

10-11-06

1 **1.14.2.3 Final Labeling Text**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 with colorectal cancer and in patients with non-small
14 cell lung cancer (NSCLC) receiving AVASTIN was 2.4% and 0.9%,
15 respectively. The typical presentation was reported as abdominal pain
16 associated with symptoms such as constipation and vomiting.

17 Gastrointestinal perforation should be included in the differential
18 diagnosis of patients presenting with abdominal pain on AVASTIN.
19 AVASTIN therapy should be permanently discontinued in patients with
20 gastrointestinal perforation. (See **WARNINGS: Gastrointestinal**
21 **Perforations** and **DOSAGE AND ADMINISTRATION: Dose**
22 **Modifications.**)

23 **Wound Healing Complications**

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

32 **Hemorrhage**

33 Fatal pulmonary hemorrhage can occur in patients with NSCLC treated
34 with chemotherapy and AVASTIN. The incidence of severe or fatal
35 hemoptysis was 31% in patients with squamous histology and 2.3% in
36 patients with NSCLC excluding predominant squamous histology.
37 Patients with recent hemoptysis ($\geq 1/2$ tsp of red blood) should not receive
38 AVASTIN. (See **WARNINGS: Hemorrhage, ADVERSE**
39 **REACTIONS: Hemorrhage, and DOSAGE AND**
40 **ADMINISTRATION: Dose Modifications.**)

41 **DESCRIPTION**

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

61 **CLINICAL PHARMACOLOGY**

62 **Mechanism of Action**

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

70 **Pharmacokinetics**

71 The pharmacokinetic profile of Bevacizumab was assessed using an assay
72 that measures total serum Bevacizumab concentrations (i.e., the assay did
73 not distinguish between free Bevacizumab and Bevacizumab bound to
74 VEGF ligand). Based on a population pharmacokinetic analysis of
75 491 patients who received 1 to 20 mg/kg of AVASTIN weekly, every
76 2 weeks, or every 3 weeks, the estimated half-life of Bevacizumab was
77 approximately 20 days (range 11–50 days). The predicted time to reach
78 steady state was 100 days. The accumulation ratio following a dose of
79 10 mg/kg of Bevacizumab every 2 weeks was 2.8.

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

92 **Special Populations**

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

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

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

101 **CLINICAL STUDIES**

102 **AVASTIN® In Metastatic Colorectal Cancer (mCRC)**

103 The safety and efficacy of AVASTIN in the treatment of patients with
104 metastatic carcinoma of the colon or rectum were studied in three
105 randomized, controlled clinical trials in combination with intravenous
106 5-fluorouracil-based chemotherapy. The activity of AVASTIN in patients
107 with metastatic colorectal cancer that progressed on or after receiving both
108 irinotecan based- and oxaliplatin based-chemotherapy regimens was
109 evaluated in an open-access trial in combination with intravenous
110 5-fluorouracil-based chemotherapy.

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

112 Study 1 was a randomized, double-blind, active-controlled clinical trial
113 evaluating AVASTIN as first-line treatment of metastatic carcinoma of the
114 colon or rectum. Patients were randomized to bolus-IFL (irinotecan
115 125 mg/m² IV, 5-fluorouracil 500 mg/m² IV, and leucovorin 20 mg/m² IV
116 given once weekly for 4 weeks every 6 weeks) plus placebo (Arm 1),
117 bolus-IFL plus AVASTIN (5 mg/kg every 2 weeks) (Arm 2), or 5-FU/LV
118 plus AVASTIN (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3
119 was discontinued, as pre-specified, when the toxicity of AVASTIN in
120 combination with the bolus-IFL regimen was deemed acceptable.

121 Of the 813 patients randomized to Arms 1 and 2, the median age was 60,
122 40% were female, and 79% were Caucasian. Fifty-seven percent had an
123 ECOG performance status of 0. Twenty-one percent had a rectal primary
124 and 28% received prior adjuvant chemotherapy. In the majority of
125 patients, 56%, the dominant site of disease was extra-abdominal, while the
126 liver was the dominant site in 38% of patients. Results are presented in
127 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^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

^ap<0.001 by stratified logrank test.

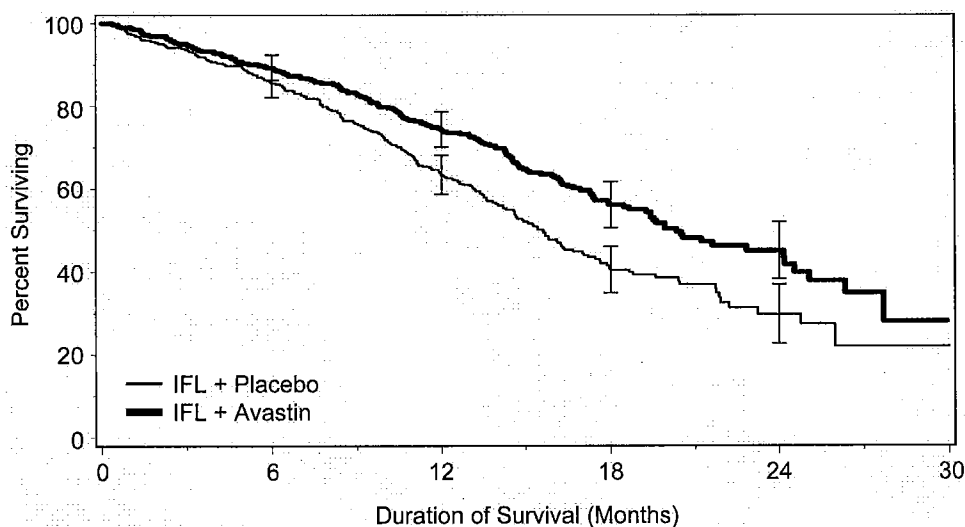
^bp<0.01 by χ^2 test.

128

129

130

Figure 1
Duration of Survival in Study 1



131

132

Error bars represent 95% confidence intervals.

133 The clinical benefit of AVASTIN, as measured by survival in the two
 134 principal arms, was seen in the subgroups defined by age (<65 yrs,
 135 ≥65 yrs) and gender.

136 Among the 110 patients enrolled in Arm 3, median overall survival was
 137 18.3 months, median progression-free survival was 8.8 months, overall
 138 response rate was 39%, and median duration of response was 8.5 months.

