

1 **1.14.1.3 Draft 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:**

21 **Gastrointestinal Perforations and DOSAGE AND**
22 **ADMINISTRATION: Dose 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.**)

Hemorrhage

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

DESCRIPTION

AVASTIN[®] (Bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay systems. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF (1). Bevacizumab is produced in a Chinese Hamster Ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin and has a molecular weight of approximately 149 kilodaltons. AVASTIN is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous (IV) infusion. AVASTIN is supplied in 100 mg and 400 mg preservative-free, single-use vials to deliver 4 mL or 16 mL of AVASTIN (25 mg/mL). The 100 mg product is formulated in 240 mg α, α -trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The 400 mg product is formulated in 960 mg α, α -trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water for Injection, 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
Overall Survival^a		
Median (months)	15.6	20.3
Hazard ratio		0.66
Progression-free Survival^a		
Median (months)	6.2	10.6
Hazard ratio		0.54
Overall Response Rate^b		
Rate (percent)	35%	45%
Duration of Response		
Median (months)	7.1	10.4

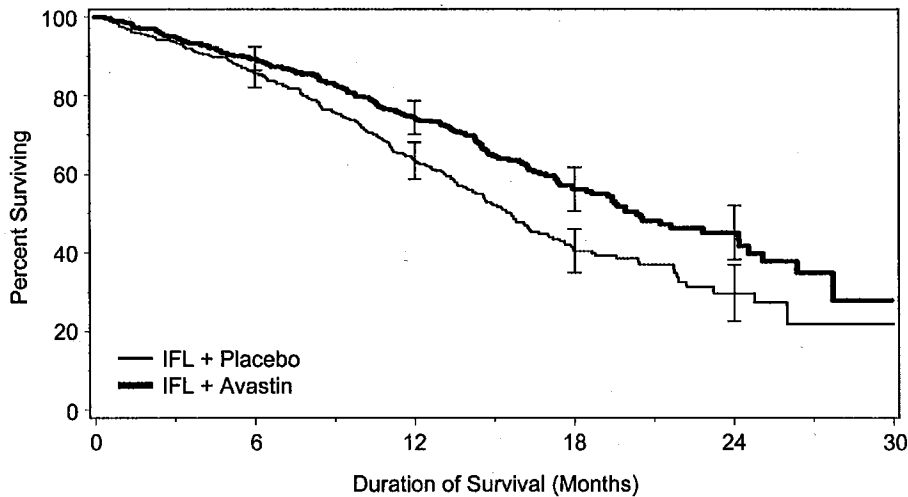
^ap<0.001 by stratified logrank test.

^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

134 The clinical benefit of AVASTIN, as measured by survival in the two
135 principal arms, was seen in the subgroups defined by age (<65 yrs,
136 ≥65 yrs) and gender.

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

140 **AVASTIN in Combination with 5-FU/LV Chemotherapy**

141 Study 2 was a randomized, active-controlled clinical trial testing
142 AVASTIN in combination with 5-FU/LV as first-line treatment of
143 metastatic colorectal cancer. Patients were randomized to receive
144 5-FU/LV (5-fluorouracil 500 mg/m², leucovorin 500 mg/m² weekly for
145 6 weeks every 8 weeks) or 5-FU/LV plus AVASTIN (5 mg/kg every
146 2 weeks) or 5-FU/LV plus AVASTIN (10 mg/kg every 2 weeks).
147 The primary endpoints of the trial were objective response rate and
148 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

149

150 Progression-free survival was significantly longer in patients receiving
151 5-FU/LV plus AVASTIN at 5 mg/kg when compared to those not
152 receiving AVASTIN. However, overall survival and overall response rate
153 were not significantly different. Outcomes for patients receiving 5-FU/LV
154 plus AVASTIN at 10 mg/kg were not significantly different than for
155 patients who did not receive AVASTIN.

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

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

170 patients in the FOLFOX4 plus AVASTIN arm, prior to the FOLFOX4
171 chemotherapy on Day 1.

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

179 The AVASTIN monotherapy arm of Study 3 was closed to accrual after
180 enrollment of 244 of the planned 290 patients following a planned interim
181 analysis by the data monitoring committee (DMC), based on evidence of
182 decreased survival in the AVASTIN alone arm as compared to the
183 FOLFOX4 alone arm. In the two remaining study arms, overall survival
184 (OS) was significantly longer in patients receiving AVASTIN in
185 combination with FOLFOX4 as compared to those receiving FOLFOX4
186 alone (median OS 13.0 mos vs. 10.8 mos; hazard ratio 0.75 [95% CI 0.63,
187 0.89], $p=0.001$ stratified log rank test). In addition, patients treated with
188 AVASTIN in combination with FOLFOX4 were reported to have
189 significantly longer progression-free survival and a higher overall
190 response rate based on investigator assessment. The clinical benefit of
191 AVASTIN, as measured by survival, was seen in the subgroups defined by
192 age (<65 yrs, ≥ 65 yrs) and gender.

