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2 **AVASTIN®**  
3 **(Bevacizumab)**

4 **For Intravenous Use**

5 **WARNINGS**

6 **Gastrointestinal Perforations**

7 AVASTIN administration can result in the development of gastrointestinal  
8 perforation, in some instances resulting in fatality. Gastrointestinal  
9 perforation, sometimes associated with intra-abdominal abscess, occurred  
10 throughout treatment with AVASTIN (i.e., was not correlated to duration  
11 of exposure). The incidence of gastrointestinal perforation  
12 (gastrointestinal perforation, fistula formation, and/or intra-abdominal  
13 abscess) in patients receiving AVASTIN was 2.4%. The typical  
14 presentation was reported as abdominal pain associated with symptoms  
15 such as constipation and vomiting. Gastrointestinal perforation should be  
16 included in the differential diagnosis of patients presenting with  
17 abdominal pain on AVASTIN. AVASTIN therapy should be permanently  
18 discontinued in patients with gastrointestinal perforation. (See  
19 **WARNINGS: Gastrointestinal Perforations** and **DOSAGE AND**  
20 **ADMINISTRATION: Dose Modifications**.)

21 **Wound Healing Complications**

22 AVASTIN administration can result in the development of wound  
23 dehiscence, in some instances resulting in fatality. AVASTIN therapy  
24 should be permanently discontinued in patients with wound dehiscence  
25 requiring medical intervention. The appropriate interval between  
26 termination of AVASTIN and subsequent elective surgery required to  
27 avoid the risks of impaired wound healing/wound dehiscence has not been  
28 determined. (See **WARNINGS: Wound Healing Complications** and  
29 **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

30 **Hemorrhage**

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

39 **DESCRIPTION**

40 AVASTIN<sup>®</sup> (Bevacizumab) is a recombinant humanized monoclonal  
41 IgG1 antibody that binds to and inhibits the biologic activity of human  
42 vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay  
43 systems. Bevacizumab contains human framework regions and the  
44 complementarity-determining regions of a murine antibody that binds to  
45 VEGF (1). Bevacizumab is produced in a Chinese Hamster Ovary  
46 mammalian cell expression system in a nutrient medium containing the  
47 antibiotic gentamicin and has a molecular weight of approximately 149  
48 kilodaltons. AVASTIN is a clear to slightly opalescent, colorless to pale  
49 brown, sterile, pH 6.2 solution for intravenous (IV) infusion. AVASTIN  
50 is supplied in 100 mg and 400 mg preservative-free, single-use vials to  
51 deliver 4 mL or 16 mL of AVASTIN (25 mg/mL). The 100 mg product is  
52 formulated in 240 mg  $\alpha,\alpha$ -trehalose dihydrate, 23.2 mg sodium phosphate  
53 (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic,  
54 anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The  
55 400 mg product is formulated in 960 mg  $\alpha,\alpha$ -trehalose dihydrate, 92.8 mg  
56 sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate  
57 (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water for Injection,  
58 USP.

59 **CLINICAL PHARMACOLOGY**

60 **Mechanism of Action**

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

68 **Pharmacokinetics**

69 The pharmacokinetic profile of Bevacizumab was assessed using an assay  
70 that measures total serum Bevacizumab concentrations (i.e., the assay did  
71 not distinguish between free Bevacizumab and Bevacizumab bound to  
72 VEGF ligand). Based on a population pharmacokinetic analysis of 491  
73 patients who received 1 to 20 mg/kg of AVASTIN weekly, every 2 weeks,  
74 or every 3 weeks, the estimated half-life of Bevacizumab was  
75 approximately 20 days (range 11–50 days). The predicted time to reach  
76 steady state was 100 days. The accumulation ratio following a dose of 10  
77 mg/kg of Bevacizumab every 2 weeks was 2.8.

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

90 **Special Populations**

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

93 *Patients with renal impairment.* No studies have been conducted to  
94 examine the pharmacokinetics of Bevacizumab in patients with renal  
95 impairment.

96 *Patients with hepatic dysfunction.* No studies have been conducted to  
97 examine the pharmacokinetics of Bevacizumab in patients with hepatic  
98 impairment.

99 **CLINICAL STUDIES**

100 The safety and efficacy of AVASTIN in the treatment of patients with  
101 metastatic carcinoma of the colon or rectum were studied in three  
102 randomized, controlled clinical trials in combination with intravenous  
103 5-fluorouracil-based chemotherapy. The activity of AVASTIN in patients  
104 with metastatic colorectal cancer that progressed on or after receiving both  
105 irinotecan based- and oxaliplatin based- chemotherapy regimens was  
106 evaluated in an open-access trial in combination with intravenous  
107 5-fluorouracil-based chemotherapy.

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

109 Study 1 was a randomized, double-blind, active-controlled clinical trial  
110 evaluating AVASTIN as first-line treatment of metastatic carcinoma of the  
111 colon or rectum. Patients were randomized to bolus-IFL (irinotecan  
112 125 mg/m<sup>2</sup> IV, 5-fluorouracil 500 mg/m<sup>2</sup> IV, and leucovorin 20 mg/m<sup>2</sup> IV  
113 given once weekly for 4 weeks every 6 weeks) plus placebo (Arm 1),  
114 bolus-IFL plus AVASTIN (5 mg/kg every 2 weeks) (Arm 2), or 5-FU/LV  
115 plus AVASTIN (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3  
116 was discontinued, as pre-specified, when the toxicity of AVASTIN in  
117 combination with the bolus-IFL regimen was deemed acceptable.

118 Of the 813 patients randomized to Arms 1 and 2, the median age was 60,  
119 40% were female, and 79% were Caucasian. Fifty-seven percent had an

120 ECOG performance status of 0. Twenty-one percent had a rectal primary  
121 and 28% received prior adjuvant chemotherapy. In the majority of  
122 patients, 56%, the dominant site of disease was extra-abdominal, while the  
123 liver was the dominant site in 38% of patients. Results are presented in  
124 [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)	6.2	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.

