

1 **1.14.2.3 Final Labeling Text**

9-15-06

2 **AVASTIN®**
3 **(Bevacizumab)**4 **For Intravenous Use**5 **WARNINGS**6 **Gastrointestinal Perforations**

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

21 **Wound Healing Complications**

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

Hemorrhage

Serious, and in some cases fatal, hemoptysis has occurred in patients with non-small cell lung cancer treated with chemotherapy and AVASTIN. In a small study, the incidence of serious or fatal hemoptysis was 31% in patients with squamous histology and 4% in patients with adenocarcinoma receiving AVASTIN as compared to no cases in patients treated with chemotherapy alone. Patients with recent hemoptysis should not receive AVASTIN. (See **WARNINGS: 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.

59 CLINICAL PHARMACOLOGY

60 Mechanism of Action

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

68 Pharmacokinetics

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

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

90 **Special Populations**

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

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

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

99 **CLINICAL STUDIES**

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

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

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

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

120 ECOG performance status of 0. Twenty-one percent had a rectal primary
121 and 28% received prior adjuvant chemotherapy. In the majority of
122 patients, 56%, the dominant site of disease was extra-abdominal, while the
123 liver was the dominant site in 38% of patients. Results are presented in
124 Table 1 and Figure 1.

Table 1
Study 1 Efficacy Results

	IFL + Placebo	IFL + AVASTIN 5 mg/kg q 2 wks
Number of Patients	411	402
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

^a p < 0.001 by stratified logrank test.

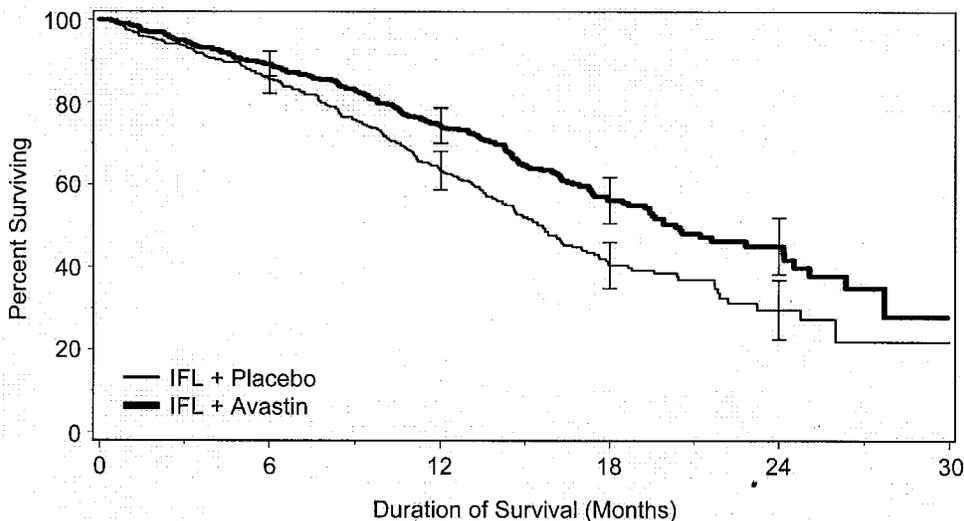
^b p < 0.01 by χ^2 test.

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126

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Figure 1
Duration of Survival in Study 1



128

129

Error bars represent 95% confidence intervals.

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

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

136 AVASTIN in Combination with 5-FU/LV Chemotherapy

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

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

Table 2
 Study 2 Efficacy Results

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

145
 146 Progression-free survival was significantly longer in patients receiving
 147 5-FU/LV plus AVASTIN at 5 mg/kg when compared to those not
 148 receiving AVASTIN. However, overall survival and overall response rate
 149 were not significantly different. Outcomes for patients receiving 5-FU/LV

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

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

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

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

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

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

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

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

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

198 **INDICATIONS AND USAGE**

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

202 **CONTRAINDICATIONS**

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

204 **WARNINGS**

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

207 Gastrointestinal perforation complicated by intra-abdominal abscesses or
208 fistula formation and in some instances with fatal outcome, occurs at an
209 increased incidence in patients receiving AVASTIN as compared to
210 controls. In Studies 1, 2, and 3, the incidence of gastrointestinal

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

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

227 Permanently discontinue AVASTIN in patients with gastrointestinal
228 perforation.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

300 (8.5% vs. 2.9%) as compared to those less than 65 (2.1% vs. 1.4%).
301 (See **PRECAUTIONS: Geriatric Use**).

