]

Hemorrhage

The incidence of epistaxis was higher (35% vs. 10%) in patients with mCRC receiving bolus-IFL plus Avastin compared with patients receiving bolus-IFL plus placebo. All but one of these events were Grade 1 in severity and resolved without medical intervention. Grade 1 or 2 hemorrhagic events were more frequent in patients receiving bolus-IFL plus Avastin when compared to those receiving bolus-IFL plus placebo and included gastrointestinal hemorrhage (24% vs. 6%), minor gum bleeding (2% vs. 0), and vaginal hemorrhage (4% vs. 2%). [See *Boxed Warning, Dosage and Administration (2.4)*, *Warnings and Precautions (5.3)*.]

Venous Thromboembolic Events

The incidence of Grade 3–4 venous thromboembolic events was higher in patients with mCRC or NSCLC receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone. The risk of developing a second subsequent thromboembolic event in mCRC patients receiving Avastin and chemotherapy was increased compared to patients receiving chemotherapy alone. In Study 1, 53 patients (14%) on the bolus-IFL plus Avastin arm and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose warfarin following a venous thromboembolic event. Among these patients, an additional thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus Avastin and 3% (1/30) of patients receiving bolus-IFL alone.

The overall incidence of Grade 3–4 venous thromboembolic events in Study 1 was 15.1% in patients receiving bolus-IFL plus Avastin and 13.6% in patients receiving bolus-IFL plus placebo. In Study 1, the incidence of the following Grade 3–4 venous thromboembolic events was higher in patients receiving bolus-IFL plus Avastin as compared to patients receiving bolus-IFL plus placebo: deep venous thrombosis (34 vs. 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

285 *Neutropenia and Infection*

286 The incidences of neutropenia and febrile neutropenia are increased in patients receiving Avastin
287 plus chemotherapy compared to chemotherapy alone. In Study 1, the incidence of Grade 3 or 4
288 neutropenia was increased in mCRC patients receiving IFL plus Avastin (21%) compared to patients
289 receiving IFL alone (14%). In Study 4, the incidence of Grade 4 neutropenia was increased in
290 NSCLC patients receiving paclitaxel/carboplatin (PC) plus Avastin (26.2%) compared with patients
291 receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus Avastin vs.
292 1.8% for PC alone). There were 19 (4.5%) infections with Grade 3 or 4 neutropenia in the PC plus
293 Avastin arm of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving
294 PC alone, of which none were fatal. During the first 6 cycles of treatment, the incidence of serious
295 infections including pneumonia, febrile neutropenia, catheter infections and wound infections was
296 increased in the PC plus Avastin arm [58 patients (13.6%)] compared to the PC alone arm
297 [29 patients (6.6%)].

298 In Study 7, one fatal event of neutropenic infection occurred in a patient with previously treated
299 glioblastoma receiving Avastin alone. The incidence of any grade of infection in patients receiving
300 Avastin alone was 55% and the incidence of Grade 3-5 infection was 10%.

301 *Proteinuria*

302 Grade 3-4 proteinuria ranged from 0.7 to 7.4% in Studies 1, 2, 4 and 9. The overall incidence of
303 proteinuria (all grades) was only adequately assessed in Study 9, in which the incidence was 20%.
304 Median onset of proteinuria was 5.6 months (range 15 days to 37 months) after initiation of Avastin.
305 Median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months). Proteinuria did not
306 resolve in 40% of patients after median follow up of 11.2 months and required permanent
307 discontinuation of Avastin in 30% of the patients who developed proteinuria (Study 9). [See
308 *Warnings and Precautions (5.8).*]

309 *Congestive Heart Failure*

310 The incidence of Grade \geq 3 left ventricular dysfunction was 1.0% in patients receiving Avastin
311 compared to 0.6% in the control arm across indications. In patients with MBC, the incidence of
312 Grade 3-4 congestive heart failure (CHF) was increased in patients in the Avastin plus paclitaxel arm
313 (2.2%) as compared to the control arm (0.3%). Among patients receiving prior anthracyclines for
314 MBC, the rate of CHF was 3.8% for patients receiving Avastin as compared to 0.6% for patients
315 receiving paclitaxel alone. The safety of continuation or resumption of Avastin in patients with
316 cardiac dysfunction has not been studied.

317 *Metastatic Colorectal Cancer (mCRC)*

318 The data in [Table 1](#) and [Table 2](#) were obtained in Study 1, a randomized, double-blind, controlled
319 trial comparing chemotherapy plus Avastin with chemotherapy plus placebo. Avastin was
320 administered at 5 mg/kg every 2 weeks.

321 All Grade 3–4 adverse events and selected Grade 1–2 adverse events (hypertension, proteinuria,
322 thromboembolic events) were collected in the entire study population. Severe and life-threatening
323 (Grade 3–4) adverse events, which occurred at a higher incidence (\geq 2%) in patients receiving
324 bolus-IFL plus Avastin as compared to bolus-IFL plus placebo, are presented in [Table 1](#).

Table 1
 NCI-CTC Grade 3–4 Adverse Events in Study 1
 (Occurring at Higher Incidence [$\geq 2\%$] Avastin vs. Control)

	Arm 1 IFL + Placebo (n = 396)	Arm 2 IFL + Avastin (n = 392)
NCI-CTC Grade 3-4 Events	74%	87%
<u>Body as a Whole</u>		
Asthenia	7%	10%
Abdominal Pain	5%	8%
Pain	5%	8%
<u>Cardiovascular</u>		
Hypertension	2%	12%
Deep Vein Thrombosis	5%	9%
Intra-Abdominal Thrombosis	1%	3%
Syncope	1%	3%
<u>Digestive</u>		
Diarrhea	25%	34%
Constipation	2%	4%
<u>Hemic/Lymphatic</u>		
Leukopenia	31%	37%
Neutropenia ^a	14%	21%

^a Central laboratories were collected on Days 1 and 21 of each cycle.
 Neutrophil counts are available in 303 patients in Arm 1 and 276 in Arm 2.