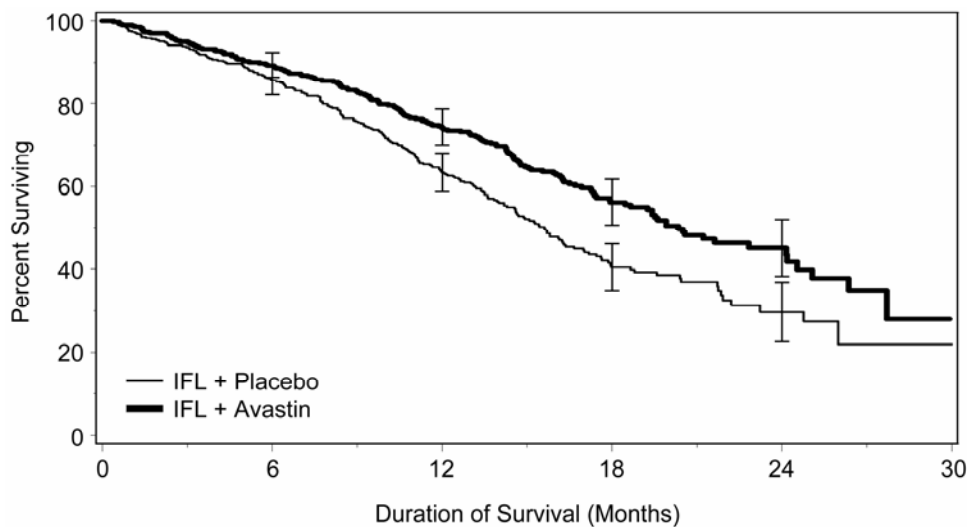
<sup>b</sup> p<0.01 by  $\chi^2$  test.

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



128

129 Error bars represent 95% confidence intervals.

130 The clinical benefit of AVASTIN, as measured by survival in the two  
131 principal arms, was seen in the subgroups defined by age (<65 yrs, ≥65  
132 yrs) and gender.

133 Among the 110 patients enrolled in Arm 3, median overall survival was  
134 18.3 months, median progression-free survival was 8.8 months, overall  
135 response rate was 39%, and median duration of response was 8.5 months.

### 136 **AVASTIN in Combination with 5-FU/LV Chemotherapy**

137 Study 2 was a randomized, active-controlled clinical trial testing  
138 AVASTIN in combination with 5-FU/LV as first-line treatment of  
139 metastatic colorectal cancer. Patients were randomized to receive  
140 5-FU/LV (5-fluorouracil 500 mg/m<sup>2</sup>, leucovorin 500 mg/m<sup>2</sup> weekly for  
141 6 weeks every 8 weeks) or 5-FU/LV plus AVASTIN (5 mg/kg every  
142 2 weeks) or 5-FU/LV plus AVASTIN (10 mg/kg every 2 weeks).

143 The primary endpoints of the trial were objective response rate and  
144 progression-free survival. Results are presented in Table 2.

**Table 2**  
Study 2 Efficacy Results

	5-FU/LV	5-FU/LV + AVASTIN 5 mg/kg	5-FU/LV + AVASTIN 10 mg/kg
Number of Patients	36	35	33
<u>Overall Survival</u>			
Median (months)	13.6	17.7	15.2
<u>Progression-Free Survival</u>			
Median (months)	5.2	9.0	7.2
<u>Overall Response Rate</u>			
Rate (percent)	17	40	24

145  
146 Progression-free survival was significantly longer in patients receiving  
147 5-FU/LV plus AVASTIN at 5 mg/kg when compared to those not

148 receiving AVASTIN. However, overall survival and overall response rate  
149 were not significantly different. Outcomes for patients receiving 5-FU/LV  
150 plus AVASTIN at 10 mg/kg were not significantly different than for  
151 patients who did not receive AVASTIN.

152 **AVASTIN in Combination with 5-FU/LV and Oxaliplatin**  
153 **Chemotherapy**

154 Study 3 was an open-label, randomized, 3-arm, active-controlled,  
155 multicenter clinical trial evaluating AVASTIN alone, AVASTIN in  
156 combination with 5-FU/LV and oxaliplatin (FOLFOX4), and FOLFOX4  
157 alone in the second-line treatment of metastatic carcinoma of the colon or  
158 rectum. Patients were previously treated with irinotecan and 5-FU for  
159 initial therapy for metastatic disease or as adjuvant therapy. Patients were  
160 randomized to FOLFOX4 (Day 1: oxaliplatin 85 mg/m<sup>2</sup> and leucovorin  
161 200 mg/m<sup>2</sup> concurrently IV, then 5-FU 400 mg/m<sup>2</sup> IV bolus followed by  
162 600 mg/m<sup>2</sup> continuously IV; Day 2: leucovorin 200 mg/m<sup>2</sup> IV, then 5-FU  
163 400 mg/m<sup>2</sup> IV bolus followed by 600 mg/m<sup>2</sup> continuously IV; repeated  
164 every 2 weeks), FOLFOX4 plus AVASTIN, or AVASTIN monotherapy.  
165 AVASTIN was administered at a dose of 10 mg/kg every 2 weeks and for  
166 patients in the FOLFOX4 plus AVASTIN arm, prior to the FOLFOX4  
167 chemotherapy on Day 1.

168 Of the 829 patients randomized to the three arms, the median age was  
169 61 years, 40% were female, 87% were Caucasian, and 49% had an ECOG  
170 performance status of 0. Twenty-six percent had received prior radiation  
171 therapy, 80% received prior adjuvant chemotherapy. Ninety-nine percent  
172 received prior irinotecan, with or without 5-FU for metastatic colorectal  
173 cancer, and 1% received prior irinotecan and 5-FU as adjuvant therapy.

174

175 The AVASTIN monotherapy arm of Study 3 was closed to accrual after  
176 enrollment of 244 of the planned 290 patients following a planned interim  
177 analysis by the data monitoring committee (DMC), based on evidence of  
178 decreased survival in the AVASTIN alone arm as compared to FOLFOX4  
179 alone arm. In the two remaining study arms, overall survival (OS) was

180 significantly longer in patients receiving AVASTIN in combination with  
181 FOLFOX 4 as compared to those receiving FOLFOX4 alone (median OS  
182 13.0 mos vs. 10.8 mos; hazard ratio 0.75 [95% CI 0.63, 0.89], p=0.001  
183 stratified log rank test). In addition, patients treated with AVASTIN in  
184 combination with FOLFOX4 were reported to have significantly longer  
185 progression-free survival and higher overall response rate based on  
186 investigator assessment. The clinical benefit of AVASTIN, as measured  
187 by survival, was seen in the subgroups defined by age (<65 yrs, ≥65 yrs)  
188 and gender.

### 189 **AVASTIN In Third Line Metastatic Colorectal Cancer**

190 Study 4 was an open access, multicenter, single arm study that evaluated  
191 the activity of AVASTIN in combination with bolus or infusional 5-  
192 FU/LV in 339 patients with metastatic colorectal cancer with disease  
193 progression following both irinotecan- and oxaliplatin-containing  
194 chemotherapy regimens. The majority (73%) of patients received  
195 concurrent 5-FU/LV according to a bolus regimen.