139 AVASTIN in Combination with 5-FU/LV Chemotherapy

140 Study 2 was a randomized, active-controlled clinical trial testing
 141 AVASTIN in combination with 5-FU/LV as first-line treatment of
 142 metastatic colorectal cancer. Patients were randomized to receive
 143 5-FU/LV (5-fluorouracil 500 mg/m², leucovorin 500 mg/m² weekly for
 144 6 weeks every 8 weeks) or 5-FU/LV plus AVASTIN (5 mg/kg every
 145 2 weeks) or 5-FU/LV plus AVASTIN (10 mg/kg every 2 weeks).

146 The primary endpoints of the trial were objective response rate and
 147 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

148
 149 Progression-free survival was significantly longer in patients receiving
 150 5-FU/LV plus AVASTIN at 5 mg/kg when compared to those not
 151 receiving AVASTIN. However, overall survival and overall response rate
 152 were not significantly different. Outcomes for patients receiving 5-FU/LV

153 plus AVASTIN at 10 mg/kg were not significantly different than for
154 patients who did not receive AVASTIN.

155 **AVASTIN in Combination with 5-FU/LV and Oxaliplatin**
156 **Chemotherapy**

157 Study 3 was an open-label, randomized, 3-arm, active-controlled,
158 multicenter clinical trial evaluating AVASTIN alone, AVASTIN in
159 combination with 5-FU/LV and oxaliplatin (FOLFOX4), and FOLFOX4
160 alone in the second-line treatment of metastatic carcinoma of the colon or
161 rectum. Patients were previously treated with irinotecan and 5-FU for
162 initial therapy for metastatic disease or as adjuvant therapy. Patients were
163 randomized to FOLFOX4 (Day 1: oxaliplatin 85 mg/m² and leucovorin
164 200 mg/m² concurrently IV, then 5-FU 400 mg/m² IV bolus followed by
165 600 mg/m² continuously IV; Day 2: leucovorin 200 mg/m² IV, then 5-FU
166 400 mg/m² IV bolus followed by 600 mg/m² continuously IV; repeated
167 every 2 weeks), FOLFOX4 plus AVASTIN, or AVASTIN monotherapy.
168 AVASTIN was administered at a dose of 10 mg/kg every 2 weeks and for
169 patients in the FOLFOX4 plus AVASTIN arm, prior to the FOLFOX4
170 chemotherapy on Day 1.

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

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

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

192 **AVASTIN in Third-Line Metastatic Colorectal Cancer**

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

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

201 **AVASTIN® In Unresectable Non-Squamous, Non-Small Cell** 202 **Lung Cancer (NSCLC)**

203 The safety and efficacy of AVASTIN as first-line treatment of patients
204 with locally advanced, metastatic, or recurrent non-squamous, NSCLC
205 was studied in a single, large, randomized, active-controlled, open-label,
206 multicenter study (Study 5, n=878), supported by a randomized, dose
207 ranging, active controlled Phase 2 study (Study 6, n=98).

208 In Study 5, chemotherapy-naïve patients with locally advanced, metastatic
209 or recurrent non-squamous NSCLC were randomized (1:1) to receive six
210 cycles of paclitaxel 200 mg/m² and carboplatin AUC=6.0, both by IV
211 infusion on day 1 (PC) or PC in combination with AVASTIN at a dose of
212 15 mg/kg by IV infusion on day 1 (PC plus AVASTIN). After completion
213 or upon discontinuation of chemotherapy, patients in the PC plus

214 AVASTIN arm continued to receive AVASTIN alone until disease
215 progression or until unacceptable toxicity. Cycles were repeated every
216 21 days. Patients with predominant squamous histology (mixed cell type
217 tumors only), central nervous system (CNS) metastasis, gross hemoptysis
218 ($\geq 1/2$ tsp of red blood), or unstable angina and those receiving therapeutic
219 anticoagulation were excluded. The main outcome measure of the study
220 was duration of survival.

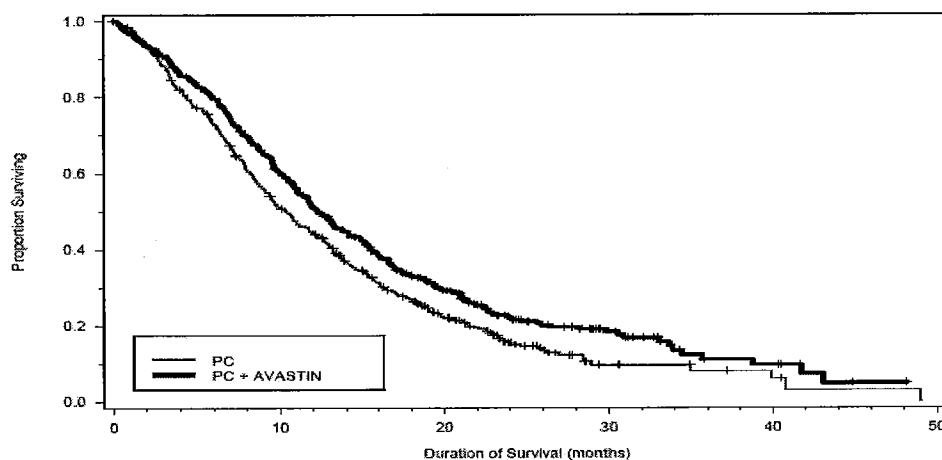
221 Among the 878 patients randomized to the two treatment arms, the median
222 age was 63, 46% were female, 43% were \geq age 65, and 28% had $\geq 5\%$
223 weight loss at study entry. Eleven percent had recurrent disease and of the
224 remaining 89% with newly diagnosed NSCLC, 12% had Stage IIIB with
225 malignant pleural effusion and 76% had Stage IV disease. The survival
226 curves are presented in Figure 2. Overall survival was statistically
227 significantly higher among patients receiving PC plus AVASTIN
228 compared with those receiving PC alone; median OS was 12.3 mos vs.
229 10.3 mos (hazard ratio 0.80 [repeated 95% CI 0.68, 0.94], final p- value
230 0.013, stratified log-rank test). Based on investigator assessment which
231 was not independently verified, patients were reported to have longer
232 progression-free survival with AVASTIN in combination with PC
233 compared to PC alone.