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

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

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

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

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

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

326 **Reversible Posterior Leukoencephalopathy Syndrome (RPLS) (See**
327 **DOSAGE AND ADMINISTRATION: Dose Modifications)**

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

336 In patients developing RPLS, discontinue AVASTIN and initiate
337 treatment of hypertension, if present. Symptoms usually resolve or
338 improve within days, although some patients have experienced ongoing
339 neurologic sequelae. The safety of reinitiating AVASTIN therapy in
340 patients previously experiencing RPLS is not known.

341 **Proteinuria (See DOSAGE AND ADMINISTRATION:**
342 **Dose Modifications)**

343 The incidence and severity of proteinuria is increased in patients receiving
344 AVASTIN as compared to control. In Studies 1 and 3, the incidence of
345 NCI-CTC Grade 3 and 4 proteinuria, characterized as >3.5 gm/24 hours,
346 ranged up to 1.8% in AVASTIN-treated patients.

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

352 The highest incidence of proteinuria was observed in a dose-ranging,
353 placebo-controlled, randomized study of AVASTIN in patients with
354 metastatic renal cell carcinoma, an indication for which AVASTIN is not
355 approved, 24-hour urine collections were obtained in approximately half
356 the patients enrolled. Among patients in whom 24-hour urine collections

357 were obtained, four of 19 (21%) patients receiving AVASTIN at 10 mg/kg
358 every two weeks, two of 14 (14%) patients receiving AVASTIN at
359 3 mg/kg every two weeks, and none of the 15 placebo patients
360 experienced NCI-CTC Grade 3 proteinuria (>3.5 gm protein/24 hours).

361 Discontinue AVASTIN in patients with nephrotic syndrome. The safety
362 of continued AVASTIN treatment in patients with moderate to severe
363 proteinuria has not been evaluated. In most clinical studies, AVASTIN
364 was interrupted for ≥ 2 grams of proteinuria/24 hours and resumed when
365 proteinuria was <2 gm/24 hours. Patients with moderate to severe
366 proteinuria based on 24-hour collections should be monitored regularly
367 until improvement and/or resolution is observed.

368 **Congestive Heart Failure**

369 Congestive heart failure (CHF), defined as NCI-CTC Grade 2–4 left
370 ventricular dysfunction, was reported in 22 of 1032 (2%) patients
371 receiving AVASTIN in clinical studies. The risk of CHF appears to be
372 higher in patients receiving AVASTIN who have received prior or
373 concurrent anthracyclines. In a controlled study in patients with breast
374 cancer (an unlabelled indication), the incidence of CHF was higher in the
375 AVASTIN plus chemotherapy arm as compared to the chemotherapy
376 alone arm. Congestive heart failure occurred in 13 of 299 (4%) patients
377 who received prior anthracyclines and/or left chest wall irradiation.
378 Congestive heart failure occurred in six of 44 (14%) patients with relapsed
379 acute leukemia (an unlabelled indication) receiving AVASTIN and
380 concurrent anthracyclines in a single arm study.

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

383 **PRECAUTIONS**

384 **General**

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

387 **Infusion Reactions**

388 In clinical studies, infusion reactions with the first dose of AVASTIN
389 were uncommon (<3%) and severe reactions occurred in 0.2% of patients.
390 Infusion reactions reported in the clinical trials and postmarketing
391 experience include hypertension, hypertensive crises associated with
392 neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3
393 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. Adequate
394 information on rechallenge is not available. AVASTIN infusion should be
395 interrupted in all patients with severe infusion reactions and appropriate
396 medical therapy administered.

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

400 **Surgery**

401 AVASTIN therapy should not be initiated for at least 28 days following
402 major surgery. The surgical incision should be fully healed prior to
403 initiation of AVASTIN. Because of the potential for impaired wound
404 healing, AVASTIN should be suspended prior to elective surgery.
405 The appropriate interval between the last dose of AVASTIN and elective
406 surgery is unknown; however, the half-life of AVASTIN is estimated to be
407 20 days (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**) and
408 the interval chosen should take into consideration the half-life of the drug.
409 (See **WARNINGS: Gastrointestinal Perforations** and
410 **Wound Healing Complications**).