196 There was one objective partial response in the first 100 evaluable patients  
197 for an overall response rate of 1% (95% CI 0–5.5%).

### 198 **INDICATIONS AND USAGE**

199 AVASTIN<sup>®</sup>, in combination with intravenous 5-fluorouracil-based  
200 chemotherapy, is indicated for first-or second-line treatment of patients  
201 with metastatic carcinoma of the colon or rectum.

### 202 **CONTRAINDICATIONS**

203 There are no known contraindications to the use of AVASTIN.

### 204 **WARNINGS**

#### 205 **Gastrointestinal Perforations (See [DOSAGE AND](#)** 206 **[ADMINISTRATION: Dose Modifications](#))**

207 Gastrointestinal perforation complicated by intra-abdominal abscesses or  
208 fistula formation and in some instances with fatal outcome, occurs at an  
209 increased incidence in patients receiving AVASTIN as compared to

210 controls. In Studies 1, 2, and 3, the incidence of gastrointestinal  
211 perforation (gastrointestinal perforation, fistula formation, and/or intra-  
212 abdominal abscess) in patients receiving AVASTIN was 2.4%. These  
213 episodes occurred with or without intra-abdominal abscesses and at  
214 various time points during treatment. The typical presentation was  
215 reported as abdominal pain associated with symptoms such as constipation  
216 and emesis.

217 In postmarketing clinical studies and reports, gastrointestinal perforation,  
218 fistula and/or intra-abdominal abscess occurred in patients receiving  
219 AVASTIN for colorectal and for other types of cancer. The overall  
220 incidence in clinical studies was 1%, but may be higher in some cancer  
221 settings. Of the reported events, approximately 30% were fatal. Patients  
222 with gastrointestinal perforation, regardless of underlying cancer, typically  
223 present with abdominal pain, nausea and fever. Events were reported at  
224 various time points during treatment ranging from one week to greater  
225 than 1 year from initiation of AVASTIN, with most events occurring  
226 within the first 50 days.

227 Permanently discontinue AVASTIN in patients with gastrointestinal  
228 perforation.

229 **Wound Healing Complications (See [DOSAGE AND](#)**  
230 **[ADMINISTRATION: Dose Modifications](#))**

231 AVASTIN impairs wound healing in animal models. In clinical studies of  
232 AVASTIN, patients were not allowed to receive AVASTIN until at least  
233 28 days had elapsed following surgery. In clinical studies of AVASTIN in  
234 combination with chemotherapy, there were 6 instances of dehiscence  
235 among 788 patients (0.8%).

236 The appropriate interval between discontinuation of AVASTIN and  
237 subsequent elective surgery required to avoid the risks of impaired wound  
238 healing has not been determined. In Study 1, 39 patients who received  
239 bolus-IFL plus AVASTIN underwent surgery following AVASTIN  
240 therapy; of these patients, six (15%) had wound healing/bleeding

241 complications. In the same study, 25 patients in the bolus-IFL arm  
242 underwent surgery; of these patients, one of 25 (4%) had wound  
243 healing/bleeding complications. The longest interval between last dose of  
244 study drug and dehiscence was 56 days; this occurred in a patient on the  
245 bolus-IFL plus AVASTIN arm.

246 The interval between termination of AVASTIN and subsequent elective  
247 surgery should take into consideration the calculated half-life of  
248 AVASTIN (approximately 20 days).

249 Discontinue AVASTIN in patients with wound healing complications  
250 requiring medical intervention.

251 **Hemorrhage (See [DOSAGE AND ADMINISTRATION: Dose](#)**  
252 **[Modifications](#))**

253 Two distinct patterns of bleeding have occurred in patients receiving  
254 AVASTIN. The first is minor hemorrhage, most commonly Grade 1  
255 epistaxis. The second is serious, and in some cases fatal, hemorrhagic  
256 events. Serious hemorrhagic events occurred primarily in patients with  
257 non–small cell lung cancer, an indication for which AVASTIN is not  
258 approved.

259 In a randomized study in patients with non–small cell lung cancer  
260 receiving chemotherapy with or without AVASTIN, four of 13 (31%)  
261 AVASTIN-treated patients with squamous cell histology and two of 53  
262 (4%) AVASTIN-treated patients with non-squamous histology  
263 experienced life-threatening or fatal pulmonary hemorrhage as compared  
264 to none of the 32 (0%) patients receiving chemotherapy alone. Of the  
265 patients experiencing events of life-threatening pulmonary hemorrhage,  
266 many had cavitation and/or necrosis of the tumor, either pre-existing or  
267 developing during AVASTIN therapy. These serious hemorrhagic events  
268 occurred suddenly and presented as major or massive hemoptysis. Do not  
269 administer AVASTIN to patients with recent hemoptysis.

270 Other serious bleeding events reported in patients receiving AVASTIN  
271 included gastrointestinal hemorrhage, subarachnoid hemorrhage, and  
272 hemorrhagic stroke.

273 The risk of central nervous system (CNS) bleeding in patients with CNS  
274 metastases receiving AVASTIN has not been evaluated because these  
275 patients were excluded from late stage clinical studies following  
276 development of CNS hemorrhage in a patient with a CNS metastasis in a  
277 Phase 1 study.

278 Discontinue AVASTIN in patients with serious hemorrhage i.e., requiring  
279 medical intervention and initiate aggressive medical management.

280 **Arterial Thromboembolic Events (see [DOSAGE AND](#)**  
281 **[ADMINISTRATION: Dose Modifications, and PRECAUTIONS:](#)**  
282 **[Geriatric Use](#))**

283 Arterial thromboembolic events occurred at a higher incidence in patients  
284 receiving AVASTIN in combination with chemotherapy as compared to  
285 those receiving chemotherapy alone. Arterial thromboembolic events  
286 included cerebral infarction, transient ischemic attacks (TIAs), myocardial  
287 infarction (MI), angina, and a variety of other arterial thromboembolic  
288 events. These events were fatal in some instances.

289 In a pooled analysis of randomized, controlled clinical trials involving  
290 1745 patients, the incidence of arterial thromboembolic events was 4.4%  
291 among patients treated with AVASTIN in combination with chemotherapy  
292 and 1.9% among patients receiving chemotherapy alone. Fatal outcomes  
293 for these events occurred in 7 of 963 patients (0.7%) who were treated  
294 with AVASTIN in combination with chemotherapy, compared to 3 of  
295 782 patients (0.4%) who were treated with chemotherapy alone. The  
296 incidences of both cerebrovascular arterial events (1.9% vs. 0.5%) and  
297 cardiovascular arterial events (2.1% vs. 1.0%) were increased in patients  
298 receiving AVASTIN compared to chemotherapy alone. The relative risk  
299 of arterial thromboembolic events was greater in patients 65 and over  
300 (8.5% vs. 2.9%) as compared to those less than 65 (2.1% vs. 1.4%). (See

301 **PRECAUTIONS: Geriatric Use).**

302 The safety of resumption of AVASTIN therapy after resolution of an  
303 arterial thromboembolic event has not been studied. Permanently  
304 discontinue AVASTIN in patients who experience a severe arterial  
305 thromboembolic event during treatment.

