

1 **1.14.1.3 Labeling Text**

2 **AVASTIN™**  
3 **(Bevacizumab)**

4 **For Intravenous Use**

5 **WARNINGS**

6 **Gastrointestinal Perforations/Wound Healing Complications**

7 AVASTIN administration can result in the development of gastrointestinal  
8 perforation and wound dehiscence, in some instances resulting in fatality.

9 Gastrointestinal perforation, sometimes associated with intra-abdominal  
10 abscess, occurred throughout treatment with AVASTIN (i.e., was not  
11 correlated to duration of exposure). The incidence of gastrointestinal  
12 perforation in patients receiving bolus-IFL with AVASTIN was 2%. The  
13 typical presentation was reported as abdominal pain associated with  
14 symptoms such as constipation and vomiting. Gastrointestinal perforation  
15 should be included in the differential diagnosis of patients presenting with  
16 abdominal pain on AVASTIN. AVASTIN therapy should be permanently  
17 discontinued in patients with gastrointestinal perforation or wound  
18 dehiscence requiring medical intervention. The appropriate interval  
19 between termination of AVASTIN and subsequent elective surgery  
20 required to avoid the risks of impaired wound healing/wound dehiscence  
21 has not been determined. (See **WARNINGS: Gastrointestinal**  
22 **Perforations/Wound Healing Complications** and **DOSAGE AND**  
23 **ADMINISTRATION: Dose Modifications**.)

24 **Hemorrhage**

25 Serious, and in some cases fatal, hemoptysis has occurred in patients with  
26 non-small cell lung cancer treated with chemotherapy and AVASTIN. In  
27 a small study, the incidence of serious or fatal hemoptysis was 31% in  
28 patients with squamous histology and 4% in patients with adenocarcinoma  
29 receiving AVASTIN as compared to no cases in patients treated with  
30 chemotherapy alone. Patients with recent hemoptysis should not receive  
31 AVASTIN. (See **WARNINGS: Hemorrhage** and **DOSAGE AND**  
32 **ADMINISTRATION: Dose Modifications**.)

33 **DESCRIPTION**

34 AVASTIN™ (Bevacizumab) is a recombinant humanized monoclonal  
35 IgG1 antibody that binds to and inhibits the biologic activity of human  
36 vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay  
37 systems. Bevacizumab contains human framework regions and the  
38 complementarity-determining regions of a murine antibody that binds to  
39 VEGF (1). Bevacizumab is produced in a Chinese Hamster Ovary  
40 mammalian cell expression system in a nutrient medium containing the  
41 antibiotic gentamicin and has a molecular weight of approximately  
42 149 kilodaltons. AVASTIN is a clear to slightly opalescent, colorless to  
43 pale brown, sterile, pH 6.2 solution for intravenous (IV) infusion.  
44 AVASTIN is supplied in 100 mg and 400 mg preservative-free, single-use  
45 vials to deliver 4 mL or 16 mL of AVASTIN (25 mg/mL). The 100 mg  
46 product is formulated in 240 mg  $\alpha,\alpha$ -trehalose dihydrate, 23.2 mg sodium  
47 phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic,  
48 anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The  
49 400 mg product is formulated in 960 mg  $\alpha,\alpha$ -trehalose dihydrate, 92.8 mg  
50 sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate  
51 (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water for Injection,  
52 USP.

53 **CLINICAL PHARMACOLOGY**

54 **Mechanism of Action**

55 Bevacizumab binds VEGF and prevents the interaction of VEGF to its  
56 receptors (Flt-1 and KDR) on the surface of endothelial cells. The  
57 interaction of VEGF with its receptors leads to endothelial cell  
58 proliferation and new blood vessel formation in *in vitro* models of  
59 angiogenesis. Administration of Bevacizumab to xenotransplant models  
60 of colon cancer in nude (athymic) mice caused reduction of microvascular  
61 growth and inhibition of metastatic disease progression.

62 **Pharmacokinetics**

63 The pharmacokinetic profile of Bevacizumab was assessed using an assay  
64 that measures total serum Bevacizumab concentrations (i.e., the assay did

65 not distinguish between free Bevacizumab and Bevacizumab bound to  
66 VEGF ligand). Based on a population pharmacokinetic analysis of  
67 491 patients who received 1 to 20 mg/kg of AVASTIN weekly, every  
68 2 weeks, or every 3 weeks, the estimated half-life of Bevacizumab was  
69 approximately 20 days (range 11–50 days). The predicted time to reach  
70 steady state was 100 days. The accumulation ratio following a dose of  
71 10 mg/kg of Bevacizumab every 2 weeks was 2.8.

72 The clearance of Bevacizumab varied by body weight, by gender, and by  
73 tumor burden. After correcting for body weight, males had a higher  
74 Bevacizumab clearance (0.262 L/day vs. 0.207 L/day) and a larger  $V_c$   
75 (3.25 L vs. 2.66 L) than females. Patients with higher tumor burden (at or  
76 above median value of tumor surface area) had a higher Bevacizumab  
77 clearance (0.249 L/day vs. 0.199 L/day) than patients with tumor burdens  
78 below the median. In a randomized study of 813 patients (Study 1), there  
79 was no evidence of lesser efficacy (hazard ratio for overall survival) in  
80 males or patients with higher tumor burden treated with AVASTIN as  
81 compared to females and patients with low tumor burden. The  
82 relationship between Bevacizumab exposure and clinical outcomes has not  
83 been explored.