234

Figure 2

235

Duration of Survival in Study 5



236

237 In an exploratory analyses across patient subgroups, the impact of
238 AVASTIN on overall survival was less robust in the following: women
239 [HR = 0.99 (95% CI: 0.79, 1.25)], age \geq 65 years [HR = 0.91 (95% CI:
240 0.72, 1.14)] and patients with \geq 5% weight loss at study entry [HR = 0.96
241 (95% CI: 0.73, 1.26)].

242 INDICATIONS AND USAGE

243 AVASTIN[®], in combination with intravenous 5-fluorouracil-based
244 chemotherapy, is indicated for first-or second-line treatment of patients
245 with metastatic carcinoma of the colon or rectum.

246 AVASTIN[®], in combination with carboplatin and paclitaxel, is indicated
247 for first-line treatment of patients with unresectable, locally advanced,
248 recurrent or metastatic non-squamous, non-small cell lung cancer.

249 CONTRAINDICATIONS

250 None.

251 **WARNINGS**

252 **Gastrointestinal Perforations (See DOSAGE AND**
253 **ADMINISTRATION: Dose Modifications)**

254 Gastrointestinal perforation complicated by intra-abdominal abscesses or
255 fistula formation and in some instances with fatal outcome, occurs at an
256 increased incidence in patients receiving AVASTIN as compared to
257 controls. In Studies 1, 2, and 3, the incidence of gastrointestinal
258 perforation (gastrointestinal perforation, fistula formation, and/or
259 intra-abdominal abscess) in patients receiving AVASTIN was 2.4%.
260 These episodes occurred with or without intra-abdominal abscesses and at
261 various time points during treatment. The typical presentation was
262 reported as abdominal pain associated with symptoms such as constipation
263 and emesis.

264 In post-marketing clinical studies and reports, gastrointestinal perforation,
265 fistula and/or intra-abdominal abscess occurred in patients receiving
266 AVASTIN for colorectal and for other types of cancer. The overall
267 incidence in clinical studies was 1%, but may be higher in some cancer
268 settings. Of the reported events, approximately 30% were fatal. Patients
269 with gastrointestinal perforation, regardless of underlying cancer, typically
270 present with abdominal pain, nausea and fever. Events were reported at
271 various time points during treatment ranging from one week to greater
272 than 1 year from initiation of AVASTIN, with most events occurring
273 within the first 50 days.

274 Permanently discontinue AVASTIN in patients with gastrointestinal
275 perforation.

276 **Wound Healing Complications (See DOSAGE AND**
277 **ADMINISTRATION: Dose Modifications)**

278 AVASTIN impairs wound healing in animal models. In clinical studies of
279 AVASTIN, patients were not allowed to receive AVASTIN until at least
280 28 days had elapsed following surgery. In clinical studies of AVASTIN in
281 combination with chemotherapy, there were 6 instances of dehiscence
282 among 788 patients (0.8%).

283 The appropriate interval between discontinuation of AVASTIN and
284 subsequent elective surgery required to avoid the risks of impaired wound
285 healing has not been determined. In Study 1, 39 patients who received
286 bolus-IFL plus AVASTIN underwent surgery following AVASTIN
287 therapy; of these patients, six (15%) had wound healing/bleeding
288 complications. In the same study, 25 patients in the bolus-IFL arm
289 underwent surgery; of these patients, one of 25 (4%) had wound
290 healing/bleeding complications. The longest interval between last dose of
291 study drug and dehiscence was 56 days; this occurred in a patient on the
292 bolus-IFL plus AVASTIN arm.

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

296 Discontinue AVASTIN in patients with wound healing complications
297 requiring medical intervention.

298 **Hemorrhage (See DOSAGE AND ADMINISTRATION:**
299 **Dose Modifications)**

300 Two distinct patterns of bleeding have occurred in patients receiving
301 AVASTIN. The first is minor hemorrhage, most commonly NCI-CTC
302 Grade 1 epistaxis. The second is serious, and in some cases fatal,
303 hemorrhagic events.

304 In Study 6, four of 13 (31%) AVASTIN-treated patients with squamous
305 cell histology and two of 53 (4%) AVASTIN-treated patients with
306 histology other than squamous cell, experienced serious or fatal
307 pulmonary hemorrhage as compared to none of the 32 (0%) patients
308 receiving chemotherapy alone. Of the patients experiencing pulmonary
309 hemorrhage requiring medical intervention, many had cavitation and/or
310 necrosis of the tumor, either pre-existing or developing during AVASTIN
311 therapy. In Study 5, the rate of pulmonary hemorrhage requiring medical
312 intervention for the PC plus AVASTIN arm was 2.3% (10 of 427)

313 compared to 0.5% (2 of 441) for the PC alone arm. There were seven
314 deaths due to pulmonary hemorrhage reported by investigators in the PC
315 plus AVASTIN arm as compared to one in the PC alone arm. Generally,
316 these serious hemorrhagic events presented as major or massive
317 hemoptysis without an antecedent history of minor hemoptysis during
318 Avastin therapy. Do not administer AVASTIN to patients with recent
319 history of hemoptysis of $\geq 1/2$ tsp of red blood. Other serious bleeding
320 events occurring in patients receiving AVASTIN across all indications
321 include gastrointestinal hemorrhage, subarachnoid hemorrhage, and
322 hemorrhagic stroke. Some of these events were fatal. (See **ADVERSE**
323 **REACTIONS: Hemorrhage.**)

324 The risk of central nervous system (CNS) bleeding in patients with CNS
325 metastases receiving AVASTIN has not been evaluated because these
326 patients were excluded from late stage clinical studies following
327 development of CNS hemorrhage in a patient with a CNS metastasis in a
328 Phase 1 study.

329 Discontinue AVASTIN in patients with serious hemorrhage (i.e., requiring
330 medical intervention) and initiate aggressive medical management. (See
331 **ADVERSE REACTIONS: Hemorrhage.**)

332 **Arterial Thromboembolic Events (see DOSAGE AND**
333 **ADMINISTRATION: Dose Modifications and PRECAUTIONS:**
334 **Geriatric Use)**

335 Arterial thromboembolic events (ATE) occurred at a higher incidence in
336 patients receiving AVASTIN in combination with chemotherapy as
337 compared to those receiving chemotherapy alone. ATE included cerebral
338 infarction, transient ischemic attacks (TIAs), myocardial infarction (MI),
339 angina, and a variety of other ATE. These events were fatal in some
340 instances.