306 **Hypertension (See DOSAGE AND ADMINISTRATION: Dose**  
307 **Modifications)**

308 The incidence of severe hypertension was increased in patients receiving  
309 AVASTIN as compared to controls. Across clinical studies the incidence  
310 of NCI-CTC Grade 3 or 4 hypertension ranged from 8-18%.

311 Medication classes used for management of patients with Grade 3  
312 hypertension receiving AVASTIN included angiotensin-converting  
313 enzyme inhibitors, beta blockers, diuretics, and calcium channel blockers.  
314 Development or worsening of hypertension can require hospitalization or  
315 require discontinuation of AVASTIN in up to 1.7% of patients.  
316 Hypertension can persist after discontinuation of AVASTIN.  
317 Complications can include hypertensive encephalopathy and CNS  
318 hemorrhage.

319 In the post-marketing experience, acute increases in blood pressure  
320 associated with initial or subsequent infusions of AVASTIN have been  
321 reported (see **PRECAUTIONS, Infusion Reactions**). Some cases were  
322 serious and associated with clinical sequelae.

323 Permanently discontinue AVASTIN in patients with hypertensive crisis.  
324 Temporarily suspend AVASTIN in patients with severe hypertension that  
325 is not controlled with medical management.

326 **Proteinuria (See DOSAGE AND ADMINISTRATION: Dose**  
327 **Modifications)**

328 The incidence and severity of proteinuria is increased in patients receiving  
329 AVASTIN as compared to control. In Studies 1 and 3, the incidence of

330 NCI-CTC Grade 3 and 4 proteinuria, characterized as >3.5 gm/24 hours,  
331 ranged up to 1.8% in AVASTIN-treated patients.

332 Nephrotic syndrome occurred in five of 1032 (0.5%) patients receiving  
333 AVASTIN in clinical studies. One patient died and one required dialysis.  
334 In three patients, proteinuria decreased in severity several months after  
335 discontinuation of AVASTIN. No patient had normalization of urinary  
336 protein levels (by 24-hour urine) following discontinuation of AVASTIN.

337 The highest incidence of proteinuria was observed in a dose-ranging,  
338 placebo-controlled, randomized study of AVASTIN in patients with  
339 metastatic renal cell carcinoma, an indication for which AVASTIN is not  
340 approved, 24-hour urine collections were obtained in approximately half  
341 the patients enrolled. Among patients in whom 24-hour urine collections  
342 were obtained, four of 19 (21%) patients receiving AVASTIN at 10 mg/kg  
343 every two weeks, two of 14 (14%) patients receiving AVASTIN at  
344 3 mg/kg every two weeks, and none of the 15 placebo patients  
345 experienced NCI-CTC Grade 3 proteinuria (> 3.5 gm protein/24 hours).

346 Discontinue AVASTIN in patients with nephrotic syndrome. The safety of  
347 continued AVASTIN treatment in patients with moderate to severe  
348 proteinuria has not been evaluated. In most clinical studies, AVASTIN  
349 was interrupted for  $\geq 2$  grams of proteinuria/24 hours and resumed when  
350 proteinuria was <2 gm/24 hours. Patients with moderate to severe  
351 proteinuria based on 24-hour collections should be monitored regularly  
352 until improvement and/or resolution is observed.

### 353 **Congestive Heart Failure**

354 Congestive heart failure (CHF), defined as NCI-CTC Grade 2–4 left  
355 ventricular dysfunction, was reported in 22 of 1032 (2%) patients  
356 receiving AVASTIN in clinical studies. The risk of CHF appears to be  
357 higher in patients receiving AVASTIN who have received prior or  
358 concurrent anthracyclines. In a controlled study in patients with breast  
359 cancer (an unlabelled indication), the incidence of CHF was higher in the

360 AVASTIN plus chemotherapy arm as compared to the chemotherapy  
361 alone arm. Congestive heart failure occurred in 13 of 299 (4%) patients  
362 who received prior anthracyclines and/or left chest wall irradiation.  
363 Congestive heart failure occurred in six of 44 (14%) patients with relapsed  
364 acute leukemia (an unlabelled indication) receiving AVASTIN and  
365 concurrent anthracyclines in a single arm study.

366 The safety of continuation or resumption of AVASTIN in patients with  
367 cardiac dysfunction has not been studied.

## 368 **PRECAUTIONS**

### 369 **General**

370 Use AVASTIN with caution in patients with known hypersensitivity to  
371 AVASTIN or any component of this drug product.

### 372 **Infusion Reactions**

373 In clinical studies, infusion reactions with the first dose of AVASTIN  
374 were uncommon (< 3%) and severe reactions occurred in 0.2% of patients.  
375 Infusion reactions reported in the clinical trials and postmarketing  
376 experience include hypertension, hypertensive crises associated with  
377 neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3  
378 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. Adequate  
379 information on rechallenge is not available. AVASTIN infusion should be  
380 interrupted in all patients with severe infusion reactions and appropriate  
381 medical therapy administered.

382 There are no data regarding the most appropriate method of identification  
383 of patients who may safely be retreated with AVASTIN after experiencing  
384 a severe infusion reaction.

### 385 **Surgery**

386 AVASTIN therapy should not be initiated for at least 28 days following  
387 major surgery. The surgical incision should be fully healed prior to  
388 initiation of AVASTIN. Because of the potential for impaired wound  
389 healing, AVASTIN should be suspended prior to elective surgery.

390 The appropriate interval between the last dose of AVASTIN and elective  
391 surgery is unknown; however, the half-life of AVASTIN is estimated to be  
392 20 days (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**) and  
393 the interval chosen should take into consideration the half-life of the drug.  
394 (See **WARNINGS: Gastrointestinal Perforations** and **Wound Healing**  
395 **Complications**.)