411 **Cardiovascular Disease**

412 Patients were excluded from participation in AVASTIN clinical trials if, in
413 the previous year, they had experienced clinically significant
414 cardiovascular disease. In an exploratory analysis pooling the data from
415 five randomized, placebo-controlled, clinical trials conducted in patients
416 without a recent history of clinically significant cardiovascular disease, the
417 overall incidence of arterial thromboembolic events, the incidence of fatal

418 arterial thromboembolic events, and the incidence of cardiovascular
419 thromboembolic events were increased in patients receiving AVASTIN
420 plus chemotherapy as compared to chemotherapy alone.

421 **Laboratory Tests**

422 Blood pressure monitoring should be conducted every two to three weeks
423 during treatment with AVASTIN. Patients who develop hypertension on
424 AVASTIN may require blood pressure monitoring at more frequent
425 intervals. Patients with AVASTIN-induced or -exacerbated hypertension
426 who discontinue AVASTIN should continue to have their blood pressure
427 monitored at regular intervals.

428 Patients receiving AVASTIN should be monitored for the development or
429 worsening of proteinuria with serial urinalyses. Patients with a 2+ or
430 greater urine dipstick reading should undergo further assessment, e.g., a
431 24-hour urine collection. (See **WARNINGS: Proteinuria** and **DOSAGE**
432 **AND ADMINISTRATION: Dose Modifications**).

433 **Drug Interactions**

434 No formal drug interaction studies with anti-neoplastic agents have been
435 conducted. In Study 1, patients with colorectal cancer were given
436 irinotecan/5-FU/leucovorin (bolus-IFL) with or without AVASTIN.
437 Irinotecan concentrations were similar in patients receiving bolus-IFL
438 alone and in combination with AVASTIN. The concentrations of SN38,
439 the active metabolite of irinotecan, were on average 33% higher in patients
440 receiving bolus-IFL in combination with AVASTIN when compared with
441 bolus-IFL alone. In Study 1, patients receiving bolus-IFL plus AVASTIN
442 had a higher incidence of Grade 3–4 diarrhea and neutropenia. Due to
443 high inter-patient variability and limited sampling, the extent of the
444 increase in SN38 levels in patients receiving concurrent irinotecan and
445 AVASTIN is uncertain.

446 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

447 No carcinogenicity data are available for AVASTIN in animals or
448 humans.

449 AVASTIN may impair fertility. Dose-related decreases in ovarian and
450 uterine weights, endometrial proliferation, number of menstrual cycles, and
451 arrested follicular development or absent corpora lutea were observed in
452 female cynomolgus monkeys treated with 10 or 50 mg/kg of AVASTIN for
453 13 or 26 weeks. Following a 4- or 12-week recovery period, which
454 examined only the high-dose group, trends suggestive of reversibility were
455 noted in the two females for each regimen that were assigned to recover.
456 After the 12-week recovery period, follicular maturation arrest was no
457 longer observed, but ovarian weights were still moderately decreased.
458 Reduced endometrial proliferation was no longer observed at the 12-week
459 recovery time point, but uterine weight decreases were still notable,
460 corpora lutea were absent in 1 out of 2 animals, and the number of
461 menstrual cycles remained reduced (67%).

462 **Pregnancy Category C**

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

469 Angiogenesis is critical to fetal development and the inhibition of
470 angiogenesis following administration of AVASTIN is likely to result in
471 adverse effects on pregnancy. There are no adequate and well-controlled
472 studies in pregnant women. AVASTIN should be used during pregnancy
473 or in any woman not employing adequate contraception only if the
474 potential benefit justifies the potential risk to the fetus. All patients should
475 be counseled regarding the potential risk of AVASTIN to the developing
476 fetus prior to initiation of therapy. If the patient becomes pregnant while

477 receiving AVASTIN, she should be apprised of the potential hazard to the
478 fetus and/or the potential risk of loss of pregnancy. Patients who
479 discontinue AVASTIN should also be counseled concerning the prolonged
480 exposure following discontinuation of therapy (half-life of approximately
481 20 days) and the possible effects of AVASTIN on fetal development.