325
326
327
328
329

Grade 1–4 adverse events which occurred at a higher incidence ($\geq 5\%$) in patients receiving bolus-IFL plus Avastin as compared to the bolus-IFL plus placebo arm are presented in [Table 2](#). Grade 1–4 adverse events were collected for the first approximately 100 patients in each of the three treatment arms who were enrolled until enrollment in Arm 3 (5-FU/LV + Avastin) was discontinued.

Table 2
NCI-CTC Grade 1-4 Adverse Events in Study 1
(Occurring at Higher Incidence [$\geq 5\%$] in IFL+Avastin vs. IFL)

	Arm 1 IFL+Placebo (n=98)	Arm 2 IFL+Avastin (n=102)	Arm 3 5-FU/LV+Avastin (n=109)
<u>Body as a Whole</u>			
Pain	55%	61%	62%
Abdominal Pain	55%	61%	50%
Headache	19%	26%	26%
<u>Cardiovascular</u>			
Hypertension	14%	23%	34%
Hypotension	7%	15%	7%
Deep Vein Thrombosis	3%	9%	6%
<u>Digestive</u>			
Vomiting	47%	52%	47%
Anorexia	30%	43%	35%
Constipation	29%	40%	29%
Stomatitis	18%	32%	30%
Dyspepsia	15%	24%	17%
GI Hemorrhage	6%	24%	19%
Weight Loss	10%	15%	16%
Dry Mouth	2%	7%	4%
Colitis	1%	6%	1%
<u>Hemic/Lymphatic</u>			
Thrombocytopenia	0%	5%	5%
<u>Nervous</u>			
Dizziness	20%	26%	19%
<u>Respiratory</u>			
Upper Respiratory Infection	39%	47%	40%
Epistaxis	10%	35%	32%
Dyspnea	15%	26%	25%
Voice Alteration	2%	9%	6%
<u>Skin/Appendages</u>			
Alopecia	26%	32%	6%
Skin Ulcer	1%	6%	6%

Table 2 (cont'd)
NCI-CTC Grade 1-4 Adverse Events in Study 1
(Occurring at Higher Incidence [$\geq 5\%$] in IFL+Avastin vs. IFL)

	Arm 1 IFL+Placebo (n=98)	Arm 2 IFL+Avastin (n=102)	Arm 3 5-FU/LV+Avastin (n=109)
<u>Special Senses</u>			
Taste Disorder	9%	14%	21%
<u>Urogenital</u>			
Proteinuria	24%	36%	36%

331

332 *Avastin in Combination with FOLFOX4 in Second-line mCRC*

333 Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events related to treatment
334 were collected in Study 2. The most frequent adverse events (selected Grade 3-5 non-hematologic
335 and Grade 4-5 hematologic adverse events) occurring at a higher incidence ($\geq 2\%$) in 287 patients
336 receiving FOLFOX4 plus Avastin compared to 285 patients receiving FOLFOX4 alone were fatigue
337 (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%),
338 vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8%
339 vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache
340 (3% vs. 0%). These data are likely to under-estimate the true adverse event rates due to the reporting
341 mechanisms used in Study 2.

342 *Unresectable Non-Squamous Non-Small Cell Lung Cancer (NSCLC)*

343 Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in
344 Study 4. Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events (occurring at a
345 higher incidence ($\geq 2\%$) in 427 patients receiving PC plus Avastin compared with 441 patients
346 receiving PC alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs.
347 0.7%), infection without neutropenia (7% vs. 3%), venous thrombus/embolism (5% vs. 3%), febrile
348 neutropenia (5% vs. 2%), pneumonitis/pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or
349 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3%
350 vs. 0%).

351 *Metastatic Breast Cancer (MBC)*

352 Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in
353 Study 5. Grade 3-4 adverse events occurring at a higher incidence ($\geq 2\%$) in 363 patients receiving
354 paclitaxel plus Avastin compared with 348 patients receiving paclitaxel alone were sensory
355 neuropathy (24% vs. 18%), hypertension (16% vs. 1%), fatigue (11% vs. 5%), infection without
356 neutropenia (9% vs. 5%), neutrophils (6% vs. 3%), vomiting (6% vs. 2%), diarrhea (5% vs. 1%),
357 bone pain (4% vs. 2%), headache (4% vs. 1%), nausea (4% vs. 1%), cerebrovascular ischemia (3%
358 vs. 0%), dehydration (3% vs. 1%), infection with unknown ANC (3% vs. 0.3%), rash/desquamation
359 (3% vs. 0.3%) and proteinuria (3% vs. 0%).

360 Sensory neuropathy, hypertension, and fatigue were reported at a $\geq 5\%$ higher absolute incidence
361 in the paclitaxel plus Avastin arm compared with the paclitaxel alone arm.

362 Fatal adverse reactions occurred in 6/363 (1.7%) of patients who received paclitaxel plus Avastin.
363 Causes of death were gastrointestinal perforation (2), myocardial infarction (2), diarrhea/abdominal,
364 and pain/weakness/hypotension (2).