### 396 **Cardiovascular Disease**

397 Patients were excluded from participation in AVASTIN clinical trials if, in  
398 the previous year, they had experienced clinically significant  
399 cardiovascular disease. In an exploratory analysis pooling the data from  
400 five randomized, placebo-controlled, clinical trials conducted in patients  
401 without a recent history of clinically significant cardiovascular disease, the  
402 overall incidence of arterial thromboembolic events, the incidence of fatal  
403 arterial thromboembolic events, and the incidence of cardiovascular  
404 thromboembolic events were increased in patients receiving AVASTIN  
405 plus chemotherapy as compared to chemotherapy alone.

### 406 **Laboratory Tests**

407 Blood pressure monitoring should be conducted every two to three weeks  
408 during treatment with AVASTIN. Patients who develop hypertension on  
409 AVASTIN may require blood pressure monitoring at more frequent  
410 intervals. Patients with AVASTIN-induced or -exacerbated hypertension  
411 who discontinue AVASTIN should continue to have their blood pressure  
412 monitored at regular intervals.

413 Patients receiving AVASTIN should be monitored for the development or  
414 worsening of proteinuria with serial urinalyses. Patients with a 2+ or  
415 greater urine dipstick reading should undergo further assessment, e.g., a  
416 24-hour urine collection. (See **WARNINGS: Proteinuria** and **DOSAGE**  
417 **AND ADMINISTRATION: Dose Modifications**.)

418 **Drug Interactions**

419 No formal drug interaction studies with anti-neoplastic agents have been  
420 conducted. In Study 1, patients with colorectal cancer were given  
421 irinotecan/5-FU/leucovorin (bolus-IFL) with or without AVASTIN.  
422 Irinotecan concentrations were similar in patients receiving bolus-IFL  
423 alone and in combination with AVASTIN. The concentrations of SN38,  
424 the active metabolite of irinotecan, were on average 33% higher in patients  
425 receiving bolus-IFL in combination with AVASTIN when compared with  
426 bolus-IFL alone. In Study 1, patients receiving bolus-IFL plus AVASTIN  
427 had a higher incidence of Grade 3–4 diarrhea and neutropenia. Due to  
428 high inter-patient variability and limited sampling, the extent of the  
429 increase in SN38 levels in patients receiving concurrent irinotecan and  
430 AVASTIN is uncertain.

431 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

432 No carcinogenicity data are available for AVASTIN in animals or  
433 humans.

434 AVASTIN may impair fertility. Dose-related decreases in ovarian and  
435 uterine weights, endometrial proliferation, number of menstrual cycles, and  
436 arrested follicular development or absent corpora lutea were observed in  
437 female cynomolgus monkeys treated with 10 or 50 mg/kg of AVASTIN for  
438 13 or 26 weeks. Following a 4- or 12-week recovery period, which  
439 examined only the high-dose group, trends suggestive of reversibility were  
440 noted in the two females for each regimen that were assigned to recover.  
441 After the 12-week recovery period, follicular maturation arrest was no  
442 longer observed, but ovarian weights were still moderately decreased.  
443 Reduced endometrial proliferation was no longer observed at the 12-week  
444 recovery time point, but uterine weight decreases were still notable,  
445 corpora lutea were absent in 1 out of 2 animals, and the number of  
446 menstrual cycles remained reduced (67%).

447 **Pregnancy Category C**

448 AVASTIN has been shown to be teratogenic in rabbits when administered  
449 in doses that approximate the human dose on a mg/kg basis. Observed  
450 effects included decreases in maternal and fetal body weights, an  
451 increased number of fetal resorptions, and an increased incidence of  
452 specific gross and skeletal fetal alterations. Adverse fetal outcomes were  
453 observed at all doses tested.

454 Angiogenesis is critical to fetal development and the inhibition of  
455 angiogenesis following administration of AVASTIN is likely to result in  
456 adverse effects on pregnancy. There are no adequate and well-controlled  
457 studies in pregnant women. AVASTIN should be used during pregnancy  
458 or in any woman not employing adequate contraception only if the  
459 potential benefit justifies the potential risk to the fetus. All patients should  
460 be counseled regarding the potential risk of AVASTIN to the developing  
461 fetus prior to initiation of therapy. If the patient becomes pregnant while  
462 receiving AVASTIN, she should be apprised of the potential hazard to the  
463 fetus and/or the potential risk of loss of pregnancy. Patients who  
464 discontinue AVASTIN should also be counseled concerning the prolonged  
465 exposure following discontinuation of therapy (half-life of approximately  
466 20 days) and the possible effects of AVASTIN on fetal development.

467 **Nursing Mothers**

468 It is not known whether AVASTIN is secreted in human milk. Because  
469 human IgG1 is secreted into human milk, the potential for absorption and  
470 harm to the infant after ingestion is unknown. Women should be advised  
471 to discontinue nursing during treatment with AVASTIN and for a  
472 prolonged period following the use of AVASTIN, taking into account the  
473 half-life of the product, approximately 20 days [range 11–50 days]. (See  
474 **CLINICAL PHARMACOLOGY: Pharmacokinetics.**)

475 **Pediatric Use**

476 The safety and effectiveness of AVASTIN in pediatric patients has not  
477 been studied. However, physal dysplasia was observed in juvenile

478 cynomolgus monkeys with open growth plates treated for four weeks with  
479 doses that were less than the recommended human dose based on mg/kg  
480 and exposure. The incidence and severity of physal dysplasia were  
481 dose-related and were at least partially reversible upon cessation of  
482 treatment.

### 483 **Geriatric Use**

484 In Study 1, NCI-CTC Grade 3–4 adverse events were collected in all  
485 patients receiving study drug (396 bolus-IFL plus placebo; 392 bolus-IFL  
486 plus AVASTIN; 109 5-FU/LV plus AVASTIN), while NCI-CTC Grade 1  
487 and 2 adverse events were collected in a subset of 309 patients. There  
488 were insufficient numbers of patients 65 years and older in the subset in  
489 which Grade 1-4 adverse events were collected to determine whether the  
490 overall adverse event profile was different in the elderly as compared to  
491 younger patients. Among the 392 patients receiving bolus-IFL plus  
492 AVASTIN, 126 were at least 65 years of age. Severe adverse events that  
493 occurred at a higher incidence ( $\geq 2\%$ ) in the elderly when compared to  
494 those less than 65 years were asthenia, sepsis, deep thrombophlebitis,  
495 hypertension, hypotension, myocardial infarction, congestive heart failure,  
496 diarrhea, constipation, anorexia, leukopenia, anemia, dehydration,  
497 hypokalemia, and hyponatremia. The effect of AVASTIN on overall  
498 survival was similar in elderly patients as compared to younger patients.

499 In Study 3, patients age 65 and older receiving AVASTIN plus FOLFOX4  
500 had a greater relative risk as compared to younger patients for the  
501 following adverse events: nausea, emesis, ileus, and fatigue.