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

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

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

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

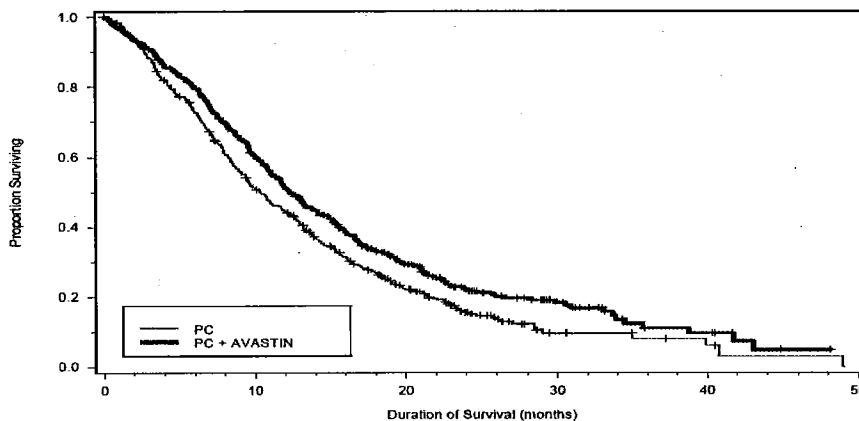
204 The safety and efficacy of AVASTIN as first-line treatment of patients
205 with locally advanced, metastatic, or recurrent non-squamous, NSCLC
206 was studied in a single, large, randomized, active-controlled, open-label,
207 multicenter study (Study 5, n=878), supported by a randomized, dose
208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

209 In Study 5, chemotherapy-naïve patients with locally advanced, metastatic
210 or recurrent non-squamous NSCLC were randomized (1:1) to receive six
211 cycles of paclitaxel 200 mg/m² and carboplatin AUC=6.0, both by IV
212 infusion on day 1 (PC) or PC in combination with AVASTIN at a dose of
213 15 mg/kg by IV infusion on day 1 (PC plus AVASTIN). After completion
214 or upon discontinuation of chemotherapy, patients in the PC plus
215 AVASTIN arm continued to receive AVASTIN alone until disease
216 progression or until unacceptable toxicity. Cycles were repeated every
217 21 days. Patients with predominant squamous histology (mixed cell type
218 tumors only), central nervous system (CNS) metastasis, gross hemoptysis
219 (≥1/2 tsp of red blood), or unstable angina and those receiving therapeutic
220 anticoagulation were excluded. The main outcome measure of the study
221 was duration of survival.

222 Among the 878 patients randomized to the two treatment arms, the median
223 age was 63, 46% were female, 43% were ≥ age 65, and 28% had ≥5%
224 weight loss at study entry. Eleven percent had recurrent disease and of the
225 remaining 89% with newly diagnosed NSCLC, 12% had Stage IIIB with
226 malignant pleural effusion and 76% had Stage IV disease. The survival
227 curves are presented in Figure 2. Overall survival was statistically
228 significantly higher among patients receiving PC plus AVASTIN
229 compared with those receiving PC alone; median OS was 12.3 mos vs.
230 10.3 mos (hazard ratio 0.80 [repeated 95% CI 0.68, 0.94], final p-value

231 0.013, stratified log-rank test). Based on investigator assessment which
 232 was not independently verified, patients were reported to have longer
 233 progression-free survival with AVASTIN in combination with PC
 234 compared to PC alone.

235 **Figure 2**
 236 Duration of Survival in Study 5



237
 238

239 In an exploratory analyses across patient subgroups, the impact of
 240 AVASTIN on overall survival was less robust in the following: women
 241 [HR=0.99 (95% CI: 0.79, 1.25)], age \geq 65 years [HR=0.91 (95% CI:
 242 0.72, 1.14)] and patients with \geq 5% weight loss at study entry [HR=0.96
 243 (95% CI: 0.73, 1.26)].

244 **INDICATIONS AND USAGE**

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

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

251 CONTRAINDICATIONS

252 None.

253 WARNINGS**254 Gastrointestinal Perforations (See DOSAGE AND
255 ADMINISTRATION: Dose Modifications)**

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

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

277 Permanently discontinue AVASTIN in patients with gastrointestinal
278 perforation (gastrointestinal perforation, fistula formation, and/or
279 intra-abdominal abscess).

280 **Non-Gastrointestinal Fistula Formation (See DOSAGE AND**
281 **ADMINISTRATION: Dose Modifications)**

282 Non-gastrointestinal fistula formation has been reported in patients treated
283 with AVASTIN in controlled clinical studies (with an incidence of
284 < 0.3%) and in post-marketing experience, in some cases with fatal
285 outcome. Fistula formation involving the following areas of the body
286 other than the gastrointestinal tract have been reported:
287 tracheo-esophageal, bronchopleural, biliary, vagina and bladder. Events
288 were reported throughout treatment with Avastin, with most events
289 occurring within the first 6 months.

290 Permanently discontinue AVASTIN in patients with fistula formation
291 involving an internal organ.

292 **Wound Healing Complications (See DOSAGE AND**
293 **ADMINISTRATION: Dose Modifications)**

294 AVASTIN impairs wound healing in animal models. In clinical studies of
295 AVASTIN, patients were not allowed to receive AVASTIN until at least
296 28 days had elapsed following surgery. In clinical studies of AVASTIN in
297 combination with chemotherapy, there were 6 instances of dehiscence
298 among 788 patients (0.8%).