365 Avastin is not approved for use in combination with capecitabine or for use in second or third line
366 treatment of MBC. The data below are presented to provide information on the overall safety profile
367 of Avastin in women with breast cancer since Study 6 is the only randomized, controlled study in
368 which all adverse events were collected for all patients. All patients in Study 6 received prior
369 anthracycline and taxane therapy in the adjuvant setting or for metastatic disease. Grade 1–4 events
370 which occurred at a higher incidence ($\geq 5\%$) in patients receiving capecitabine plus Avastin
371 compared to the capecitabine alone arm are presented in Table 3.
372

Table 3
NCI-CTC Grade 1–4 Adverse Events in Study 6 (Occurring at Higher
Incidence [$\geq 5\%$] in Capecitabine + Avastin vs. Capecitabine Alone)

	Capecitabine (n=215)	Capecitabine+ Avastin (n=229)
<u>Body as a Whole</u>		
Asthenia	47%	57%
Headache	13%	33%
Pain	25%	31%
<u>Cardiovascular</u>		
Hypertension	2%	24%
<u>Digestive</u>		
Stomatitis	19%	25%
<u>Metabolic/Nutrition</u>		
Weight loss	4%	9%
<u>Musculoskeletal</u>		
Myalgia	8%	14%
<u>Respiratory</u>		
Dyspnea	18%	27%
Epistaxis	1%	16%
<u>Skin/Appendages</u>		
Exfoliative dermatitis	75%	84%
<u>Urogenital</u>		
Albuminuria	7%	22%

373

374 *Glioblastoma*

375 All adverse events were collected in 163 patients enrolled in Study 7 who either received Avastin
376 alone or Avastin plus irinotecan. All patients received prior radiotherapy and temozolomide.
377 Avastin was administered at 10 mg/kg every 2 weeks alone or in combination with irinotecan.
378 Avastin was discontinued due to adverse events in 4.8% of patients treated with Avastin alone.

379 In patients receiving Avastin alone (N=84), the most frequently reported adverse events of any
380 grade were infection (55%), fatigue (45%), headache (37%), hypertension (30%), epistaxis (19%)
381 and diarrhea (21%). Of these, the incidence of Grade ≥ 3 adverse events was infection (10%), fatigue
382 (4%), headache (4%), hypertension (8%) and diarrhea (1%). Two deaths on study were possibly
383 related to Avastin: one retroperitoneal hemorrhage and one neutropenic infection.

384 In patients receiving Avastin alone or Avastin plus irinotecan (N=163), the incidence of
385 Avastin-related adverse events (Grade 1–4) were bleeding/hemorrhage (40%), epistaxis (26%), CNS
386 hemorrhage (5%), hypertension (32%), venous thromboembolic event (8%), arterial thromboembolic
387 event (6%), wound-healing complications (6%), proteinuria (4%), gastrointestinal perforation (2%),
388 and RPLS (1%). The incidence of Grade 3–5 events in these 163 patients were bleeding/hemorrhage
389 (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial
390 thromboembolic event (3%), wound-healing complications (3%), proteinuria (1%), and
391 gastrointestinal perforation (2%).

392 *Metastatic Renal Cell Carcinoma (mRCC)*

393 All grade adverse events were collected in Study 9. Grade 3–5 adverse events occurring at a
394 higher incidence ($\geq 2\%$) in 337 patients receiving interferon alfa (IFN- α) plus Avastin compared to
395 304 patients receiving IFN- α plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%),
396 proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis),
397 and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured,
398 gastric ulcer hemorrhage, gingival bleeding, haemoptysis, hemorrhage intracranial, large intestinal
399 hemorrhage, respiratory tract hemorrhage, and traumatic hematoma).

400 Grade 1–5 adverse events occurring at a higher incidence ($\geq 5\%$) in patients receiving IFN- α plus
401 Avastin compared to the IFN- α plus placebo arm are presented in [Table 4](#).

Table 4

NCI-CTC Grades 1–5 Adverse Events in Study 9 (Occurring at Higher Incidence [$\geq 5\%$] in IFN- α + Avastin vs. IFN- α + Placebo)

System Organ Class/Preferred term*	IFN- α + Placebo (n= 304)	IFN- α + Avastin (n= 337)
<u>Gastrointestinal disorders</u>		
Diarrhea	16%	21%
<u>General disorders and administration site conditions</u>		
Fatigue	27%	33%
<u>Investigations</u>		
Weight decreased	15%	20%
<u>Metabolism and nutrition disorders</u>		
Anorexia	31%	36%
<u>Musculoskeletal and connective tissue disorders</u>		
Myalgia	14%	19%
Back pain	6%	12%
<u>Nervous system disorders</u>		
Headache	16%	24%
<u>Renal and urinary disorders</u>		
Proteinuria	3%	20%
<u>Respiratory, thoracic and mediastinal disorders</u>		
Epistaxis	4%	27%
Dysphonia	0%	5%
<u>Vascular disorders</u>		
Hypertension	9%	28%

*Adverse events were encoded using MedDRA, Version 10.1.

402

403 The following adverse events were reported at a 5-fold greater incidence in the IFN- α plus
404 Avastin arm compared to IFN- α alone and not represented in Table 4: gingival bleeding (13 patients
405 vs. 1 patient); rhinitis (9 vs.0); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux
406 disease (8 vs.1); tinnitus (7 vs. 1); tooth abscess (7 vs.0); mouth ulceration (6 vs. 0); acne (5 vs. 0);
407 deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

408 6.2 Immunogenicity

409 As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of
410 antibody development in patients receiving Avastin has not been adequately determined because the
411 assay sensitivity was inadequate to reliably detect lower titers. Enzyme-linked immunosorbent
412 assays (ELISAs) were performed on sera from approximately 500 patients treated with Avastin,
413 primarily in combination with chemotherapy. High titer human anti-Avastin antibodies were not
414 detected.