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

509 In an exploratory, pooled analysis of 1745 patients treated in  
510 five randomized, controlled studies, there were 618 (35%) patients age 65  
511 or older and 1127 patients less than 65 years of age. The overall incidence  
512 of arterial thromboembolic events was increased in all patients receiving  
513 AVASTIN with chemotherapy as compared to those receiving  
514 chemotherapy alone, regardless of age. However, the increase in arterial  
515 thromboembolic events incidence was greater in patients 65 and over  
516 (8.5% vs. 2.9%) as compared to those less than 65 (2.1% vs. 1.4%). (See  
517 **WARNINGS: Arterial Thromboembolic Events**)

518 **ADVERSE REACTIONS**The most serious adverse reactions in patients  
519 receiving AVASTIN were:

- 520 • Gastrointestinal Perforations (see **WARNINGS**)
- 521 • Wound Healing Complications (see **WARNINGS**)
- 522 • Hemorrhage (see **WARNINGS**)
- 523 • Arterial Thromboembolic Events (see **WARNINGS**)
- 524 • Hypertensive Crises (see **WARNINGS; Hypertension**)
- 525 • Nephrotic Syndrome (see **WARNINGS; Proteinuria**)
- 526 • Congestive Heart Failure (see **WARNINGS**)

527 The most common adverse events in patients receiving AVASTIN were  
528 asthenia, pain, abdominal pain, headache, hypertension, diarrhea, nausea,  
529 vomiting, anorexia, stomatitis, constipation, upper respiratory infection,  
530 epistaxis, dyspnea, exfoliative dermatitis, and proteinuria.

### 531 **Adverse Reactions in Clinical Trials**

532 Because clinical trials are conducted under widely varying conditions,  
533 adverse reaction rates observed in the clinical trials of a drug cannot be  
534 directly compared to rates in the clinical trials of another drug and may not  
535 reflect the rates observed in practice. The adverse reaction information  
536 from clinical trials does, however, provide a basis for identifying the  
537 adverse events that appear to be related to drug use and for approximating  
538 rates.

539 The data described below reflect exposure to AVASTIN<sup>®</sup> in 1106 patients,  
540 including 506 receiving AVASTIN<sup>®</sup> for at least 6 months and 147  
541 receiving AVASTIN<sup>®</sup> for at least one year. AVASTIN<sup>®</sup> was studied  
542 primarily in placebo- and active-controlled trials (n = 501, and n = 605,  
543 respectively). Among 569 patients with metastatic colorectal cancer  
544 (mCRC) receiving first-line therapy for metastatic disease, the median age  
545 was 60, 40% were female, and 79% were Caucasian. Fifty-seven percent  
546 had an ECOG performance status of 0. Twenty-one percent had a rectal  
547 primary and 28% received prior adjuvant chemotherapy. In the majority  
548 of patients, 56%, the dominant site of disease was extra-abdominal, while  
549 the liver was the dominant site in 38% of patients. Most patients received  
550 doses of 5 mg/kg every 2 weeks; all patients received concurrent  
551 chemotherapy. Among 537 patients with metastatic colorectal cancer  
552 (mCRC) receiving second-line therapy for metastatic disease, the median  
553 age was 61 years, 40% were female, 87% were Caucasian, and 49% had  
554 an ECOG performance status of 0. Twenty-six percent had received prior  
555 radiation therapy, 80% received prior adjuvant chemotherapy, and 99%  
556 received prior chemotherapy for metastatic colorectal cancer. Patients  
557 received doses of 10 mg/kg every 2 weeks, alone (n=244) or with  
558 chemotherapy (n=293).

#### 559 Gastrointestinal Perforation

560 Across all studies, the incidence of gastrointestinal perforation, in some  
561 cases fatal, in patients with metastatic colorectal cancer (mCRC) receiving  
562 AVASTIN alone or in combination with chemotherapy was 2.4%  
563 compared to 0.3% in patients receiving only chemotherapy. The incidence  
564 of gastrointestinal perforation ranged from 0 – 3.7%.

#### 565 Wound Healing Complications

566 The incidence of post-operative wound healing and/or bleeding  
567 complications was increased in patients receiving AVASTIN. Among  
568 patients requiring surgery on or within 60 days of receiving study  
569 treatment, wound healing and/or bleeding complications occurred in 15%  
570 (6/39) of patients receiving bolus-IFL plus AVASTIN as compared to 4%

571 (1/25) of patients who received bolus-IFL alone. In the same study, the  
572 incidence of wound dehiscence was also higher in the AVASTIN-treated  
573 patients (1% vs. 0.5%).

#### 574 Hemorrhage

575 In clinical studies of CRC, both serious and non-serious hemorrhagic  
576 events occurred at a higher incidence in patients receiving AVASTIN.

577 (See **WARNINGS: Hemorrhage.**)

578 In Study 3, the incidence of NCI-CTC Grade 3–5 bleeding events was  
579 increased in patients receiving AVASTIN with chemotherapy (5.2%) and  
580 in those receiving AVASTIN alone (3.8%) compared to patients receiving  
581 FOLFOX4 alone (0.7%). Two patients receiving AVASTIN had fatal  
582 CNS hemorrhage.

583 In Study 1, the incidence of epistaxis was higher (35% vs. 10%) in  
584 patients receiving bolus-IFL plus AVASTIN compared with patients  
585 receiving bolus-IFL plus placebo. These events were generally mild in  
586 severity (NCI-CTC Grade 1) and resolved without medical intervention.  
587 Additional mild to moderate hemorrhagic events reported more frequently  
588 in patients receiving bolus-IFL plus AVASTIN when compared to those  
589 receiving bolus-IFL plus placebo included gastrointestinal hemorrhage  
590 (24% vs. 6%), minor gum bleeding (2% vs. 0), and vaginal hemorrhage  
591 (4% vs. 2%).

#### 592 Venous Thromboembolic Events

593 In Study 1, the incidence of NCI CTC grade 3-4 venous thromboembolic  
594 events was slightly higher in patients receiving AVASTIN with  
595 chemotherapy as compared to those receiving chemotherapy alone. In  
596 addition, the risk of developing a second thromboembolic event in patients  
597 receiving AVASTIN and chemotherapy is increased compared to patients  
598 receiving chemotherapy alone who have experienced a venous  
599 thromboembolic event.