299 The appropriate interval between discontinuation of AVASTIN and
300 subsequent elective surgery required to avoid the risks of impaired wound
301 healing has not been determined. In Study 1, 39 patients who received
302 bolus-IFL plus AVASTIN underwent surgery following AVASTIN
303 therapy; of these patients, six (15%) had wound healing/bleeding
304 complications. In the same study, 25 patients in the bolus-IFL arm
305 underwent surgery; of these patients, one of 25 (4%) had wound
306 healing/bleeding complications. The longest interval between last dose of
307 study drug and dehiscence was 56 days; this occurred in a patient on the
308 bolus-IFL plus AVASTIN arm.

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

312 Discontinue AVASTIN in patients with wound healing complications
313 requiring medical intervention.

314 **Hemorrhage (See DOSAGE AND ADMINISTRATION:**
315 **Dose Modifications)**

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

320 In Study 6, four of 13 (31%) AVASTIN-treated patients with squamous
321 cell histology and two of 53 (4%) AVASTIN-treated patients with
322 histology other than squamous cell, experienced serious or fatal
323 pulmonary hemorrhage as compared to none of the 32 (0%) patients
324 receiving chemotherapy alone. Of the patients experiencing pulmonary
325 hemorrhage requiring medical intervention, many had cavitation and/or
326 necrosis of the tumor, either pre-existing or developing during AVASTIN
327 therapy. In Study 5, the rate of pulmonary hemorrhage requiring medical
328 intervention for the PC plus AVASTIN arm was 2.3% (10 of 427)
329 compared to 0.5% (2 of 441) for the PC alone arm. There were seven
330 deaths due to pulmonary hemorrhage reported by investigators in the PC
331 plus AVASTIN arm as compared to one in the PC alone arm. Generally,
332 these serious hemorrhagic events presented as major or massive
333 hemoptysis without an antecedent history of minor hemoptysis during
334 Avastin therapy. Do not administer AVASTIN to patients with recent
335 history of hemoptysis of $\geq 1/2$ tsp of red blood. Other serious bleeding
336 events occurring in patients receiving AVASTIN across all indications
337 include gastrointestinal hemorrhage, subarachnoid hemorrhage, and
338 hemorrhagic stroke. Some of these events were fatal. (See **ADVERSE**
339 **REACTIONS: Hemorrhage.**)

340 The risk of central nervous system (CNS) bleeding in patients with CNS
341 metastases receiving AVASTIN has not been evaluated because these
342 patients were excluded from late stage clinical studies following
343 development of CNS hemorrhage in a patient with a CNS metastasis in a
344 Phase 1 study.

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

348 **Arterial Thromboembolic Events (see DOSAGE AND**
349 **ADMINISTRATION: Dose Modifications and PRECAUTIONS:**
350 **Geriatric Use)**

351 Arterial thromboembolic events (ATE) occurred at a higher incidence in
352 patients receiving AVASTIN in combination with chemotherapy as
353 compared to those receiving chemotherapy alone. ATE included cerebral
354 infarction, transient ischemic attacks (TIAs), myocardial infarction (MI),
355 angina, and a variety of other ATE. These events were fatal in some
356 instances.

357 In a pooled analysis of randomized, controlled clinical trials involving
358 1745 patients, the incidence of ATE was 4.4% among patients treated with
359 AVASTIN in combination with chemotherapy and 1.9% among patients
360 receiving chemotherapy alone. Fatal outcomes for these events occurred
361 in 7 of 963 patients (0.7%) who were treated with AVASTIN in
362 combination with chemotherapy, compared to 3 of 782 patients (0.4%)
363 who were treated with chemotherapy alone. The incidences of both
364 cerebrovascular arterial events (1.9% vs. 0.5%) and cardiovascular arterial
365 events (2.1% vs. 1.0%) were increased in patients receiving AVASTIN
366 compared to chemotherapy alone. The relative risk of ATE was greater in
367 patients 65 and over (8.5% vs. 2.9%) as compared to those less than 65
368 (2.1% vs. 1.4%). (See **PRECAUTIONS: Geriatric Use.**)

369 The safety of resumption of AVASTIN therapy after resolution of an ATE
370 has not been studied. Permanently discontinue AVASTIN in patients who

371 experience a severe ATE during treatment. (See **DOSAGE AND**
372 **ADMINISTRATION: Dose Modifications** and **PRECAUTIONS:**
373 **Geriatric Use.**)

374 **Hypertension (See DOSAGE AND ADMINISTRATION:**
375 **Dose Modifications)**

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

379 Medication classes used for management of patients with NCI-CTC
380 Grade 3 hypertension receiving AVASTIN included
381 angiotensin-converting enzyme inhibitors, beta blockers, diuretics, and
382 calcium channel blockers. Development or worsening of hypertension can
383 require hospitalization or require discontinuation of AVASTIN in up to
384 1.7% of patients. Hypertension can persist after discontinuation of
385 AVASTIN. Complications can include hypertensive encephalopathy
386 (in some cases fatal) and CNS hemorrhage.