415 Immunogenicity data are highly dependent on the sensitivity and specificity of the assay.
416 Additionally, the observed incidence of antibody positivity in an assay may be influenced by several
417 factors, including sample handling, timing of sample collection, concomitant medications, and

418 underlying disease. For these reasons, comparison of the incidence of antibodies to Avastin with the
419 incidence of antibodies to other products may be misleading.

420 **6.3 Postmarketing Experience**

421 The following adverse reactions have been identified during post-approval use of Avastin.
422 Because these reactions are reported voluntarily from a population of uncertain size, it is not always
423 possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

424 *Body as a Whole:* Polyserositis

425 *Cardiovascular:* Pulmonary hypertension, RPLS

426 *Digestive:* Intestinal necrosis, mesenteric venous occlusion, anastomotic ulceration

427 *Hemic and lymphatic:* Pancytopenia

428 *Renal:* Renal thrombotic microangiopathy (manifested as severe proteinuria)

429 *Respiratory:* Nasal septum perforation, dysphonia

430 **7 DRUG INTERACTIONS**

431 A drug interaction study was performed in which irinotecan was administered as part of the
432 FOLFIRI regimen with or without Avastin. The results demonstrated no significant effect of
433 bevacizumab on the pharmacokinetics of irinotecan or its active metabolite SN38.

434 In a randomized study in 99 patients with NSCLC, based on limited data, there did not appear to
435 be a difference in the mean exposure of either carboplatin or paclitaxel when each was administered
436 alone or in combination with Avastin. However, 3 of the 8 patients receiving Avastin plus
437 paclitaxel/carboplatin had substantially lower paclitaxel exposure after four cycles of treatment (at
438 Day 63) than those at Day 0, while patients receiving paclitaxel/carboplatin without Avastin had a
439 greater paclitaxel exposure at Day 63 than at Day 0.

440 In Study 9, there was no difference in the mean exposure of interferon alfa administered in
441 combination with Avastin when compared to interferon alfa alone.

442 **8 USE IN SPECIFIC POPULATIONS**

443 **8.1 Pregnancy**

444 *Pregnancy Category C*

445 *There are no studies of bevacizumab in pregnant women. Reproduction studies in rabbits treated*
446 *with approximately 1 to 12 times the recommended human dose of bevacizumab resulted in*
447 *teratogenicity, including an increased incidence of specific gross and skeletal fetal alterations.*
448 *Adverse fetal outcomes were observed at all doses tested. Other observed effects included decreases*
449 *in maternal and fetal body weights and an increased number of fetal resorptions. [See Nonclinical*
450 *Toxicology (13.3).]*

451 Human IgG is known to cross the placental barrier; therefore, bevacizumab may be transmitted
452 from the mother to the developing fetus, and has the potential to cause fetal harm when administered
453 to pregnant women. Because of the observed teratogenic effects of known inhibitors of angiogenesis
454 in humans, bevacizumab should be used during pregnancy only if the potential benefit to the
455 pregnant woman justifies the potential risk to the fetus.

456 **8.3 Nursing Mothers**

457 It is not known whether Avastin is secreted in human milk, but human IgG is excreted in human
458 milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant
459 circulation in substantial amounts. Because many drugs are secreted in human milk and because of
460 the potential for serious adverse reactions in nursing infants from bevacizumab, a decision should be
461 made whether to discontinue nursing or discontinue drug, taking into account the half-life of the
462 bevacizumab (approximately 20 days [range 11–50 days]) and the importance of the drug to the
463 mother. [See *Clinical Pharmacology (12.3).*]

8.4 Pediatric Use

The safety, effectiveness and pharmacokinetic profile of Avastin in pediatric patients have not been established.

Juvenile cynomolgus monkeys with open growth plates exhibited physal dysplasia following 4 to 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure). The incidence and severity of physal dysplasia were dose-related and were partially reversible upon cessation of treatment.

8.5 Geriatric Use

In Study 1, severe adverse events that occurred at a higher incidence ($\geq 2\%$) in patients aged ≥ 65 years as compared to younger patients were asthenia, sepsis, deep thrombophlebitis, hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation, anorexia, leukopenia, anemia, dehydration, hypokalemia, and hyponatremia. The effect of Avastin on overall survival was similar in elderly patients as compared to younger patients.

In Study 2, patients aged ≥ 65 years receiving Avastin plus FOLFOX4 had a greater relative risk as compared to younger patients for the following adverse events: nausea, emesis, ileus, and fatigue.

In Study 4, patients aged ≥ 65 years receiving carboplatin, paclitaxel, and Avastin had a greater relative risk for proteinuria as compared to younger patients. [See Warnings and Precautions (5.8).]

In Study 5, there were insufficient numbers of patients ≥ 65 years old to determine whether the overall adverse events profile was different in the elderly as compared with younger patients.

Of the 742 patients enrolled in Genentech-sponsored clinical studies in which all adverse events were captured, 212 (29%) were age 65 or older and 43 (6%) were age 75 or older. Adverse events of any severity that occurred at a higher incidence in the elderly as compared to younger patients, in addition to those described above, were dyspepsia, gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice alteration.

In an exploratory, pooled analysis of 1745 patients treated in five randomized, controlled studies, there were 618 (35%) patients aged ≥ 65 years and 1127 patients < 65 years of age. The overall incidence of arterial thromboembolic events was increased in all patients receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone, regardless of age. However, the increase in arterial thromboembolic events incidence was greater in patients aged ≥ 65 years (8.5% vs. 2.9%) as compared to those < 65 years (2.1% vs. 1.4%). [See Warnings and Precautions (5.5).]

10 OVERDOSAGE

The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of 16 patients and with severe headache in three of 16 patients.