482 **Nursing Mothers**

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

490 **Pediatric Use**

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

498 **Geriatric Use**

499 In Study 1, NCI-CTC Grade 3–4 adverse events were collected in all
500 patients receiving study drug (396 bolus-IFL plus placebo; 392 bolus-IFL
501 plus AVASTIN; 109 5-FU/LV plus AVASTIN), while NCI-CTC Grade 1
502 and 2 adverse events were collected in a subset of 309 patients. There
503 were insufficient numbers of patients 65 years and older in the subset in
504 which Grade 1–4 adverse events were collected to determine whether the
505 overall adverse event profile was different in the elderly as compared to
506 younger patients. Among the 392 patients receiving bolus-IFL plus
507 AVASTIN, 126 were at least 65 years of age. Severe adverse events that

508 occurred at a higher incidence ($\geq 2\%$) in the elderly when compared to
509 those less than 65 years were asthenia, sepsis, deep thrombophlebitis,
510 hypertension, hypotension, myocardial infarction, congestive heart failure,
511 diarrhea, constipation, anorexia, leukopenia, anemia, dehydration,
512 hypokalemia, and hyponatremia. The effect of AVASTIN on overall
513 survival was similar in elderly patients as compared to younger patients.

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

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

524 In an exploratory, pooled analysis of 1745 patients treated in
525 five randomized, controlled studies, there were 618 (35%) patients age
526 65 or older and 1127 patients less than 65 years of age. The overall
527 incidence of arterial thromboembolic events was increased in all patients
528 receiving AVASTIN with chemotherapy as compared to those receiving
529 chemotherapy alone, regardless of age. However, the increase in arterial
530 thromboembolic events incidence was greater in patients 65 and over
531 (8.5% vs. 2.9%) as compared to those less than 65 (2.1% vs. 1.4%).
532 (See **WARNINGS: Arterial Thromboembolic Events.**)

533 **ADVERSE REACTIONS**

534 The most serious adverse reactions in patients receiving AVASTIN were:
535 • Gastrointestinal Perforations (see **WARNINGS**)
536 • Wound Healing Complications (see **WARNINGS**)
537 • Hemorrhage (see **WARNINGS**)

- 538 • Arterial Thromboembolic Events (see **WARNINGS**)
- 539 • Hypertensive Crises (see **WARNINGS: Hypertension**)
- 540 • Reversible Posterior Leukoencephalopathy Syndrome (see
- 541 **WARNINGS**)
- 542 • Nephrotic Syndrome (see **WARNINGS: Proteinuria**)
- 543 • Congestive Heart Failure (see **WARNINGS**)

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

548 **Adverse Reactions in Clinical Trials**

549 Because clinical trials are conducted under widely varying conditions,
550 adverse reaction rates observed in the clinical trials of a drug cannot be
551 directly compared to rates in the clinical trials of another drug and may not
552 reflect the rates observed in practice. The adverse reaction information
553 from clinical trials does, however, provide a basis for identifying the
554 adverse events that appear to be related to drug use and for approximating
555 rates.

556 The data described below reflect exposure to AVASTIN[®] in 1106 patients,
557 including 506 receiving AVASTIN[®] for at least 6 months and
558 147 receiving AVASTIN[®] for at least one year. AVASTIN[®] was studied
559 primarily in placebo- and active-controlled trials (n = 501, and n = 605,
560 respectively). Among 569 patients with metastatic colorectal cancer
561 (mCRC) receiving first-line therapy for metastatic disease, the median age
562 was 60, 40% were female, and 79% were Caucasian. Fifty-seven percent
563 had an ECOG performance status of 0. Twenty-one percent had a rectal
564 primary and 28% received prior adjuvant chemotherapy. In the majority
565 of patients, 56%, the dominant site of disease was extra-abdominal, while
566 the liver was the dominant site in 38% of patients. Most patients received
567 doses of 5 mg/kg every 2 weeks; all patients received concurrent
568 chemotherapy. Among 537 patients with mCRC receiving second-line

569 therapy for metastatic disease, the median age was 61 years, 40% were
570 female, 87% were Caucasian, and 49% had an ECOG performance status
571 of 0. Twenty-six percent had received prior radiation therapy, 80%
572 received prior adjuvant chemotherapy, and 99% received prior
573 chemotherapy for mCRC. Patients received doses of 10 mg/kg every 2
574 weeks, alone (n=244) or with chemotherapy (n=293).

575 Gastrointestinal Perforation

576 Across all studies, the incidence of gastrointestinal perforation, in some
577 cases fatal, in patients with mCRC receiving AVASTIN alone or in
578 combination with chemotherapy was 2.4% compared to 0.3% in patients
579 receiving only chemotherapy. The incidence of gastrointestinal
580 perforation ranged from 0%–3.7%.