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

391 Permanently discontinue AVASTIN in patients with hypertensive crisis or
392 hypertensive encephalopathy. Temporarily suspend AVASTIN in patients
393 with severe hypertension that is not controlled with medical management.
394 (See **DOSAGE AND ADMINISTRATION: Dose Modifications.**)

395 **Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**
396 **(See DOSAGE AND ADMINISTRATION: Dose Modifications)**

397 RPLS has been reported in clinical studies (with an incidence of <0.1%)
398 and in post-marketing experience. RPLS is a neurological disorder which
399 can present with headache, seizure, lethargy, confusion, blindness and
400 other visual and neurologic disturbances. Mild to severe hypertension

401 may be present, but is not necessary for diagnosis of RPLS. Magnetic
402 Resonance Imaging (MRI) is necessary to confirm the diagnosis of RPLS.
403 The onset of symptoms has been reported to occur from 16 hours to 1 year
404 after initiation of AVASTIN.

405 In patients developing RPLS, discontinue AVASTIN and initiate
406 treatment of hypertension, if present. Symptoms usually resolve or
407 improve within days, although some patients have experienced ongoing
408 neurologic sequelae. The safety of reinitiating AVASTIN therapy in
409 patients previously experiencing RPLS is not known.

410 **Neutropenia and Infection (See PRECAUTIONS: Geriatric Use**
411 **and ADVERSE REACTIONS: Neutropenia and Infection)**

412 Increased rates of severe neutropenia, febrile neutropenia, and infection
413 with severe neutropenia (including some fatalities) have been observed in
414 patients treated with myelosuppressive chemotherapy plus AVASTIN.
415 (See PRECAUTIONS: Geriatric Use and ADVERSE REACTIONS:
416 Neutropenia and Infection.)

417 **Proteinuria (See DOSAGE AND ADMINISTRATION:**
418 **Dose Modifications)**

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

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

428 The highest incidence of proteinuria was observed in a dose-ranging,
429 placebo-controlled, randomized study of AVASTIN in patients with
430 metastatic renal cell carcinoma, an indication for which AVASTIN is not

431 approved, 24-hour urine collections were obtained in approximately half
432 the patients enrolled. Among patients in whom 24-hour urine collections
433 were obtained, four of 19 (21%) patients receiving AVASTIN at 10 mg/kg
434 every two weeks, two of 14 (14%) patients receiving AVASTIN at
435 3 mg/kg every two weeks, and none of the 15 placebo patients
436 experienced NCI-CTC Grade 3 proteinuria (>3.5 gm protein/24 hours).

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

445 **Congestive Heart Failure**

446 Congestive heart failure (CHF), defined as NCI-CTC Grade 2–4 left
447 ventricular dysfunction, was reported in 25 of 1459 (1.7%) patients
448 receiving AVASTIN in clinical studies. The risk of CHF appears to be
449 higher in patients receiving AVASTIN who have received prior or
450 concurrent anthracyclines. In a controlled study in patients with breast
451 cancer (an unlabelled indication), the incidence of CHF was higher in the
452 AVASTIN plus chemotherapy arm as compared to the chemotherapy
453 alone arm. Congestive heart failure occurred in 13 of 299 (4%) patients
454 who received prior anthracyclines and/or left chest wall irradiation.
455 Congestive heart failure occurred in six of 44 (14%) patients with relapsed
456 acute leukemia (an unlabelled indication) receiving AVASTIN and
457 concurrent anthracyclines in a single arm study.

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

460 PRECAUTIONS**461 General**

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

464 Infusion Reactions

465 In clinical studies, infusion reactions with the first dose of AVASTIN
466 were uncommon (<3%) and severe reactions occurred in 0.2% of patients.
467 Infusion reactions reported in the clinical trials and post-marketing
468 experience include hypertension, hypertensive crises associated with
469 neurologic signs and symptoms, wheezing, oxygen desaturation,
470 NCI-CTC Grade 3 hypersensitivity, chest pain, headaches, rigors, and
471 diaphoresis. Adequate information on rechallenge is not available.
472 AVASTIN infusion should be interrupted in all patients with severe
473 infusion reactions and appropriate medical therapy administered.

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

477 Surgery

478 AVASTIN therapy should not be initiated for at least 28 days following
479 major surgery. The surgical incision should be fully healed prior to
480 initiation of AVASTIN. Because of the potential for impaired wound
481 healing, AVASTIN should be suspended prior to elective surgery.
482 The appropriate interval between the last dose of AVASTIN and elective
483 surgery is unknown; however, the half-life of AVASTIN is estimated to be
484 20 days (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**) and
485 the interval chosen should take into consideration the half-life of the drug.
486 (See **WARNINGS: Gastrointestinal Perforations and**
487 **Wound Healing Complications.**)

488 Cardiovascular Disease

489 Patients were excluded from participation in AVASTIN clinical trials if, in
490 the previous year, they had experienced clinically significant
491 cardiovascular disease. In an exploratory analysis pooling the data from
492 five randomized, placebo-controlled, clinical trials conducted in patients
493 without a recent history of clinically significant cardiovascular disease, the
494 overall incidence of arterial thromboembolic events, the incidence of fatal
495 arterial thromboembolic events, and the incidence of cardiovascular
496 thromboembolic events were increased in patients receiving AVASTIN
497 plus chemotherapy as compared to chemotherapy alone.

498 Laboratory Tests

499 Blood pressure monitoring should be conducted every two to three weeks
500 during treatment with AVASTIN. Patients who develop hypertension on
501 AVASTIN may require blood pressure monitoring at more frequent
502 intervals. Patients with AVASTIN-induced or -exacerbated hypertension
503 who discontinue AVASTIN should continue to have their blood pressure
504 monitored at regular intervals.