11 DESCRIPTION

Avastin (bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay systems. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Avastin has an approximate molecular weight of 149 kD. Bevacizumab is produced in a mammalian cell (Chinese Hamster Ovary) expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Avastin is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous infusion. Avastin is supplied in 100 mg and 400 mg preservative-free, single-use vials to deliver 4 mL or 16 mL of Avastin (25 mg/mL). The 100 mg product is formulated in 240 mg α, α -trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The 400 mg

512 product is formulated in 960 mg α,α -trehalose dihydrate, 92.8 mg sodium phosphate (monobasic,
513 monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water
514 for Injection, USP.

515 516 **12 CLINICAL PHARMACOLOGY**

517 **12.1 Mechanism of Action**

518 Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR)
519 on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial
520 cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis. Administration
521 of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction
522 of microvascular growth and inhibition of metastatic disease progression.

523 **12.3 Pharmacokinetics**

524 The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total
525 serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and
526 bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of
527 491 patients who received 1 to 20 mg/kg of Avastin weekly, every 2 weeks, or every 3 weeks, the
528 estimated half-life of bevacizumab was approximately 20 days (range 11–50 days). The predicted
529 time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of
530 bevacizumab every 2 weeks was 2.8.

531 The clearance of bevacizumab varied by body weight, gender, and tumor burden. After correcting
532 for body weight, males had a higher bevacizumab clearance (0.262 L/day vs. 0.207 L/day) and a
533 larger V_c (3.25 L vs. 2.66 L) than females. Patients with higher tumor burden (at or above median
534 value of tumor surface area) had a higher bevacizumab clearance (0.249 L/day vs. 0.199 L/day) than
535 patients with tumor burdens below the median. In Study 1, there was no evidence of lesser efficacy
536 (hazard ratio for overall survival) in males or patients with higher tumor burden treated with Avastin
537 as compared to females and patients with low tumor burden. The relationship between bevacizumab
538 exposure and clinical outcomes has not been explored.

539 540 **13 NONCLINICAL TOXICOLOGY**

541 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

542 No carcinogenicity or mutagenicity studies of bevacizumab have been conducted.

543 Bevacizumab may impair fertility. Female cynomolgus monkeys treated with 0.4 to 20 times the
544 recommended human dose of bevacizumab exhibited arrested follicular development or absent
545 corpora lutea as well as dose-related decreases in ovarian and uterine weights, endometrial
546 proliferation, and the number of menstrual cycles. Following a 4- or 12-week recovery period, there
547 was a trend suggestive of reversibility. After the 12-week recovery period, follicular maturation
548 arrest was no longer observed, but ovarian weights were still moderately decreased. Reduced
549 endometrial proliferation was no longer observed at the 12-week recovery time point; however,
550 decreased uterine weight, absent corpora lutea, and reduced number of menstrual cycles remained
551 evident.

552 **13.2 Animal Toxicology and/or Pharmacology**

553 In cynomolgus monkeys, when bevacizumab was administered at doses of 0.4 to 20 times the
554 weekly human exposure, anatomical pathology revealed several adverse effects on general growth
555 and skeletal development, fertility and wound healing capacity. Severe physal dysplasia was
556 consistently reported in juvenile monkeys with open growth plates receiving 0.4 to 20 times the
557 human dose. The physal dysplasia was characterized by a linear cessation of growth line and
558 chondrocyte hyperplasia which did not completely resolve after the 4 to 12 weeks recovery period
559 without drug exposure.

560 Rabbits dosed with bevacizumab exhibited reduced wound healing capacity. Using full-thickness
561 skin incision and partial thickness circular dermal wound models, bevacizumab dosing resulted in
562 reductions in wound tensile strength, decreased granulation and re-epithelialization, and delayed
563 time to wound closure.

564 **13.3 Reproductive and Developmental Toxicology**

565 Pregnant rabbits dosed with 1 to 12 times the human dose of bevacizumab every three days during
566 the period of organogenesis (gestation day 6-18) exhibited teratogenic effects, decreases in maternal
567 and fetal body weights, and increased number of fetal resorptions. Teratogenic effects included:
568 reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws;
569 meningocele; fontanel, rib and hindlimb deformities; corneal opacity; and absent hindlimb
570 phalanges. There are no data available regarding the level of bevacizumab exposure in the offspring.
571

572 **14 CLINICAL STUDIES**

573 **14.1 Metastatic Colorectal Cancer (mCRC)**

574 *Study 1*

575 In this double-blind, active-controlled study, patients were randomized (1:1:1) to IV bolus-IFL
576 (irinotecan 125 mg/m², 5-FU 500 mg/m², and leucovorin (LV) 20 mg/m² given once weekly for
577 4 weeks every 6 weeks) plus placebo (Arm 1), bolus-IFL plus Avastin (5 mg/kg every 2 weeks)
578 (Arm 2), or 5-FU/LV plus Avastin (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3 was
579 discontinued, as pre-specified, when the toxicity of Avastin in combination with the bolus-IFL
580 regimen was deemed acceptable. The main outcome measure was overall survival (OS).

581 Of the 813 patients randomized to Arms 1 and 2, the median age was 60, 40% were female, 79%
582 were Caucasian, 57% had an ECOG performance status of 0, 21% had a rectal primary and 28%
583 received prior adjuvant chemotherapy. In 56% of the patients, the dominant site of disease was
584 extra-abdominal, while the liver was the dominant site in 38% of patients.

585 The addition of Avastin resulted in an improvement in survival across subgroups defined by age
586 (< 65 yrs, ≥ 65 yrs) and gender. Results are presented in [Table 5](#) and [Figure 1](#).