#### 84 **Special Populations**

85 Analyses of demographic data suggest that no dose adjustments are  
86 necessary for age or sex.

87 *Patients with renal impairment.* No studies have been conducted to  
88 examine the pharmacokinetics of Bevacizumab in patients with renal  
89 impairment.

90 *Patients with hepatic dysfunction.* No studies have been conducted to  
91 examine the pharmacokinetics of Bevacizumab in patients with hepatic  
92 impairment.

93 **CLINICAL STUDIES**

94 The safety and efficacy of AVASTIN in the initial treatment of patients  
95 with metastatic carcinoma of the colon and rectum were studied in two  
96 randomized, controlled clinical trials in combination with intravenous  
97 5-fluorouracil-based chemotherapy.

98 **AVASTIN in Combination with Bolus-IFL**

99 Study 1 was a randomized, double-blind, active-controlled clinical trial  
100 evaluating AVASTIN as first-line treatment of metastatic carcinoma of the  
101 colon or rectum. Patients were randomized to bolus-IFL (irinotecan  
102 125 mg/m<sup>2</sup> IV, 5-fluorouracil 500 mg/m<sup>2</sup> IV, and leucovorin 20 mg/m<sup>2</sup> IV  
103 given once weekly for 4 weeks every 6 weeks) plus placebo (Arm 1),  
104 bolus-IFL plus AVASTIN (5 mg/kg every 2 weeks) (Arm 2), or 5-FU/LV  
105 plus AVASTIN (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3  
106 was discontinued, as pre-specified, when the toxicity of AVASTIN in  
107 combination with the bolus-IFL regimen was deemed acceptable.

108 Of the 813 patients randomized to Arms 1 and 2, the median age was 60,  
109 40% were female, and 79% were Caucasian. Fifty-seven percent had an  
110 ECOG performance status of 0. Twenty-one percent had a rectal primary  
111 and 28% received prior adjuvant chemotherapy. In the majority of  
112 patients, 56%, the dominant site of disease was extra-abdominal, while the  
113 liver was the dominant site in 38% of patients. The patient characteristics  
114 were similar across the study arms. The primary endpoint of this trial was  
115 overall survival. Results are presented in Table 1 and Figure 1.

**Table 1**  
Study 1 Efficacy Results

	IFL + Placebo	IFL + AVASTIN 5 mg/kg q 2 wks
Number of Patients	411	402
<u>Overall Survival<sup>a</sup></u>		
Median (months)	15.6	20.3
Hazard ratio		0.66
<u>Progression-Free Survival<sup>a</sup></u>		
Median (months)	6.4	10.6
Hazard ratio		0.54
<u>Overall Response Rate<sup>b</sup></u>		
Rate (percent)	35%	45%
<u>Duration of Response</u>		
Median (months)	7.1	10.4

<sup>a</sup> p < 0.001 by stratified logrank test.

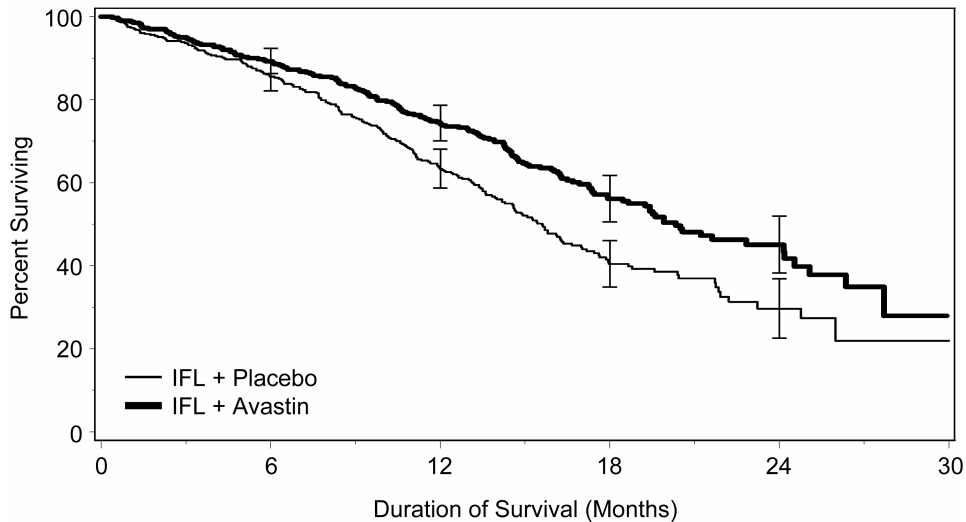
<sup>b</sup> p < 0.01 by  $\chi^2$  test.

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117

118

**Figure 1**  
Duration of Survival in Study 1



119

120 Error bars represent 95% confidence intervals.

121 The clinical benefit of AVASTIN, as measured by survival in the two

122 principal arms, was seen in all subgroups tested. The subgroups examined

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