581 Wound Healing Complications

582 The incidence of post-operative wound healing and/or bleeding
583 complications was increased in patients receiving AVASTIN. Among
584 patients requiring surgery on or within 60 days of receiving study
585 treatment, wound healing and/or bleeding complications occurred in
586 15% (6/39) of patients receiving bolus-IFL plus AVASTIN as compared
587 to 4% (1/25) of patients who received bolus-IFL alone. In the same study,
588 the incidence of wound dehiscence was also higher in the
589 AVASTIN-treated patients (1% vs. 0.5%).

590 Hemorrhage

591 In clinical studies of CRC, both serious and non-serious hemorrhagic
592 events occurred at a higher incidence in patients receiving AVASTIN.
593 (See **WARNINGS: Hemorrhage**).

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

599 In Study 1, the incidence of epistaxis was higher (35% vs. 10%) in
600 patients receiving bolus-IFL plus AVASTIN compared with patients
601 receiving bolus-IFL plus placebo. These events were generally mild in
602 severity (NCI-CTC Grade 1) and resolved without medical intervention.
603 Additional mild to moderate hemorrhagic events reported more frequently
604 in patients receiving bolus-IFL plus AVASTIN when compared to those
605 receiving bolus-IFL plus placebo included gastrointestinal hemorrhage
606 (24% vs. 6%), minor gum bleeding (2% vs. 0), and vaginal hemorrhage
607 (4% vs. 2%).

608 Venous Thromboembolic Events

609 In Study 1, the incidence of NCI CTC grade 3-4 venous thromboembolic
610 events was slightly higher in patients receiving AVASTIN with
611 chemotherapy as compared to those receiving chemotherapy alone. In
612 addition, the risk of developing a second thromboembolic event in patients
613 receiving AVASTIN and chemotherapy is increased compared to patients
614 receiving chemotherapy alone who have experienced a venous
615 thromboembolic event.

616 In Study 1, 53 patients (14%) on the bolus-IFL plus AVASTIN arm and
617 30 patients (8%) on the bolus-IFL plus placebo arm received full dose
618 warfarin following a venous thromboembolic event. Among these
619 patients, an additional thromboembolic event occurred in 21% (11/53) of
620 patients receiving bolus-IFL plus AVASTIN and 3% (1/30) of patients
621 receiving bolus-IFL alone.

622 The overall incidence of Grade 3-4 venous thromboembolic events in
623 Study 1 was 15.1% in patients receiving bolus-IFL plus AVASTIN and
624 13.6% in patients receiving bolus-IFL plus placebo. In Study 1, the
625 incidence of the following Grade 3 and 4 venous thromboembolic events
626 was higher in patients receiving bolus-IFL plus AVASTIN as compared to
627 patients receiving bolus-IFL plus placebo: deep venous thrombosis
628 (34 vs. 19 patients) and intra-abdominal venous thrombosis
629 (10 vs. 5 patients).

630 Hypertension
 631 The incidences of hypertension and of severe hypertension were increased
 632 in patients receiving AVASTIN in Study 1 (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.

633
 634 Among patients with severe hypertension in the AVASTIN arms, slightly
 635 over half the patients (51%) had a diastolic reading greater than
 636 110 mmHg associated with a systolic reading less than 200 mmHg.

637 Similar results were seen in patients receiving AVASTIN alone or in
 638 combination with FOLFOX4.

639 Fatal CNS hemorrhage complicating hypertension can occur.

640 Proteinuria

641 See **WARNINGS** and **DOSAGE AND ADMINISTRATION:**
 642 **Dose Modifications.**

643 Immunogenicity

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

651 Immunogenicity data are highly dependent on the sensitivity and
652 specificity of the assay. Additionally, the observed incidence of antibody
653 positivity in an assay may be influenced by several factors, including
654 sample handling, timing of sample collection, concomitant medications,
655 and underlying disease. For these reasons, comparison of the incidence of
656 antibodies to AVASTIN with the incidence of antibodies to other products
657 may be misleading.