Table 5
 Study 1 Efficacy Results

	IFL+Placebo	IFL+Avastin 5 mg/kg q 2 wks
Number of Patients	411	402
<u>Overall Survival^a</u>		
Median (months)	15.6	20.3
Hazard ratio		0.66
<u>Progression-free Survival^a</u>		
Median (months)	6.2	10.6
Hazard ratio		0.54
<u>Overall Response Rate^b</u>		
Rate (percent)	35%	45%
<u>Duration of Response</u>		
Median (months)	7.1	10.4

^a p<0.001 by stratified log rank test.

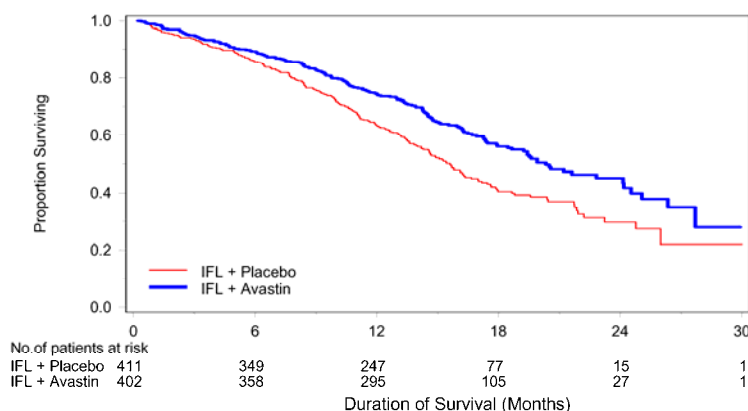
^b p<0.01 by χ^2 test.

587

588

589

Figure 1
 Duration of Survival in Study 1



590

591

Among the 110 patients enrolled in Arm 3, median OS was 18.3 months, median progression-free survival (PFS) was 8.8 months, objective response rate (ORR) was 39%, and median duration of response was 8.5 months.

Study 2

Study 2 was a randomized, open-label, active-controlled trial in patients who were previously treated with irinotecan +/- 5-FU for initial therapy for metastatic disease or as adjuvant therapy. Patients were randomized (1:1:1) to IV FOLFOX4 (Day 1: oxaliplatin 85 mg/m² and LV 200 mg/m² concurrently, then 5-FU 400 mg/m² bolus followed by 600 mg/m² continuously; Day 2: LV 200 mg/m², then 5-FU 400 mg/m² bolus followed by 600 mg/m² continuously; repeated every

600

601 2 weeks), FOLFOX4 plus Avastin (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1), or
602 Avastin monotherapy(10 mg/kg every 2 weeks). The main outcome measure was OS.

603 The Avastin monotherapy arm was closed to accrual after enrollment of 244 of the planned
604 290 patients following a planned interim analysis by the data monitoring committee based on
605 evidence of decreased survival compared to FOLFOX4 alone.

606 Of the 829 patients randomized to the three arms, the median age was 61 years, 40% were female,
607 87% were Caucasian, 49% had an ECOG performance status of 0, 26% received prior radiation
608 therapy, and 80% received prior adjuvant chemotherapy, 99% received prior irinotecan, with or
609 without 5-FU as therapy for metastatic disease, and 1% received prior irinotecan and 5-FU as
610 adjuvant therapy.

611 The addition of Avastin to FOLFOX4 resulted in significantly longer survival as compared to
612 FOLFOX4 alone (median OS 13.0 months vs. 10.8 months; hazard ratio 0.75 [95% CI 0.63, 0.89],
613 $p=0.001$ stratified log rank test) with clinical benefit seen in subgroups defined by age (<65 yrs,
614 ≥ 65 yrs) and gender. PFS and ORR based on investigator assessment were higher in the Avastin
615 plus FOLFOX4 arm.

616 *Study 3*

617 The activity of Avastin in combination with bolus or infusional 5-FU/LV was evaluated in a
618 single arm study enrolling 339 patients with mCRC with disease progression following both
619 irinotecan- and oxaliplatin-containing chemotherapy regimens. Seventy-three percent of patients
620 received concurrent bolus 5-FU/LV. One objective partial response was verified in the first
621 100 evaluable patients for an overall response rate of 1% (95% CI 0–5.5%).

622 **14.2 Unresectable Non–Squamous Non–Small Cell Lung Cancer (NSCLC)**

623 *Study 4*

624 The safety and efficacy of Avastin as first-line treatment of patients with locally advanced,
625 metastatic, or recurrent non–squamous NSCLC was studied in a single, large, randomized,
626 active-controlled, open-label, multicenter study.

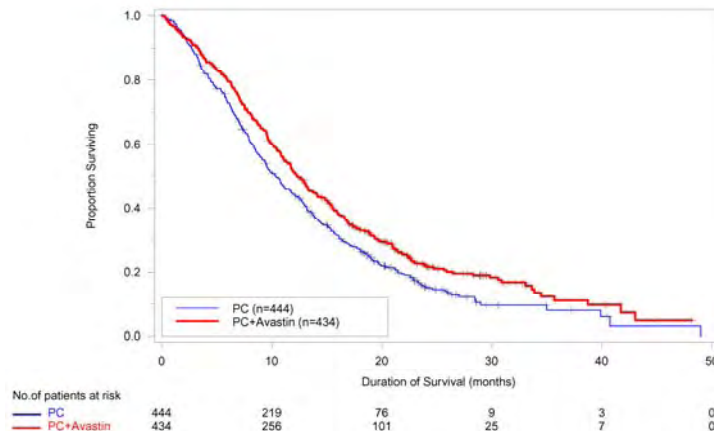
627 Chemotherapy-naïve patients with locally advanced, metastatic or recurrent non–squamous
628 NSCLC were randomized (1:1) to receive six 21-day cycles of paclitaxel 200 mg/m² and carboplatin
629 AUC=6.0, by IV on day 1 (PC) or PC in combination with Avastin 15 mg/kg by IV on day 1 (PC
630 plus Avastin). After completion or upon discontinuation of chemotherapy, patients in the PC plus
631 Avastin arm continued to receive Avastin alone until disease progression or until unacceptable
632 toxicity. Patients with predominant squamous histology (mixed cell type tumors only), central
633 nervous system (CNS) metastasis, gross hemoptysis ($\geq 1/2$ tsp of red blood), unstable angina, or
634 receiving therapeutic anticoagulation were excluded. The main outcome measure was duration of
635 survival.