341 In a pooled analysis of randomized, controlled clinical trials involving

342 1745 patients, the incidence of ATE was 4.4% among patients treated with
343 AVASTIN in combination with chemotherapy and 1.9% among patients
344 receiving chemotherapy alone. Fatal outcomes for these events occurred
345 in 7 of 963 patients (0.7%) who were treated with AVASTIN in
346 combination with chemotherapy, compared to 3 of 782 patients (0.4%)
347 who were treated with chemotherapy alone. The incidences of both
348 cerebrovascular arterial events (1.9% vs. 0.5%) and cardiovascular arterial
349 events (2.1% vs. 1.0%) were increased in patients receiving AVASTIN
350 compared to chemotherapy alone. The relative risk of ATE was greater in
351 patients 65 and over (8.5% vs. 2.9%) as compared to those less than 65
352 (2.1% vs. 1.4%). (See **PRECAUTIONS: Geriatric Use.**)

353 The safety of resumption of AVASTIN therapy after resolution of an ATE
354 has not been studied. Permanently discontinue AVASTIN in patients who
355 experience a severe ATE during treatment. (See **DOSAGE AND**
356 **ADMINISTRATION: Dose Modifications** and **PRECAUTIONS:**
357 **Geriatric Use.**)

358 **Hypertension (See DOSAGE AND ADMINISTRATION:**
359 **Dose Modifications)**

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

363 Medication classes used for management of patients with NCI-CTC
364 Grade 3 hypertension receiving AVASTIN included
365 angiotensin-converting enzyme inhibitors, beta blockers, diuretics, and
366 calcium channel blockers. Development or worsening of hypertension can
367 require hospitalization or require discontinuation of AVASTIN in up to
368 1.7% of patients. Hypertension can persist after discontinuation of
369 AVASTIN. Complications can include hypertensive encephalopathy (in
370 some cases fatal) and CNS hemorrhage.

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

375 Permanently discontinue AVASTIN in patients with hypertensive crisis or
376 hypertensive encephalopathy. Temporarily suspend AVASTIN in patients
377 with severe hypertension that is not controlled with medical management.
378 (See **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

379 **Reversible Posterior Leukoencephalopathy Syndrome (RPLS) (See**
380 **DOSAGE AND ADMINISTRATION: Dose Modifications)**

381 RPLS has been reported in clinical studies (with an incidence of <0.1%)
382 and in post-marketing experience. RPLS is a neurological disorder which
383 can present with headache, seizure, lethargy, confusion, blindness and
384 other visual and neurologic disturbances. Mild to severe hypertension
385 may be present, but is not necessary for diagnosis of RPLS. Magnetic
386 Resonance Imaging (MRI) is necessary to confirm the diagnosis of RPLS.
387 The onset of symptoms has been reported to occur from 16 hours to 1 year
388 after initiation of AVASTIN.

389 In patients developing RPLS, discontinue AVASTIN and initiate
390 treatment of hypertension, if present. Symptoms usually resolve or
391 improve within days, although some patients have experienced ongoing
392 neurologic sequelae. The safety of reinitiating AVASTIN therapy in
393 patients previously experiencing RPLS is not known.

394 **Neutropenia and Infection (See PRECAUTIONS: Geriatric Use and**
395 **ADVERSE REACTIONS: Neutropenia and Infection)**

396 Increased rates of severe neutropenia, febrile neutropenia, and infection
397 with severe neutropenia (including some fatalities) have been observed in
398 patients treated with myelosuppressive chemotherapy plus AVASTIN.
399 (See **PRECAUTIONS: Geriatric Use and ADVERSE REACTIONS:**
400 **Neutropenia and Infection**.)

401 **Proteinuria (See DOSAGE AND ADMINISTRATION:**
402 **Dose Modifications)**

403 The incidence and severity of proteinuria is increased in patients receiving
404 AVASTIN as compared to control. In Studies 1, 3 and 5 the incidence of
405 NCI-CTC Grade 3 and 4 proteinuria, characterized as >3.5 gm/24 hours,
406 ranged up to 3.0% in AVASTIN-treated patients.

407 Nephrotic syndrome occurred in seven of 1459 (0.5%) patients receiving
408 AVASTIN in clinical studies. One patient died and one required dialysis.
409 In three patients, proteinuria decreased in severity several months after
410 discontinuation of AVASTIN. No patient had normalization of urinary
411 protein levels (by 24-hour urine) following discontinuation of AVASTIN.

412 The highest incidence of proteinuria was observed in a dose-ranging,
413 placebo-controlled, randomized study of AVASTIN in patients with
414 metastatic renal cell carcinoma, an indication for which AVASTIN is not
415 approved, 24-hour urine collections were obtained in approximately half
416 the patients enrolled. Among patients in whom 24-hour urine collections
417 were obtained, four of 19 (21%) patients receiving AVASTIN at 10 mg/kg
418 every two weeks, two of 14 (14%) patients receiving AVASTIN at
419 3 mg/kg every two weeks, and none of the 15 placebo patients
420 experienced NCI-CTC Grade 3 proteinuria (> 3.5 gm protein/24 hours).

421 Discontinue AVASTIN in patients with nephrotic syndrome. The safety
422 of continued AVASTIN treatment in patients with moderate to severe
423 proteinuria has not been evaluated. In most clinical studies, AVASTIN
424 was interrupted for ≥ 2 grams of proteinuria/24 hours and resumed when
425 proteinuria was <2 gm/24 hours. Patients with moderate to severe
426 proteinuria based on 24-hour collections should be monitored regularly
427 until improvement and/or resolution is observed. (See **DOSAGE AND**
428 **ADMINISTRATION: Dose Modifications.**)

429 **Congestive Heart Failure**

430 Congestive heart failure (CHF), defined as NCI-CTC Grade 2–4 left
431 ventricular dysfunction, was reported in 25 of 1459 (1.7%) patients

432 receiving AVASTIN in clinical studies. The risk of CHF appears to be
433 higher in patients receiving AVASTIN who have received prior or
434 concurrent anthracyclines. In a controlled study in patients with breast
435 cancer (an unlabelled indication), the incidence of CHF was higher in the
436 AVASTIN plus chemotherapy arm as compared to the chemotherapy
437 alone arm. Congestive heart failure occurred in 13 of 299 (4%) patients
438 who received prior anthracyclines and/or left chest wall irradiation.
439 Congestive heart failure occurred in six of 44 (14%) patients with relapsed
440 acute leukemia (an unlabelled indication) receiving AVASTIN and
441 concurrent anthracyclines in a single arm study.