505 Patients receiving AVASTIN should be monitored for the development or
506 worsening of proteinuria with serial urinalyses. Patients with a 2+ or
507 greater urine dipstick reading should undergo further assessment, e.g., a
508 24-hour urine collection. (See **WARNINGS: Proteinuria** and **DOSAGE**
509 **AND ADMINISTRATION: Dose Modifications.**)

510 Drug Interactions

511 No formal drug interaction studies with anti-neoplastic agents have been
512 conducted. In Study 1, patients with colorectal cancer were given
513 irinotecan/5-FU/leucovorin (bolus-IFL) with or without AVASTIN.
514 Irinotecan concentrations were similar in patients receiving bolus-IFL
515 alone and in combination with AVASTIN. The concentrations of SN38,
516 the active metabolite of irinotecan, were on average 33% higher in patients
517 receiving bolus-IFL in combination with AVASTIN when compared with
518 bolus-IFL alone. In Study 1, patients receiving bolus-IFL plus AVASTIN

519 had a higher incidence of NCI-CTC Grade 3–4 diarrhea and neutropenia.
520 Due to high inter-patient variability and limited sampling, the extent of the
521 increase in SN38 levels in patients receiving concurrent irinotecan and
522 AVASTIN is uncertain.

523 In Study 6, based on limited data, there did not appear to be a difference in
524 the mean exposure of either carboplatin or paclitaxel when each was
525 administered alone or in combination with AVASTIN. However, 3 of the
526 8 patients receiving AVASTIN plus paclitaxel/carboplatin had
527 substantially lower paclitaxel exposure after four cycles of treatment (at
528 Day 63) than those at Day 0, while patients receiving
529 paclitaxel/carboplatin without AVASTIN had a greater paclitaxel
530 exposure at Day 63 than at Day 0.

531 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

532 No carcinogenicity data are available for AVASTIN in animals or
533 humans.

534 AVASTIN may impair fertility. Dose-related decreases in ovarian and
535 uterine weights, endometrial proliferation, number of menstrual cycles,
536 and arrested follicular development or absent corpora lutea were observed
537 in female cynomolgus monkeys treated with 10 or 50 mg/kg of AVASTIN
538 for 13 or 26 weeks. Following a 4- or 12-week recovery period, which
539 examined only the high-dose group, trends suggestive of reversibility
540 were noted in the two females for each regimen that were assigned to
541 recover. After the 12-week recovery period, follicular maturation arrest
542 was no longer observed, but ovarian weights were still moderately
543 decreased. Reduced endometrial proliferation was no longer observed at
544 the 12-week recovery time point, but uterine weight decreases were still
545 notable, corpora lutea were absent in 1 out of 2 animals, and the number of
546 menstrual cycles remained reduced (67%).

547 Pregnancy Category C

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

554 Angiogenesis is critical to fetal development and the inhibition of
555 angiogenesis following administration of AVASTIN is likely to result in
556 adverse effects on pregnancy. There are no adequate and well-controlled
557 studies in pregnant women. AVASTIN should be used during pregnancy
558 or in any woman not employing adequate contraception only if the
559 potential benefit justifies the potential risk to the fetus. All patients should
560 be counseled regarding the potential risk of AVASTIN to the developing
561 fetus prior to initiation of therapy. If the patient becomes pregnant while
562 receiving AVASTIN, she should be apprised of the potential hazard to the
563 fetus and/or the potential risk of loss of pregnancy. Patients who
564 discontinue AVASTIN should also be counseled concerning the prolonged
565 exposure following discontinuation of therapy (half-life of approximately
566 20 days) and the possible effects of AVASTIN on fetal development.

567 Nursing Mothers

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

575 Pediatric Use

576 The safety and effectiveness of AVASTIN in pediatric patients has not
577 been studied. However, physeal dysplasia was observed in juvenile

578 cynomolgus monkeys with open growth plates treated for four weeks with
579 doses that were less than the recommended human dose based on mg/kg
580 and exposure. The incidence and severity of physeal dysplasia were
581 dose-related and were at least partially reversible upon cessation of
582 treatment.

583 **Geriatric Use**

584 In Study 1, NCI-CTC Grade 3–4 adverse events were collected in all
585 patients receiving study drug (396 bolus-IFL plus placebo; 392 bolus-IFL
586 plus AVASTIN; 109 5-FU/LV plus AVASTIN), while NCI-CTC Grade 1
587 and 2 adverse events were collected in a subset of 309 patients. There
588 were insufficient numbers of patients 65 years and older in the subset in
589 which NCI-CTC Grade 1-4 adverse events were collected to determine
590 whether the overall adverse event profile was different in the elderly as
591 compared to younger patients. Among the 392 patients receiving
592 bolus-IFL plus AVASTIN, 126 were at least 65 years of age. Severe
593 adverse events that occurred at a higher incidence ($\geq 2\%$) in the elderly
594 when compared to those less than 65 years were asthenia, sepsis, deep
595 thrombophlebitis, hypertension, hypotension, myocardial infarction,
596 congestive heart failure, diarrhea, constipation, anorexia, leukopenia,
597 anemia, dehydration, hypokalemia, and hyponatremia. The effect of
598 AVASTIN on overall survival was similar in elderly patients as compared
599 to younger patients.