636 Of the 878 patients randomized, the median age was 63, 46% were female, 43% were \geq age 65,
637 and 28% had $\geq 5\%$ weight loss at study entry. Eleven percent had recurrent disease and of the 89%
638 with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had
639 Stage IV disease.

640 The results are presented in [Figure 2](#). OS was statistically significantly higher among patients
641 receiving PC plus Avastin compared with those receiving PC alone; median OS was 12.3 months vs.
642 10.3 months [hazard ratio 0.80 (repeated 95% CI 0.68, 0.94), final p - value 0.013, stratified log-rank
643 test]. Based on investigator assessment which was not independently verified, patients were
644 reported to have longer PFS with Avastin in combination with PC compared to PC alone.

645
646

Figure 2
Duration of Survival in Study 4



647

648 In an exploratory analyses across patient subgroups, the impact of Avastin on OS was less robust
649 in the following: women [HR = 0.99 (95% CI: 0.79, 1.25)], age \geq 65 years [HR = 0.91 (95% CI:
650 0.72, 1.14)] and patients with \geq 5% weight loss at study entry [HR = 0.96 (95% CI: 0.73, 1.26)].

651 14.3 Metastatic Breast Cancer (MBC)

652 Study 5

653 The efficacy and safety of Avastin as first-line treatment of patients with MBC was studied in a
654 single, open-label, randomized, multicenter study. Patients who had not received chemotherapy for
655 locally recurrent or MBC were randomized (1:1) to receive paclitaxel (90 mg/m² IV once weekly for
656 3 out of 4 weeks) alone or in combination with Avastin (10 mg/kg IV infusion every 2 weeks).
657 Patients were treated until disease progression or unacceptable toxicity. In situations where
658 paclitaxel was discontinued or held, treatment with Avastin alone could be continued until disease
659 progression. Patients with breast cancer overexpressing HER2 were not eligible unless they had
660 received prior therapy with trastuzumab.

661 Prior hormonal therapy for the treatment of metastatic disease was allowed, as was prior adjuvant
662 chemotherapy or hormonal therapy. Adjuvant taxane therapy, if received, must have been
663 completed 12 or more months prior to study entry. Patients with central nervous system metastasis
664 were excluded. The main outcome measure of the study was PFS as assessed by independent
665 radiographic review. Secondary outcome measures were OS and ORR.

666 Of the 722 patients randomized, the median age was 55 years, 76% were white, 55% were
667 postmenopausal, and 64% were ER and/or PR positive. Patient characteristics were similar across
668 treatment arms. Thirty-six percent had received prior hormonal therapy for advanced disease, and
669 66% had received adjuvant chemotherapy, including 20% with prior taxane use and 50% with prior
670 anthracycline use. Efficacy results are summarized in Table 6.

Table 6
Avastin Efficacy Results from Study 5

Efficacy Parameter	Avastin + Paclitaxel (n=368)	Paclitaxel Alone (n=354)	p-value	HR (95% CI)
<u>Progression-free Survival</u>	11.3	5.8		0.48
[median, months (95% CI)]	(10.5, 13.3)	(5.4, 8.2)	<0.0001	(0.39, 0.61)
<u>Overall Survival</u>	26.5	24.8		0.87
[median, months (95% CI)]	(23.7, 29.2)	(21.4, 27.4)	0.14	(0.72, 1.05)
Partial Response Rate ¹ (PR)	48.9% ²	22.2%	<0.001	—

¹ Includes only patients with measurable disease.

² The difference in partial response rates is 26.7% with a 95% CI (18.4%, 35.0%).

671

672 The addition of Avastin to paclitaxel resulted in an improvement in PFS with no significant
673 improvement in OS. Partial response rates in patients with measurable disease were higher with
674 Avastin plus paclitaxel. No complete responses were observed.

675 Thirty-four percent of the patients had incomplete follow-up for disease progression; therefore an
676 exploratory analysis using similar imputation between arms was performed, which yielded a hazard
677 ratio of 0.57.

678 *Study 6*

679 The efficacy and safety of Avastin as second- and third-line treatment of patients with MBC was
680 studied in a single open-label randomized study. Patients who had received prior anthracycline and
681 taxane therapy in the adjuvant setting or for their MBC were randomized (1:1) to receive
682 capecitabine alone or in combination with Avastin. Of the 462 enrolled patients, the median age was
683 51 years, 81% were white, and 50% were ER positive. Patient characteristics were similar across the
684 treatment arms.

685 The study failed to demonstrate a statistically significant effect on PFS or OS. The median PFS
686 was 4.2 months in the capecitabine arm and 4.9 months in the capecitabine plus Avastin arm
687 (log-rank p-value = 0.86, hazard ratio 0.98). The median OS was 14.5 months in the capecitabine
688 arm and 15.1 months in the capecitabine plus Avastin arm (hazard ratio of 1.08).