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

444 **PRECAUTIONS**

445 **General**

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

448 **Infusion Reactions**

449 In clinical studies, infusion reactions with the first dose of AVASTIN
450 were uncommon (<3%) and severe reactions occurred in 0.2% of patients.

451 Infusion reactions reported in the clinical trials and post-marketing
452 experience include hypertension, hypertensive crises associated with
453 neurologic signs and symptoms, wheezing, oxygen desaturation, NCI-
454 CTC Grade 3 hypersensitivity, chest pain, headaches, rigors, and
455 diaphoresis. Adequate information on rechallenge is not available.
456 AVASTIN infusion should be interrupted in all patients with severe
457 infusion reactions and appropriate medical therapy administered.

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

461 **Surgery**

462 AVASTIN therapy should not be initiated for at least 28 days following
463 major surgery. The surgical incision should be fully healed prior to
464 initiation of AVASTIN. Because of the potential for impaired wound
465 healing, AVASTIN should be suspended prior to elective surgery.
466 The appropriate interval between the last dose of AVASTIN and elective
467 surgery is unknown; however, the half-life of AVASTIN is estimated to be
468 20 days (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**) and
469 the interval chosen should take into consideration the half-life of the drug.
470 (See **WARNINGS: Gastrointestinal Perforations** and
471 **Wound Healing Complications**.)

472 **Cardiovascular Disease**

473 Patients were excluded from participation in AVASTIN clinical trials if, in
474 the previous year, they had experienced clinically significant
475 cardiovascular disease. In an exploratory analysis pooling the data from
476 five randomized, placebo-controlled, clinical trials conducted in patients
477 without a recent history of clinically significant cardiovascular disease, the
478 overall incidence of arterial thromboembolic events, the incidence of fatal
479 arterial thromboembolic events, and the incidence of cardiovascular
480 thromboembolic events were increased in patients receiving AVASTIN
481 plus chemotherapy as compared to chemotherapy alone.

482 **Laboratory Tests**

483 Blood pressure monitoring should be conducted every two to three weeks
484 during treatment with AVASTIN. Patients who develop hypertension on
485 AVASTIN may require blood pressure monitoring at more frequent
486 intervals. Patients with AVASTIN-induced or -exacerbated hypertension
487 who discontinue AVASTIN should continue to have their blood pressure
488 monitored at regular intervals.

489 Patients receiving AVASTIN should be monitored for the development or
490 worsening of proteinuria with serial urinalyses. Patients with a 2+ or
491 greater urine dipstick reading should undergo further assessment, e.g., a

492 24-hour urine collection. (See **WARNINGS: Proteinuria** and **DOSAGE**
493 **AND ADMINISTRATION: Dose Modifications.**)

494 **Drug Interactions**

495 No formal drug interaction studies with anti-neoplastic agents have been
496 conducted. In Study 1, patients with colorectal cancer were given
497 irinotecan/5-FU/leucovorin (bolus-IFL) with or without AVASTIN.
498 Irinotecan concentrations were similar in patients receiving bolus-IFL
499 alone and in combination with AVASTIN. The concentrations of SN38,
500 the active metabolite of irinotecan, were on average 33% higher in patients
501 receiving bolus-IFL in combination with AVASTIN when compared with
502 bolus-IFL alone. In Study 1, patients receiving bolus-IFL plus AVASTIN
503 had a higher incidence of NCI-CTC Grade 3–4 diarrhea and neutropenia.
504 Due to high inter-patient variability and limited sampling, the extent of the
505 increase in SN38 levels in patients receiving concurrent irinotecan and
506 AVASTIN is uncertain.

507 In Study 6, based on limited data, there did not appear to be a difference in
508 the mean exposure of either carboplatin or paclitaxel when each was
509 administered alone or in combination with AVASTIN. However, 3 of the
510 8 patients receiving AVASTIN plus paclitaxel/carboplatin had
511 substantially lower paclitaxel exposure after four cycles of treatment (at
512 Day 63) than those at Day 0, while patients receiving
513 paclitaxel/carboplatin without AVASTIN had a greater paclitaxel
514 exposure at Day 63 than at Day 0.

515 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

516 No carcinogenicity data are available for AVASTIN in animals or
517 humans.

518 AVASTIN may impair fertility. Dose-related decreases in ovarian and
519 uterine weights, endometrial proliferation, number of menstrual cycles, and
520 arrested follicular development or absent corpora lutea were observed in
521 female cynomolgus monkeys treated with 10 or 50 mg/kg of AVASTIN for

551 **Nursing Mothers**

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

559 **Pediatric Use**

560 The safety and effectiveness of AVASTIN in pediatric patients has not
561 been studied. However, physeal dysplasia was observed in juvenile
562 cynomolgus monkeys with open growth plates treated for four weeks with
563 doses that were less than the recommended human dose based on mg/kg
564 and exposure. The incidence and severity of physeal dysplasia were
565 dose-related and were at least partially reversible upon cessation of
566 treatment.

567 **Geriatric Use**

568 In Study 1, NCI-CTC Grade 3–4 adverse events were collected in all
569 patients receiving study drug (396 bolus-IFL plus placebo; 392 bolus-IFL
570 plus AVASTIN; 109 5-FU/LV plus AVASTIN), while NCI-CTC Grade 1
571 and 2 adverse events were collected in a subset of 309 patients. There
572 were insufficient numbers of patients 65 years and older in the subset in
573 which NCI-CTC Grade 1-4 adverse events were collected to determine
574 whether the overall adverse event profile was different in the elderly as
575 compared to younger patients. Among the 392 patients receiving
576 bolus-IFL plus AVASTIN, 126 were at least 65 years of age. Severe
577 adverse events that occurred at a higher incidence ($\geq 2\%$) in the elderly
578 when compared to those less than 65 years were asthenia, sepsis, deep
579 thrombophlebitis, hypertension, hypotension, myocardial infarction,
580 congestive heart failure, diarrhea, constipation, anorexia, leukopenia,
581 anemia, dehydration, hypokalemia, and hyponatremia. The effect of

582 AVASTIN on overall survival was similar in elderly patients as compared
583 to younger patients.

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

587 In Study 5 patients age 65 and older receiving carboplatin, paclitaxel, and
588 AVASTIN had a greater relative risk for proteinuria as compared to
589 younger patients.