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

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

606 Of the 742 patients enrolled in Genentech-sponsored clinical studies in
607 which all adverse events were captured, 212 (29%) were age 65 or older

608 and 43 (6%) were age 75 or older. Adverse events of any severity that
609 occurred at a higher incidence in the elderly as compared to younger
610 patients, in addition to those described above, were dyspepsia,
611 gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice
612 alteration.

613 In an exploratory, pooled analysis of 1745 patients treated in
614 five randomized, controlled studies, there were 618 (35%) patients age
615 65 or older and 1127 patients less than 65 years of age. The overall
616 incidence of arterial thromboembolic events was increased in all patients
617 receiving AVASTIN with chemotherapy as compared to those receiving
618 chemotherapy alone, regardless of age. However, the increase in arterial
619 thromboembolic events incidence was greater in patients 65 and over
620 (8.5% vs. 2.9%) as compared to those less than 65 (2.1% vs. 1.4%).
621 (See **WARNINGS: Arterial Thromboembolic Events.**)

622 **ADVERSE REACTIONS**

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

- 624 • Gastrointestinal Perforations (see **WARNINGS**)
- 625 • Non-Gastrointestinal Fistula Formation (see **WARNINGS**)
- 626 • Wound Healing Complications (see **WARNINGS**)
- 627 • Hemorrhage (see **WARNINGS**)
- 628 • Arterial Thromboembolic Events (see **WARNINGS**)
- 629 • Hypertensive Crises (see **WARNINGS: Hypertension**)
- 630 • Reversible Posterior Leukoencephalopathy Syndrome
631 (see **WARNINGS**)
- 632 • Neutropenia and Infection (see **WARNINGS**)
- 633 • Nephrotic Syndrome (see **WARNINGS: Proteinuria**)
- 634 • Congestive Heart Failure (see **WARNINGS**)

635 The most common adverse events in patients receiving AVASTIN were
636 asthenia, pain, abdominal pain, headache, hypertension, diarrhea, nausea,

637 vomiting, anorexia, stomatitis, constipation, upper respiratory infection,
638 epistaxis, dyspnea, exfoliative dermatitis, and proteinuria.

639 **Adverse Reactions in Clinical Trials**

640 Because clinical trials are conducted under widely varying conditions,
641 adverse reaction rates observed in the clinical trials of a drug cannot be
642 directly compared to rates in the clinical trials of another drug and may not
643 reflect the rates observed in practice. The adverse reaction information
644 from clinical trials does, however, provide a basis for identifying the
645 adverse events that appear to be related to drug use and for approximating
646 rates.

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

651 **Gastrointestinal Perforation**

652 The incidence of gastrointestinal perforation across all studies ranged from
653 0–3.7%. The incidence of gastrointestinal perforation, in some cases fatal,
654 in patients with mCRC receiving AVASTIN alone or in combination with
655 chemotherapy was 2.4% compared to 0.3% in patients receiving only
656 chemotherapy. The incidence of gastrointestinal perforation in NSCLC
657 patients receiving AVASTIN was 0.9% compared to 0% in patients
658 receiving only chemotherapy. (See **WARNINGS:**

659 **Gastrointestinal Perforations and DOSAGE AND**
660 **ADMINISTRATION: Dose Modifications.**)

661 **Non-Gastrointestinal Fistula Formation**

662 (See **WARNINGS: Non-Gastrointestinal Fistula Formation,**
663 **DOSAGE AND ADMINISTRATION: Dose Modifications.**)

664 Wound Healing Complications

665 The incidence of post-operative wound healing and/or bleeding
666 complications was increased in patients with mCRC receiving AVASTIN
667 as compared to patients receiving only chemotherapy. Among patients
668 requiring surgery on or within 60 days of receiving study treatment,
669 wound healing and/or bleeding complications occurred in 15% (6/39) of
670 patients receiving bolus-IFL plus AVASTIN as compared to 4% (1/25) of
671 patients who received bolus-IFL alone. In the same study, the incidence
672 of wound dehiscence was also higher in the AVASTIN-treated patients
673 (1% vs. 0.5%).

674 Hemorrhage

675 Severe or fatal hemorrhages, including hemoptysis, gastrointestinal
676 bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding
677 occurred up to five-fold more frequently in AVASTIN treated patients
678 compared to patients treated with chemotherapy alone. NCI-CTC
679 Grade 3–5 hemorrhagic events occurred in 4.7% of NSCLC patients and
680 5.2% of mCRC patients receiving AVASTIN compared to 1.1% and 0.7%
681 for the control groups respectively. (See **WARNINGS: Hemorrhage.**)

682 The incidence of epistaxis was higher (35% vs. 10%) in patients with
683 mCRC receiving bolus-IFL plus AVASTIN compared with patients
684 receiving bolus-IFL plus placebo. These events were generally mild in
685 severity (NCI-CTC Grade 1) and resolved without medical intervention.
686 Additional mild to moderate hemorrhagic events reported more frequently
687 in patients receiving bolus-IFL plus AVASTIN when compared to those
688 receiving bolus-IFL plus placebo included gastrointestinal hemorrhage
689 (24% vs. 6%), minor gum bleeding (2% vs. 0), and vaginal hemorrhage
690 (4% vs. 2%). (See **WARNINGS: Hemorrhage** and **DOSAGE AND**
691 **ADMINISTRATION: Dose Modifications.**)