658 **First-Line Treatment of Metastatic Carcinoma of the Colon and**
659 **Rectum**

660 The data in Table 4 and Table 5 were obtained in Study 1. All NCI-CTC
661 Grade 3 and 4 adverse events and selected Grade 1 and 2 adverse events
662 (hypertension, proteinuria, thromboembolic events) were reported for the
663 overall study population. In Study 1; the median age was 60, 60% were
664 male, 78% had colon primary lesion, and 29% had prior adjuvant or
665 neoadjuvant chemotherapy. The median duration of exposure to
666 AVASTIN in Study 1 was 8 months in Arm 2 and 7 months in Arm 3.
667 Severe and life-threatening (NCI-CTC Grade 3 and 4) adverse events,
668 which occurred at a higher incidence ($\geq 2\%$) in patients receiving
669 bolus-IFL plus AVASTIN as compared to bolus-IFL plus placebo, are
670 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)
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.

671

672 Grade 1-4 adverse events which occurred at a higher incidence ($\geq 5\%$) in
 673 patients receiving bolus-IFL plus AVASTIN as compared to the bolus-IFL
 674 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%)

675

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%)

676

677 **Second-Line Treatment of Metastatic Carcinoma of the Colon and**
 678 **Rectum**

679 The data in Table 6 were obtained in Study 3. Selected NCI-CTC Grade
 680 3–5 non-hematologic and Grade 4–5 hematologic adverse events which
 681 occurred at a higher incidence in patients receiving FOLFOX4 plus
 682 AVASTIN as compared to those who received FOLFOX4 alone, are
 683 presented in Table 6. These data are likely to under-estimate the true
 684 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%)

685

686 **Other Serious Adverse Events**

687 The following additional serious adverse events occurred in at least one
 688 subject treated with AVASTIN in clinical studies or post-marketing
 689 experience:

690 *Body as a Whole: polyserositis*691 *Digestive: intestinal necrosis, mesenteric venous occlusion, anastomotic*
692 *ulceration*693 *Hemic and lymphatic: pancytopenia*694 *Metabolic and nutritional disorders: hyponatremia*

695 *Respiratory: nasal septum perforation*

696 **OVERDOSAGE**

697 The maximum tolerated dose of AVASTIN has not been determined.

698 The highest dose tested in humans (20 mg/kg IV) was associated with
699 headache in nine of 16 patients and with severe headache in three of
700 16 patients.

701 **DOSAGE AND ADMINISTRATION**

702 AVASTIN, used in combination with intravenous 5-FU-based
703 chemotherapy, is administered as an intravenous infusion (5 mg/kg or
704 10 mg/kg) every 14 days until disease progression.

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

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

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

712 **Dose Modifications**

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

716 AVASTIN should be permanently discontinued in patients who develop
717 gastrointestinal perforation, wound dehiscence requiring medical
718 intervention, serious bleeding, a severe arterial thromboembolic event,
719 nephrotic syndrome, hypertensive crisis or hypertensive encephalopathy.

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

723 Temporary suspension of AVASTIN is recommended in patients with
724 evidence of moderate to severe proteinuria pending further evaluation and
725 in patients with severe hypertension that is not controlled with medical
726 management. The risk of continuation or temporary suspension of
727 AVASTIN in patients with moderate to severe proteinuria is unknown.

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

732 **Preparation for Administration**

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

740 Diluted AVASTIN solutions for infusion may be stored at 2°C–8°C
741 (36°F–46°F) for up to 8 hours. No incompatibilities between AVASTIN
742 and polyvinylchloride or polyolefin bags have been observed.

743 **AVASTIN infusions should not be administered or mixed with**
744 **dextrose solutions.**

745 **Administration**

746 **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** The initial
747 AVASTIN dose should be delivered over 90 minutes as an IV infusion
748 following chemotherapy. If the first infusion is well tolerated, the second
749 infusion may be administered over 60 minutes. If the 60-minute infusion
750 is well tolerated, all subsequent infusions may be administered over
751 30 minutes.

752 **Stability and Storage**

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

756 **HOW SUPPLIED**

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

760 Single unit 100 mg carton: Contains one 4 mL vial of AVASTIN
761 (25 mg/mL). NDC 50242-060-01

762 Single unit 400 mg carton: Contains one 16 mL vial of AVASTIN
763 (25 mg/mL). NDC 50242-061-01

764 **REFERENCES**

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769

AVASTIN[®]

(Bevacizumab)

For Intravenous Use

Manufactured by:

Genentech, Inc.

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South San Francisco, CA 94080-4990

7455305

LV0017

4833702

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