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

597 In an exploratory, pooled analysis of 1745 patients treated in
598 five randomized, controlled studies, there were 618 (35%) patients age
599 65 or older and 1127 patients less than 65 years of age. The overall
600 incidence of arterial thromboembolic events was increased in all patients
601 receiving AVASTIN with chemotherapy as compared to those receiving
602 chemotherapy alone, regardless of age. However, the increase in arterial
603 thromboembolic events incidence was greater in patients 65 and over
604 (8.5% vs. 2.9%) as compared to those less than 65 (2.1% vs. 1.4%).
605 (See **WARNINGS: Arterial Thromboembolic Events.**)

606 **ADVERSE REACTIONS**

607 The most serious adverse reactions in patients receiving AVASTIN were:

- 608 • Gastrointestinal Perforations (see **WARNINGS**)
- 609 • Wound Healing Complications (see **WARNINGS**)
- 610 • Hemorrhage (see **WARNINGS**)

- 611 • Arterial Thromboembolic Events (see **WARNINGS**)
- 612 • Hypertensive Crises (see **WARNINGS: Hypertension**)
- 613 • Reversible Posterior Leukoencephalopathy Syndrome (see
614 **WARNINGS**)
- 615 • Neutropenia and Infection (see **WARNINGS**)
- 616 • Nephrotic Syndrome (see **WARNINGS: Proteinuria**)
- 617 • Congestive Heart Failure (see **WARNINGS**)

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

622 **Adverse Reactions in Clinical Trials**

623 Because clinical trials are conducted under widely varying conditions,
624 adverse reaction rates observed in the clinical trials of a drug cannot be
625 directly compared to rates in the clinical trials of another drug and may not
626 reflect the rates observed in practice. The adverse reaction information
627 from clinical trials does, however, provide a basis for identifying the
628 adverse events that appear to be related to drug use and for approximating
629 rates.

630 The data described below reflect exposure to AVASTIN in 1529 patients,
631 including 665 receiving AVASTIN for at least 6 months and 199 receiving
632 AVASTIN for at least one year. AVASTIN was studied primarily in
633 placebo- and active-controlled trials (n = 501, and n = 1028, respectively).

634 **Gastrointestinal Perforation**

635 The incidence of gastrointestinal perforation across all studies ranged from
636 0-3.7%. The incidence of gastrointestinal perforation, in some cases fatal,
637 in patients with mCRC receiving AVASTIN alone or in combination with
638 chemotherapy was 2.4% compared to 0.3% in patients receiving only
639 chemotherapy. The incidence of gastrointestinal perforation in NSCLC
640 patients receiving AVASTIN was 0.9% compared to 0% in patients
641 receiving only chemotherapy. (See **WARNINGS: Gastrointestinal**

642 **Perforations and DOSAGE AND ADMINISTRATION: Dose**
643 **Modifications.)**

644 **Wound Healing Complications**

645 The incidence of post-operative wound healing and/or bleeding
646 complications was increased in patients with mCRC receiving AVASTIN
647 as compared to patients receiving only chemotherapy. Among patients
648 requiring surgery on or within 60 days of receiving study treatment,
649 wound healing and/or bleeding complications occurred in 15% (6/39) of
650 patients receiving bolus-IFL plus AVASTIN as compared to 4% (1/25) of
651 patients who received bolus-IFL alone. In the same study, the incidence
652 of wound dehiscence was also higher in the AVASTIN-treated patients
653 (1% vs. 0.5%).

654 **Hemorrhage**

655 Severe or fatal hemorrhages, including hemoptysis, gastrointestinal
656 bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding
657 occurred up to five-fold more frequently in AVASTIN treated patients
658 compared to patients treated with chemotherapy alone. NCI-CTC Grade 3-
659 5 hemorrhagic events occurred in 4.7% of NSCLC patients and 5.2% of
660 mCRC patients receiving AVASTIN compared to 1.1% and 0.7% for the
661 control groups respectively. (See **WARNINGS: Hemorrhage.**)

662 The incidence of epistaxis was higher (35% vs. 10%) in patients with
663 mCRC receiving bolus-IFL plus AVASTIN compared with patients
664 receiving bolus-IFL plus placebo. These events were generally mild in
665 severity (NCI-CTC Grade 1) and resolved without medical intervention.
666 Additional mild to moderate hemorrhagic events reported more frequently
667 in patients receiving bolus-IFL plus AVASTIN when compared to those
668 receiving bolus-IFL plus placebo included gastrointestinal hemorrhage
669 (24% vs. 6%), minor gum bleeding (2% vs. 0), and vaginal hemorrhage
670 (4% vs. 2%). (See **WARNINGS: Hemorrhage** and **DOSAGE AND**
671 **ADMINISTRATION: Dose Modifications.**)

672 **Arterial Thromboembolic Events**

673 The incidence of arterial thromboembolic events was increased in NSCLC
674 patients receiving PC plus AVASTIN (3.0%) compared with patients
675 receiving PC alone (1.4%). Five events were fatal in the PC plus
676 AVASTIN arm, compared with 1 event in the PC alone arm. This
677 increased risk is consistent with that observed in patients with mCRC.
678 (See **WARNINGS: Arterial Thromboembolic Events, DOSAGE AND**
679 **ADMINISTRATION: Dose Modifications, and PRECAUTIONS:**
680 **Geriatric Use.**)

681 **Venous Thromboembolic Events**

682 The incidence of NCI-CTC Grade 3–4 venous thromboembolic events
683 was higher in patients with mCRC or NSCLC receiving AVASTIN with
684 chemotherapy as compared to those receiving chemotherapy alone. In
685 addition, in patients with mCRC the risk of developing a second
686 subsequent thromboembolic event in patients receiving AVASTIN and
687 chemotherapy is increased compared to patients receiving chemotherapy
688 alone. In Study 1, 53 patients (14%) on the bolus-IFL plus AVASTIN arm
689 and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose
690 warfarin following a venous thromboembolic event. Among these
691 patients, an additional thromboembolic event occurred in 21% (11/53) of
692 patients receiving bolus-IFL plus AVASTIN and 3% (1/30) of patients
693 receiving bolus-IFL alone.