692 Arterial Thromboembolic Events

693 The incidence of arterial thromboembolic events was increased in NSCLC
694 patients receiving PC plus AVASTIN (3.0%) compared with patients

695 receiving PC alone (1.4%). Five events were fatal in the PC plus
696 AVASTIN arm, compared with 1 event in the PC alone arm. This
697 increased risk is consistent with that observed in patients with mCRC.
698 (See **WARNINGS: Arterial Thromboembolic Events, DOSAGE AND**
699 **ADMINISTRATION: Dose Modifications, and PRECAUTIONS:**
700 **Geriatric Use.**)

701 Venous Thromboembolic Events

702 The incidence of NCI-CTC Grade 3–4 venous thromboembolic events
703 was higher in patients with mCRC or NSCLC receiving AVASTIN with
704 chemotherapy as compared to those receiving chemotherapy alone. In
705 addition, in patients with mCRC the risk of developing a second
706 subsequent thromboembolic event in patients receiving AVASTIN and
707 chemotherapy is increased compared to patients receiving chemotherapy
708 alone. In Study 1, 53 patients (14%) on the bolus-IFL plus AVASTIN arm
709 and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose
710 warfarin following a venous thromboembolic event. Among these
711 patients, an additional thromboembolic event occurred in 21% (11/53) of
712 patients receiving bolus-IFL plus AVASTIN and 3% (1/30) of patients
713 receiving bolus-IFL alone.

714 The overall incidence of NCI-CTC Grade 3–4 venous thromboembolic
715 events in Study 1 was 15.1% in patients receiving bolus-IFL plus
716 AVASTIN and 13.6% in patients receiving bolus-IFL plus placebo.
717 In Study 1, the incidence of the following NCI-CTC Grade 3 and 4 venous
718 thromboembolic events was higher in patients receiving bolus-IFL plus
719 AVASTIN as compared to patients receiving bolus-IFL plus placebo:
720 deep venous thrombosis (34 vs. 19 patients) and intra-abdominal venous
721 thrombosis (10 vs. 5 patients).

722 Hypertension

723 Fatal CNS hemorrhage complicating AVASTIN induced hypertension can
724 occur.

725 In Study 1, the incidences of hypertension and of severe hypertension
 726 were increased in patients with mCRC receiving AVASTIN compared to
 727 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.

728

729 Among patients with severe hypertension in the AVASTIN arms, slightly
 730 over half the patients (51%) had a diastolic reading greater than
 731 110 mmHg associated with a systolic reading less than 200 mmHg.

732 Similar results were seen in patients receiving AVASTIN alone or in
 733 combination with FOLFOX4 or carboplatin and paclitaxel.

734 (See **WARNINGS: Hypertension and DOSAGE AND**
 735 **ADMINISTRATION: Dose Modifications.**)

736 **Neutropenia and Infection**

737 An increased incidence of neutropenia has been reported in patients
 738 receiving AVASTIN and chemotherapy compared to chemotherapy alone.
 739 In Study 1, the incidence of NCI-CTC Grade 3 or 4 neutropenia was
 740 increased in patients with mCRC receiving IFL+AVASTIN (21%)
 741 compared to patients receiving IFL alone (14%). In Study 5, the incidence
 742 of NCI-CTC Grade 4 neutropenia was increased in patients with NSCLC
 743 receiving PC plus AVASTIN (26.2%) compared with patients receiving
 744 PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC
 745 plus AVASTIN vs. 1.8% for PC alone). There were 19 (4.5%) infections
 746 with NCI-CTC Grade 3 or 4 neutropenia in the PC plus AVASTIN arm of

747 which 3 were fatal compared to 9 (2%) neutropenic infections in patients
748 receiving PC alone, of which none were fatal. During the first 6 cycles of
749 treatment the incidence of serious infections including pneumonia, febrile
750 neutropenia, catheter infections and wound infections was increased in the
751 PC plus AVASTIN arm [58 patients (13.6%)] compared to the PC alone
752 arm [29 patients (6.6%)].

753 Proteinuria

754 (See **WARNINGS: Proteinuria, DOSAGE AND**
755 **ADMINISTRATION: Dose Modifications, and PRECAUTIONS:**
756 **Geriatric Use.**)

757 Immunogenicity

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

765 Immunogenicity data are highly dependent on the sensitivity and
766 specificity of the assay. Additionally, the observed incidence of antibody
767 positivity in an assay may be influenced by several factors, including
768 sample handling, timing of sample collection, concomitant medications,
769 and underlying disease. For these reasons, comparison of the incidence of
770 antibodies to AVASTIN with the incidence of antibodies to other products
771 may be misleading.

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

773 The data in Tables 4 and 5 were obtained in Study 1. All NCI-CTC
774 Grade 3 and 4 adverse events and selected NCI-CTC Grade 1 and 2
775 adverse events (hypertension, proteinuria, thromboembolic events) were
776 reported for the overall study population. The median age was 60, 60%

777 were male, 79% were Caucasian, 78% had a colon primary lesion, 56%
 778 had extra-abdominal disease, 29% had prior adjuvant or neoadjuvant
 779 chemotherapy, and 57% had ECOG performance status of 0. The median
 780 duration of exposure to AVASTIN was 8 months in Arm 2 and 7 months
 781 in Arm 3. Severe and life-threatening (NCI-CTC Grade 3 and 4) adverse
 782 events, which occurred at a higher incidence ($\geq 2\%$) in patients receiving
 783 bolus-IFL plus AVASTIN as compared to bolus-IFL plus placebo, are
 784 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.