600 In Study 1, 53 patients (14%) on the bolus-IFL plus AVASTIN arm and  
601 30 patients (8%) on the bolus-IFL plus placebo arm received full dose  
602 warfarin following a venous thromboembolic event. Among these  
603 patients, an additional thromboembolic event occurred in 21% (11/53) of  
604 patients receiving bolus-IFL plus AVASTIN and 3% (1/30) of patients  
605 receiving bolus-IFL alone.

606 The overall incidence of Grade 3-4 venous thromboembolic events in  
607 Study 1 was 15.1% in patients receiving bolus-IFL plus AVASTIN and  
608 13.6% in patients receiving bolus-IFL plus placebo. In Study 1, the  
609 incidence of the following Grade 3 and 4 venous thromboembolic events  
610 was higher in patients receiving bolus-IFL plus AVASTIN as compared to  
611 patients receiving bolus-IFL plus placebo: deep venous thrombosis (34  
612 vs. 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

613

#### 614 Hypertension

615 The incidences of hypertension and of severe hypertension were increased  
616 in patients receiving AVASTIN in Study 1 (see Table 4).

**Table 4**  
Incidence of Hypertension and Severe Hypertension in Study 1

	Arm 1 IFL+Placebo (n=394)	Arm 2 IFL+AVASTIN (n=392)	Arm 3 5-FU/LV+AVASTIN (n=109)
Hypertension <sup>a</sup> (>150/100 mmHg)	43%	60%	67%
Severe Hypertension <sup>a</sup> (>200/110 mmHg)	2%	7%	10%

<sup>a</sup> This includes patients with either a systolic or diastolic reading greater than the cutoff value on one or more occasions.

617

618 Among patients with severe hypertension in the AVASTIN arms, slightly  
619 over half the patients (51%) had a diastolic reading greater than 110  
620 mmHg associated with a systolic reading less than 200 mmHg.

621 Similar results were seen in patients receiving AVASTIN alone or in  
622 combination with FOLFOX 4.

623 Fatal CNS hemorrhage complicating hypertension can occur.

624 Proteinuria

625 See WARNINGS and DOSAGE AND ADMINISTRATION: Dose  
626 Modifications

627

628 Immunogenicity

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

636 Immunogenicity data are highly dependent on the sensitivity and  
637 specificity of the assay. Additionally, the observed incidence of antibody  
638 positivity in an assay may be influenced by several factors, including  
639 sample handling, timing of sample collection, concomitant medications,  
640 and underlying disease. For these reasons, comparison of the incidence of  
641 antibodies to AVASTIN with the incidence of antibodies to other products  
642 may be misleading.

643 **First-Line Treatment of Metastatic Carcinoma of the Colon and**  
644 **Rectum**

645 The data in Tables 5 and 6 were obtained in Study 1. All NCI-CTC  
646 Grade 3 and 4 adverse events and selected Grade 1 and 2 adverse events  
647 (hypertension, proteinuria, thromboembolic events) were reported for the  
648 overall study population. In Study 1, the median age was 60, 60% were  
649 male, 78% had colon primary lesion, and 29% had prior adjuvant or  
650 neoadjuvant chemotherapy. The median duration of exposure to

651 AVASTIN in Study 1 was 8 months in Arm 2 and 7 months in Arm 3.  
652 Severe and life-threatening (NCI-CTC Grade 3 and 4) adverse events,  
653 which occurred at a higher incidence ( $\geq 2\%$ ) in patients receiving  
654 bolus-IFL plus AVASTIN as compared to bolus-IFL plus placebo, are  
655 presented in [Table 5](#).

**Table 5**  
NCI-CTC Grade 3 and 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)
Grade 3–4 Events	295 (74%)	340 (87%)
<u>Body as a Whole</u>		
Asthenia	28 (7%)	38 (10%)
Abdominal Pain	20 (5%)	32 (8%)
Pain	21 (5%)	30 (8%)
<u>Cardiovascular</u>		
Hypertension	10 (2%)	46 (12%)
Deep Vein Thrombosis	19 (5%)	34 (9%)
Intra-Abdominal Thrombosis	5 (1%)	13 (3%)
Syncope	4 (1%)	11 (3%)
<u>Digestive</u>		
Diarrhea	99 (25%)	133 (34%)
Constipation	9 (2%)	14 (4%)
<u>Hemic/Lymphatic</u>		
Leukopenia	122 (31%)	145 (37%)
Neutropenia <sup>a</sup>	41 (14%)	58 (21%)

<sup>a</sup> 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.

656  
657 Grade 1-4 adverse events which occurred at a higher incidence ( $\geq 5\%$ ) in  
658 patients receiving bolus-IFL plus AVASTIN as compared to the  
659 bolus-IFL plus placebo arm, are presented in [Table 6](#).

**Table 6**  
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	54 (55%)	62 (61%)	67 (62%)
Abdominal Pain	54 (55%)	62 (61%)	55 (50%)
Headache	19 (19%)	27 (26%)	30 (26%)
<u>Cardiovascular</u>			
Hypertension	14 (14%)	23 (23%)	37 (34%)
Hypotension	7 (7%)	15 (15%)	8 (7%)
Deep Vein Thrombosis	3 (3%)	9 (9%)	6 (6%)
<u>Digestive</u>			
Vomiting	46 (47%)	53 (52%)	51 (47%)
Anorexia	29 (30%)	44 (43%)	38 (35%)
Constipation	28 (29%)	41 (40%)	32 (29%)
Stomatitis	18 (18%)	33 (32%)	33 (30%)
Dyspepsia	15 (15%)	25 (24%)	19 (17%)
GI Hemorrhage	6 (6%)	25 (24%)	21 (19%)
Weight Loss	10 (10%)	15 (15%)	18 (16%)
Dry Mouth	2 (2%)	7 (7%)	4 (4%)
Colitis	1 (1%)	6 (6%)	1 (1%)
<u>Hemic/Lymphatic</u>			
Thrombocytopenia	0	5 (5%)	5 (5%)
<u>Nervous</u>			
Dizziness	20 (20%)	27 (26%)	21 (19%)

660

**Table 6 (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>Respiratory</u>			
Upper Respiratory Infection	38 (39%)	48 (47%)	44 (40%)
Epistaxis	10 (10%)	36 (35%)	35 (32%)
Dyspnea	15 (15%)	26 (26%)	27 (25%)
Voice Alteration	2 (2%)	9 (9%)	6 (6%)
<u>Skin/Appendages</u>			
Alopecia	25 (26%)	33 (32%)	6 (6%)
Skin Ulcer	1 (1%)	6 (6%)	7 (6%)
<u>Special Senses</u>			
Taste Disorder	9 (9%)	14 (14%)	23 (21%)
<u>Urogenital</u>			
Proteinuria	24 (24%)	37 (36%)	39 (36%)

661

662 **Second-Line Treatment of Metastatic Carcinoma of the Colon**  
 663 **and Rectum**

664 The data in Table 7 were obtained in Study 3. Selected NCI-CTC Grade  
 665 3–5 non-hematologic and Grade 4–5 hematologic adverse events which  
 666 occurred at a higher incidence in patients receiving FOLFOX4 plus  
 667 AVASTIN as compared to those who received FOLFOX4 alone, are  
 668 presented in Table 7. These data are likely to under-estimate the true  
 669 adverse event rates due to the reporting mechanisms used in Study 3.