694 The overall incidence of NCI-CTC Grade 3–4 venous thromboembolic
695 events in Study 1 was 15.1% in patients receiving bolus-IFL plus
696 AVASTIN and 13.6% in patients receiving bolus-IFL plus placebo. In
697 Study 1, the incidence of the following NCI-CTC Grade 3 and 4 venous
698 thromboembolic events was higher in patients receiving bolus-IFL plus
699 AVASTIN as compared to patients receiving bolus-IFL plus placebo:
700 deep venous thrombosis (34 vs. 19 patients) and intra-abdominal venous
701 thrombosis (10 vs. 5 patients).

702 Hypertension

703 Fatal CNS hemorrhage complicating AVASTIN induced hypertension can
704 occur.

705 In Study 1, the incidences of hypertension and of severe hypertension
706 were increased in patients with mCRC receiving AVASTIN compared to
707 those receiving chemotherapy alone (see Table 3).

Table 3
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 ^a (>150/100 mmHg)	43%	60%	67%
Severe Hypertension ^a (>200/110 mmHg)	2%	7%	10%

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

708

709 Among patients with severe hypertension in the AVASTIN arms, slightly
710 over half the patients (51%) had a diastolic reading greater than
711 110 mmHg associated with a systolic reading less than 200 mmHg.

712 Similar results were seen in patients receiving AVASTIN alone or in
713 combination with FOLFOX4 or carboplatin and paclitaxel. (See

714 **WARNINGS: Hypertension and DOSAGE AND**

715 **ADMINISTRATION: Dose Modifications.**)

716 Neutropenia and Infection

717 An increased incidence of neutropenia has been reported in patients
718 receiving AVASTIN and chemotherapy compared to chemotherapy alone.
719 In Study 1, the incidence of NCI-CTC Grade 3 or 4 neutropenia was
720 increased in patients with mCRC receiving IFL+AVASTIN (21%)
721 compared to patients receiving IFL alone (14%). In Study 5, the incidence

722 of NCI-CTC Grade 4 neutropenia was increased in patients with NSCLC
723 receiving PC plus AVASTIN (26.2%) compared with patients receiving
724 PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC
725 plus AVASTIN vs. 1.8% for PC alone). There were 19 (4.5%) infections
726 with NCI-CTC Grade 3 or 4 neutropenia in the PC plus AVASTIN arm of
727 which 3 were fatal compared to 9 (2%) neutropenic infections in patients
728 receiving PC alone, of which none were fatal. During the first 6 cycles of
729 treatment the incidence of serious infections including pneumonia, febrile
730 neutropenia, catheter infections and wound infections was increased in the
731 PC plus AVASTIN arm [58 patients (13.6%)] compared to the PC alone
732 arm [29 patients (6.6%)].

733 Proteinuria

734 (See **WARNINGS: Proteinuria, DOSAGE AND**
735 **ADMINISTRATION: Dose Modifications, and PRECAUTIONS:**
736 **Geriatric Use.**)

737 Immunogenicity

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

745 Immunogenicity data are highly dependent on the sensitivity and
746 specificity of the assay. Additionally, the observed incidence of antibody
747 positivity in an assay may be influenced by several factors, including
748 sample handling, timing of sample collection, concomitant medications,
749 and underlying disease. For these reasons, comparison of the incidence of
750 antibodies to AVASTIN with the incidence of antibodies to other products
751 may be misleading.

752 **Metastatic Carcinoma of the Colon and Rectum**

753 The data in Tables 4 and 5 were obtained in Study 1. All NCI-CTC
754 Grade 3 and 4 adverse events and selected NCI-CTC Grade 1 and 2
755 adverse events (hypertension, proteinuria, thromboembolic events) were
756 reported for the overall study population. The median age was 60, 60%
757 were male, 79% were Caucasian, 78% had a colon primary lesion, 56%
758 had extra-abdominal disease, 29% had prior adjuvant or neoadjuvant
759 chemotherapy, and 57% had ECOG performance status of 0. The median
760 duration of exposure to AVASTIN was 8 months in Arm 2 and 7 months
761 in Arm 3. Severe and life-threatening (NCI-CTC Grade 3 and 4) adverse
762 events, which occurred at a higher incidence ($\geq 2\%$) in patients receiving
763 bolus-IFL plus AVASTIN as compared to bolus-IFL plus placebo, are
764 presented in Table 4.

Table 4
 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)
NCI-CTC 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 ^a	41 (14%)	58 (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.

765

766 NCI-CTC Grade 1–4 adverse events which occurred at a higher incidence
 767 ($\geq 5\%$) in patients receiving bolus-IFL plus AVASTIN as compared to the
 768 bolus-IFL plus placebo arm, are presented in Table 5.

Table 5
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%)

Table 5 (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%)

770

771 The data in Table 6 were obtained in Study 3. Only NCI-CTC Grade 3-5
 772 non-hematologic and Grade 4-5 hematologic adverse events related to
 773 treatment were reported. The median age was a 61 years, 40% were
 774 female, 87% were Caucasian, 99% received prior chemotherapy for
 775 metastatic colorectal cancer, 26% had received prior radiation therapy, and
 776 the 49% had an ECOG performance status of 0. Selected NCI-CTC
 777 Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events
 778 which occurred at a higher incidence in patients receiving FOLFOX4 plus
 779 AVASTIN as compared to those who received FOLFOX4 alone, are
 780 presented in Table 6. These data are likely to under-estimate the true
 781 adverse event rates due to the reporting mechanisms used in Study 3.