785
 786 NCI-CTC Grade 1–4 adverse events which occurred at a higher incidence
 787 ($\geq 5\%$) in patients receiving bolus-IFL plus AVASTIN as compared to the
 788 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%)

789

Table 5 (cont'd)
 NCI-CTC Grade 1–4 Adverse Events in Study 1
 (Occurring at Higher Incidence (≥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%)

790

791 The data in Table 6 were obtained in Study 3. Only NCI-CTC Grade 3–5
 792 non-hematologic and Grade 4–5 hematologic adverse events related to
 793 treatment were reported. The median age was a 61 years, 40% were
 794 female, 87% were Caucasian, 99% received prior chemotherapy for
 795 metastatic colorectal cancer, 26% had received prior radiation therapy, and
 796 the 49% had an ECOG performance status of 0. Selected NCI-CTC
 797 Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events
 798 which occurred at a higher incidence in patients receiving FOLFOX4 plus
 799 AVASTIN as compared to those who received FOLFOX4 alone, are
 800 presented in Table 6. These data are likely to under-estimate the true
 801 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%)

802

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

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

811 NCI-CTC Grade 3, 4, and 5 adverse events that occurred at a $\geq 2\%$ higher
812 incidence in patients receiving PC plus AVASTIN as compared with PC
813 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.

815 Other Serious Adverse Events

816 The following additional serious adverse events occurred in at least one
817 subject treated with AVASTIN in clinical studies or post-marketing
818 experience:

819 *Body as a Whole: polyserositis*

820 *Digestive: intestinal necrosis, mesenteric venous occlusion, anastomotic*
821 *ulceration*

822 *Hemic and lymphatic: pancytopenia*

823 *Respiratory: nasal septum perforation*

824 OVERDOSAGE

825 The highest dose tested in humans (20 mg/kg IV) was associated with
826 headache in nine of 16 patients and with severe headache in three of
827 16 patients.

828 DOSAGE AND ADMINISTRATION

829 Do not initiate AVASTIN until at least 28 days following major surgery.

830 The surgical incision should be fully healed prior to initiation of
831 AVASTIN.

832 Metastatic Carcinoma of the Colon or Rectum

833 AVASTIN, used in combination with intravenous 5-FU-based
834 chemotherapy, is administered as an intravenous infusion (5 mg/kg or
835 10 mg/kg) every 14 days.

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

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

840 Non-Squamous, Non-Small Cell Lung Cancer

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

843 Dose Modifications

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

845 If needed, AVASTIN should be either discontinued or temporarily
846 suspended as described below.

847 AVASTIN should be permanently discontinued in patients who develop
848 gastrointestinal perforation (gastrointestinal perforation, fistula formation
849 in the gastrointestinal tract, intra-abdominal abscess), fistula formation
850 involving an internal organ, wound dehiscence requiring medical
851 intervention, serious bleeding, a severe arterial thromboembolic event,
852 nephrotic syndrome, hypertensive crisis or hypertensive encephalopathy.

853 In patients developing RPLS, discontinue AVASTIN and initiate
854 treatment of hypertension, if present. (See **WARNINGS:**
855 **Reversible Posterior Leukoencephalopathy Syndrome.**)

856 Temporary suspension of AVASTIN is recommended in patients with
857 evidence of moderate to severe proteinuria pending further evaluation and
858 in patients with severe hypertension that is not controlled with medical
859 management. The risk of continuation or temporary suspension of
860 AVASTIN in patients with moderate to severe proteinuria is unknown.

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

866 Preparation for Administration

867 AVASTIN should be diluted for infusion by a healthcare professional
868 using aseptic technique. Withdraw the necessary amount of AVASTIN to
869 obtain the required dose and dilute in a total volume of 100 mL of 0.9%
870 Sodium Chloride Injection, USP. Discard any unused portion left in a
871 vial, as the product contains no preservatives. Parenteral drug products

872 should be inspected visually for particulate matter and discoloration prior
873 to administration.

874 Diluted AVASTIN solutions for infusion may be stored at 2°C–8°C
875 (36°F–46°F) for up to 8 hours. No incompatibilities between AVASTIN
876 and polyvinylchloride or polyolefin bags have been observed.

877 **AVASTIN infusions should not be administered or mixed with**
878 **dextrose solutions.**

879 **Administration**

880 **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** The initial
881 AVASTIN dose should be delivered over 90 minutes as an IV infusion
882 following chemotherapy. If the first infusion is well tolerated, the second
883 infusion may be administered over 60 minutes. If the 60-minute infusion
884 is well tolerated, all subsequent infusions may be administered over
885 30 minutes.

886 **Stability and Storage**

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

890 **HOW SUPPLIED**

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

894 Single unit 100 mg carton: Contains one 4 mL vial of AVASTIN
895 (25 mg/mL). NDC 50242-060-01

896 Single unit 400 mg carton: Contains one 16 mL vial of AVASTIN
897 (25 mg/mL). NDC 50242-061-01