<b>Table 7</b>			
<b>NCI-CTC Grade 3–5 Non-Hematologic and Grade 4-5 Hematologic Adverse Events in Study 3</b>			
<b>(Occurring at Higher Incidence (≥ 2%) with AVASTIN + FOLFOX4 vs. FOLFOX4)</b>			
	FOLFOX4 (n=285)	FOLFOX4+ AVASTIN (n=287)	AVASTIN (n=234)
Patients with at least one event	171 (60%)	219 (76%)	87 (37%)
<b>Gastrointestinal</b>			
Diarrhea	36 (13%)	51 (18%)	5 (2%)
Nausea	13 (5%)	35 (12%)	14 (6%)
Vomiting	11 (4%)	32 (11%)	15 (6%)
Dehydration	14 (5%)	29 (10%)	15 (6%)
Ileus	4 (1%)	10 (4%)	11 (5%)
<b>Neurology</b>			
Neuropathy–sensory	26 (9%)	48 (17%)	2 (1%)
Neurologic–other	8 (3%)	15 (5%)	3 (1%)
<b>Constitutional symptoms</b>			
Fatigue	37 (13%)	56 (19%)	12 (5%)
<b>Pain</b>			
Abdominal pain	13 (5%)	24 (8%)	19 (8%)
Headache	0 (0%)	8 (3%)	4 (2%)
<b>Cardiovascular (general)</b>			
Hypertension	5 (2%)	26 (9%)	19 (8%)
<b>Hemorrhage</b>			
Hemorrhage	2 (1%)	15 (5%)	9 (4%)

670

671 **Other Serious Adverse Events**

672 The following additional serious adverse events occurred in at least one  
673 subject treated with AVASTIN in clinical studies.

674 *Body as a Whole: polyserositis*

675 *Digestive: intestinal necrosis, mesenteric venous occlusion, anastomotic*  
676 *ulceration*

677 *Hemic and lymphatic: pancytopenia*

678 *Metabolic and nutritional disorders: hyponatremia*

679

680

681 **OVERDOSAGE**

682 The maximum tolerated dose of AVASTIN has not been determined.  
683 The highest dose tested in humans (20 mg/kg IV) was associated with  
684 headache in nine of 16 patients and with severe headache in three of  
685 16 patients.

686 **DOSAGE AND ADMINISTRATION**

687 AVASTIN, used in combination with intravenous 5-FU-based  
688 chemotherapy, is administered as an intravenous infusion (5 mg/kg or 10  
689 mg/kg) every 14 days until disease progression.

690 The recommended dose of AVASTIN, when used in combination with  
691 bolus IFL, is 5 mg/kg.

692 The recommended dose of AVASTIN, when used in combination with  
693 FOLFOX4, is 10 mg/kg.

694 Do not initiate AVASTIN until at least 28 days following major surgery.  
695 The surgical incision should be fully healed prior to initiation of  
696 AVASTIN.

697 **Dose Modifications**

698 There are no recommended dose reductions for the use of AVASTIN.  
699 If needed, AVASTIN should be either discontinued or temporarily  
700 suspended as described below.

701 AVASTIN should be permanently discontinued in patients who develop  
702 gastrointestinal perforation, wound dehiscence requiring medical  
703 intervention, serious bleeding, a severe arterial thromboembolic event,  
704 nephrotic syndrome, or hypertensive crisis.

705 Temporary suspension of AVASTIN is recommended in patients with  
706 evidence of moderate to severe proteinuria pending further evaluation and  
707 in patients with severe hypertension that is not controlled with medical

708 management. The risk of continuation or temporary suspension of  
709 AVASTIN in patients with moderate to severe proteinuria is unknown.

710 AVASTIN should be suspended at least several weeks prior to elective  
711 surgery. (See **WARNINGS: Gastrointestinal Perforation** and **Wound**  
712 **Healing Complications** and **PRECAUTIONS: Surgery**.) AVASTIN  
713 should not be resumed until the surgical incision is fully healed.

#### 714 **Preparation for Administration**

715 AVASTIN should be diluted for infusion by a healthcare professional  
716 using aseptic technique. Withdraw the necessary amount of AVASTIN to  
717 obtain the required dose and dilute in a total volume of 100 mL of 0.9%  
718 Sodium Chloride Injection, USP. Discard any unused portion left in a  
719 vial, as the product contains no preservatives. Parenteral drug products  
720 should be inspected visually for particulate matter and discoloration prior  
721 to administration.

722 Diluted AVASTIN solutions for infusion may be stored at 2–8°C  
723 (36–46°F) for up to 8 hours. No incompatibilities between AVASTIN and  
724 polyvinylchloride or polyolefin bags have been observed.

725 **AVASTIN infusions should not be administered or mixed with**  
726 **dextrose solutions.**

#### 727 **Administration**

728 **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** The initial  
729 AVASTIN dose should be delivered over 90 minutes as an IV infusion  
730 following chemotherapy. If the first infusion is well tolerated, the second  
731 infusion may be administered over 60 minutes. If the 60-minute infusion  
732 is well tolerated, all subsequent infusions may be administered over  
733 30 minutes.

734 **Stability and Storage**

735 AVASTIN vials must be refrigerated at 2–8°C (36–46°F). AVASTIN  
736 vials should be protected from light. Store in the original carton until time  
737 of use. **DO NOT FREEZE. DO NOT SHAKE.**

738 **HOW SUPPLIED**

739 AVASTIN is supplied as 4 mL and 16 mL of a sterile solution in  
740 single-use glass vials to deliver 100 and 400 mg of Bevacizumab per vial,  
741 respectively.

742 Single unit 100 mg carton: Contains one 4 mL vial of AVASTIN  
743 (25 mg/mL). NDC 50242-060-01

744 Single unit 400 mg carton: Contains one 16 mL vial of AVASTIN  
745 (25 mg/mL). NDC 50242-061-01

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**AVASTIN<sup>®</sup>**

**(Bevacizumab)**

**For Intravenous Use**

Manufactured by:

**Genentech, Inc.**

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