Table 6
 NCI-CTC Grade 3-5 Non-Hematologic and
 Grade 4-5 Hematologic Adverse Events in Study 3
 (Occurring at Higher Incidence ($\geq 2\%$)
 with AVASTIN+FOLFOX4 vs. FOLFOX4)

	FOLFOX4 (n=285)	FOLFOX4+ AVASTIN (n=287)	AVASTIN (n=234)
Patients with at least one event	171 (60%)	219 (76%)	87 (37%)
Gastrointestinal			
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%)
Neurology			
Neuropathy—sensory	26 (9%)	48 (17%)	2 (1%)
Neurologic—other	8 (3%)	15 (5%)	3 (1%)
Constitutional symptoms			
Fatigue	37 (13%)	56 (19%)	12 (5%)
Pain			
Abdominal pain	13 (5%)	24 (8%)	19 (8%)
Headache	0 (0%)	8 (3%)	4 (2%)
Cardiovascular (general)			
Hypertension	5 (2%)	26 (9%)	19 (8%)
Hemorrhage			
Hemorrhage	2 (1%)	15 (5%)	9 (4%)

782

783 **Non-Squamous, Non-Small Cell Lung Cancer**

784 The data in Table 7 were obtained in Study 5. Only NCI-CTC Grade 3-5
 785 non-hematologic and Grade 4-5 hematologic adverse events were
 786 reported. The median age was 63, 46% were female, no patients had
 787 received prior chemotherapy, 76% had Stage IV disease, 12% had Stage
 788 IIIB disease with malignant pleural effusion, 11% had recurrent disease,
 789 and 40% had an ECOG performance status of 0. The median duration of
 790 exposure to AVASTIN was 4.9 months.

Reference

791 NCI-CTC Grade 3, 4, and 5 adverse events that occurred at a $\geq 2\%$ higher
792 incidence in patients receiving PC plus AVASTIN as compared with PC
793 alone are presented in Table 7.

Table 7
NCI-CTC Grade 3–5 Non-Hematologic and
Grade 4 and 5 Hematologic Adverse Events in Study 5
(Occurring at a $\geq 2\%$ Higher Incidence in
AVASTIN-Treated Patients Compared with Control)

NCI-CTC Category Term ^a	No. (%) of NSCLC Patients	
	PC (n=441)	PC + AVASTIN (n=427)
Any event	286 (65%)	334 (78%)
Blood/bone marrow		
Neutropenia	76 (17%)	113 (27%)
Constitutional symptoms		
Fatigue	57 (13%)	67 (16%)
Cardiovascular (general)		
Hypertension	3 (0.7%)	33 (8%)
Vascular		
Venous thrombus/embolism	14 (3%)	23 (5%)
Infection/febrile neutropenia		
Infection without neutropenia	12 (3%)	30 (7%)
Infection with NCI-CTC Grade 3 or 4 neutropenia	9 (2%)	19 (4%)
Febrile neutropenia	8 (2%)	23 (5%)
Pulmonary/upper respiratory		
Pneumonitis/pulmonary infiltrates	11 (3%)	21 (5%)
Metabolic/laboratory		
Hyponatremia	5 (1%)	16 (4%)
Pain		
Headache	2 (0.5%)	13 (3%)
Renal/genitourinary		
Proteinuria	0 (0%)	13 (3%)

^a Events were reported and graded according to NCI-CTC, Version 2.0. Per protocol, investigators were required to report NCI-CTC Grade 3–5 non-hematologic and Grade 4 and 5 hematologic events.

795 **Other Serious Adverse Events**

796 The following additional serious adverse events occurred in at least one
797 subject treated with AVASTIN in clinical studies or post-marketing
798 experience:

799 *Body as a Whole: polyserositis*

800 *Digestive: intestinal necrosis, mesenteric venous occlusion, anastomotic*
801 *ulceration*

802 *Hemic and lymphatic: pancytopenia*

803 *Respiratory: nasal septum perforation*

804 **OVERDOSAGE**

805 The highest dose tested in humans (20 mg/kg IV) was associated with
806 headache in nine of 16 patients and with severe headache in three of
807 16 patients.

808 **DOSAGE AND ADMINISTRATION**

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

812 **Metastatic Carcinoma of the Colon or Rectum**

813 AVASTIN, used in combination with intravenous 5-FU-based
814 chemotherapy, is administered as an intravenous infusion (5 mg/kg or
815 10 mg/kg) every 14 days.

816 The recommended dose of AVASTIN, when used in combination with
817 bolus-IFL, is 5 mg/kg.

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

820 **Non-Squamous, Non-Small Cell Lung Cancer**

821 The recommended dose of AVASTIN is 15 mg/kg, as an IV infusion
822 every 3 weeks.

823 **Dose Modifications**

824 There are no recommended dose reductions for the use of AVASTIN.

825 If needed, AVASTIN should be either discontinued or temporarily
826 suspended as described below.

827 AVASTIN should be permanently discontinued in patients who develop
828 gastrointestinal perforation, wound dehiscence requiring medical
829 intervention, serious bleeding, a severe arterial thromboembolic event,
830 nephrotic syndrome, hypertensive crisis or hypertensive encephalopathy.
831 In patients developing RPLS, discontinue AVASTIN and initiate
832 treatment of hypertension, if present. (See **WARNINGS: Reversible**
833 **Posterior Leukoencephalopathy Syndrome.**)

834 Temporary suspension of AVASTIN is recommended in patients with
835 evidence of moderate to severe proteinuria pending further evaluation and
836 in patients with severe hypertension that is not controlled with medical
837 management. The risk of continuation or temporary suspension of
838 AVASTIN in patients with moderate to severe proteinuria is unknown.

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

843 **Preparation for Administration**

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

851 Diluted AVASTIN solutions for infusion may be stored at 2°C–8°C
852 (36°F–46°F) for up to 8 hours. No incompatibilities between AVASTIN
853 and polyvinylchloride or polyolefin bags have been observed.

854 **AVASTIN infusions should not be administered or mixed with**
855 **dextrose solutions.**

856 **Administration**

857 **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** The initial
858 AVASTIN dose should be delivered over 90 minutes as an IV infusion
859 following chemotherapy. If the first infusion is well tolerated, the second
860 infusion may be administered over 60 minutes. If the 60-minute infusion
861 is well tolerated, all subsequent infusions may be administered over
862 30 minutes.

863 **Stability and Storage**

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

867 **HOW SUPPLIED**

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

871 Single unit 100 mg carton: Contains one 4 mL vial of AVASTIN
872 (25 mg/mL). NDC 50242-060-01

873 Single unit 400 mg carton: Contains one 16 mL vial of AVASTIN
874 (25 mg/mL). NDC 50242-061-01

875 **REFERENCES**

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878 growth factor monoclonal antibody for the therapy of solid tumors
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AVASTIN[®]

(Bevacizumab)

For Intravenous Use

Manufactured by:

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7455309

LV0017

4835701

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