689 **14.4 Glioblastoma**

690 *Study 7*

691 The efficacy and safety of Avastin was evaluated in Study 7, an open-label, multicenter,
692 randomized, non-comparative study of patients with previously treated glioblastoma. Patients
693 received Avastin (10 mg/kg IV) alone or Avastin plus irinotecan every 2 weeks until disease
694 progression or until unacceptable toxicity. All patients received prior radiotherapy (completed at
695 least 8 weeks prior to receiving Avastin) and temozolomide. Patients with active brain hemorrhage
696 were excluded.

697 Of the 85 patients randomized to the Avastin arm, the median age was 54 years, 32% were
698 female, 81% were in first relapse, Karnofsky performance status was 90–100 for 45% and 70–80 for
699 55%.

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

705 *Study 8*

706 Study 8, was a single-arm, single institution trial with 56 patients with glioblastoma. All patients
707 had documented disease progression after receiving temozolomide and radiation therapy. Patients
708 received Avastin 10 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity.

709 The median age was 54, 54% were male, 98% Caucasian, and 68% had a Karnofsky Performance
710 Status of 90–100.

711 The efficacy of Avastin was supported by an objective response rate of 19.6% (95% CI 10.9%,
712 31.3%) using the same response criteria as in Study 7. Median duration of response was 3.9 months
713 (95% CI 2.4, 17.4).

714 **14.5 Metastatic Renal Cell Carcinoma (mRCC)**

715 *Study 9*

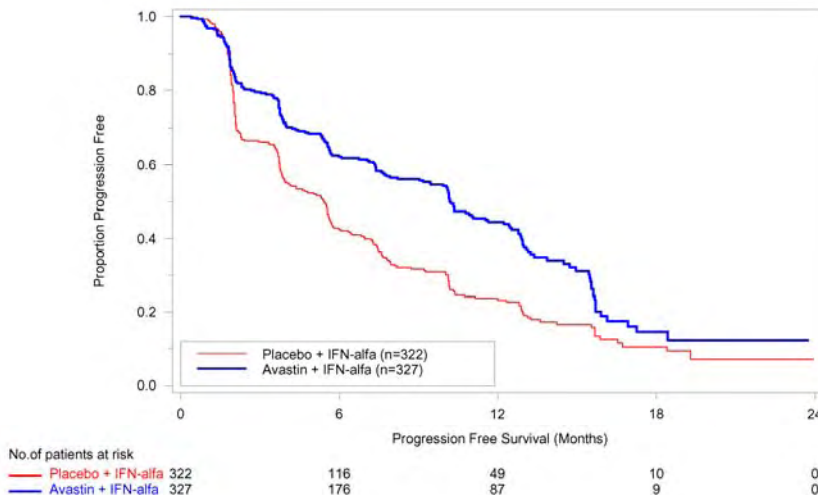
716 Patients with treatment-naïve mRCC were evaluated in a multicenter, randomized, double-blind,
717 international study comparing Avastin plus interferon alfa 2a (IFN- α 2a) versus placebo plus
718 IFN- α 2a. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to
719 receive either Avastin (10 mg/kg IV infusion every 2 weeks; n=327) or placebo (IV every 2 weeks;
720 n=322) in combination with IFN- α 2a (9 MIU subcutaneously three times weekly, for a maximum of
721 52 weeks). Patients were treated until disease progression or unacceptable toxicity. The main
722 outcome measure of the study was investigator-assessed PFS. Secondary outcome measures were
723 ORR and OS.

724 The median age was 60 years (range 18–82), 96% were white, and 70% were male. The study
725 population was characterized by Motzer scores as follows: 28% favorable (0), 56% intermediate (1-
726 2), 8% poor (3-5), and 7% missing.

727 The results are presented in [Figure 3](#). PFS was statistically significantly prolonged among
728 patients receiving Avastin plus IFN- α 2a compared to those receiving IFN- α 2a alone; median PFS
729 was 10.2 months vs. 5.4 months [HR 0.60 (95% CI 0.49, 0.72), p-value < 0.0001, stratified log-rank
730 test]. Among the 595 patients with measureable disease, ORR was also significantly higher (30%
731 vs. 12%, p < 0.0001, stratified CMH test). There was no improvement in OS based on the final
732 analysis conducted after 444 deaths, with a median OS of 23 months in the Avastin plus IFN- α 2a
733 arm and 21 months in the IFN- α 2a plus placebo arm [HR 0.86, (95% CI 0.72, 1.04)].

734
735

Figure 3
 Progression-Free Survival in Study 9



736
737

16 HOW SUPPLIED/STORAGE AND HANDLING

Avastin vials [100 mg (NDC 50242-060-01) and 400 mg (NDC 50242-061-01)] are stable at 2–8°C (36–46°F). Avastin vials should be protected from light. **Do not freeze or shake.**

Diluted Avastin solutions may be stored at 2–8°C (36–46°F) for up to 8 hours. Store in the original carton until time of use. No incompatibilities between Avastin and polyvinylchloride or polyolefin bags have been observed.

744

17 PATIENT COUNSELING INFORMATION

Advise patients:

- To undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated.
- To immediately contact their health care provider for unusual bleeding, high fever, rigors, sudden onset of worsening neurological function, or persistent or severe abdominal pain, severe constipation, or vomiting.
- Of increased risk of wound healing complications during and following Avastin.
- Of increased risk of an arterial thromboembolic event.
- Of the potential risk to the fetus during and following Avastin and the need to continue adequate contraception for at least 6 months following last dose of Avastin.

756

Manufactured by:
 Genentech, Inc.
 1 DNA Way
 South San Francisco, CA
 94080-4990

745316
 LV0017
 4835706
 Initial U.S. Approval: February 2004
 Code Revision Date: July 2009
 © 2009 Genentech, Inc

757