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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

STN-125085/0

Approved Labeling

1 **1.14.1.3 Labeling Text**

2 **AVASTIN™**
3 **(Bevacizumab)**

4 **For Intravenous Use**

5 **WARNINGS**

6 **Gastrointestinal Perforations/Wound Healing Complications**

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

24 **Hemorrhage**

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

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.

CLINICAL PHARMACOLOGY

Mechanism of Action

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

Pharmacokinetics

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

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

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

84 **Special Populations**

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

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

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

CLINICAL STUDIES

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

AVASTIN in Combination with Bolus-IFL

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

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

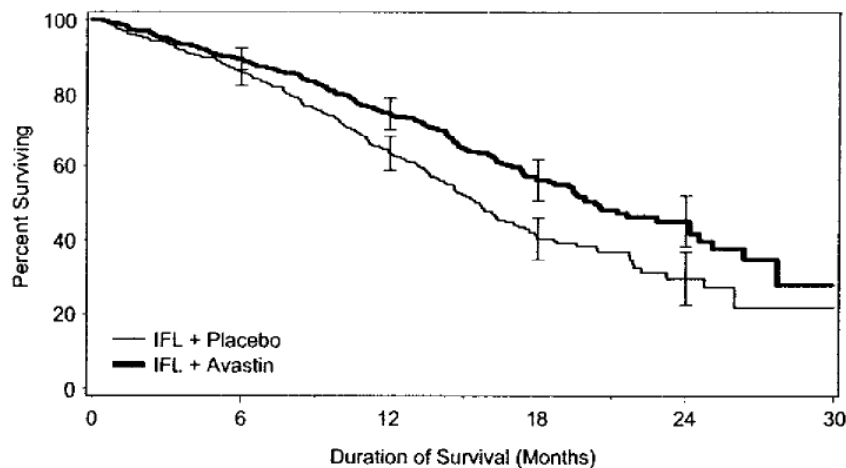
Table 1
Study 1 Efficacy Results

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

^a $p < 0.001$ by stratified logrank test.

^b $p < 0.01$ by χ^2 test.

Figure 1
Duration of Survival in Study 1



Error bars represent 95% confidence intervals.

The clinical benefit of AVASTIN, as measured by survival in the two principal arms, was seen in all subgroups tested. The subgroups examined

123 were based on age, sex, race, ECOG performance status, location of
124 primary tumor, prior adjuvant therapy, number of metastatic sites, and
125 tumor burden.

126 Among the 110 patients enrolled in Arm 3, median overall survival was
127 18.3 months, median progression-free survival was 8.8 months, overall
128 response rate was 39%, and median duration of response was 8.5 months.

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

130 Study 2 was a randomized, active-controlled clinical trial testing
131 AVASTIN in combination with 5-FU/LV as first-line treatment of
132 metastatic colorectal cancer. Patients were randomized to receive
133 5-FU/LV (5-fluorouracil 500 mg/m², leucovorin 500 mg/m² weekly for
134 6 weeks every 8 weeks) or 5-FU/LV plus AVASTIN (5 mg/kg every
135 2 weeks) or 5-FU/LV plus AVASTIN (10 mg/kg every 2 weeks). Patients
136 were treated until disease progression. The primary endpoints of the trial
137 were objective response rate and progression-free survival. Results are
138 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

139
140 Progression-free survival was significantly better in patients receiving
141 5-FU/LV plus AVASTIN at 5 mg/kg when compared to those not
142 receiving AVASTIN. However, overall survival and overall response rate

143 were not significantly different. Outcomes for patients receiving 5-FU/LV
144 plus AVASTIN at 10 mg/kg were not significantly different than for
145 patients who did not receive AVASTIN.

146 **AVASTIN as a Single Agent**

147 The efficacy of AVASTIN as a single agent in colorectal cancer has not
148 been established. However, in an ongoing, randomized study of patients
149 with metastatic colorectal cancer that had progressed following a
150 5-fluorouracil and irinotecan-based regimen, the arm in which patients
151 were treated with single-agent AVASTIN was closed early due to
152 evidence of an inferior survival in that arm as compared with patients
153 treated with the FOLFOX regimen of 5-fluorouracil, leucovorin, and
154 oxaliplatin.

155 **INDICATIONS AND USAGE**

156 AVASTIN, used in combination with intravenous 5-fluorouracil-based
157 chemotherapy, is indicated for first-line treatment of patients with
158 metastatic carcinoma of the colon or rectum.

159 **CONTRAINDICATIONS**

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

161 **WARNINGS**

162 **Gastrointestinal Perforations/Wound Healing Complications** 163 **(See DOSAGE AND ADMINISTRATION: Dose Modifications)**

164 Gastrointestinal perforation and wound dehiscence, complicated by
165 intra-abdominal abscesses, occurred at an increased incidence in patients
166 receiving AVASTIN as compared to controls. AVASTIN has also been
167 shown to impair wound healing in pre-clinical animal models.

168 In Study 1, one of 396 (0.3%) patients receiving bolus-IFL plus placebo,
169 six of 392 (2%) patients receiving bolus-IFL plus AVASTIN, and four of
170 109 (4%) patients receiving 5-FU/LV plus AVASTIN developed
171 gastrointestinal perforation, in some instances with fatal outcome. These
172 episodes occurred with or without intra-abdominal abscesses and at

173 various time points during treatment. The typical presentation was
174 reported as abdominal pain associated with symptoms such as constipation
175 and vomiting.

176 In addition, two of 396 (0.5%) patients receiving bolus-IFL plus placebo,
177 four of 392 (1%) patients receiving bolus-IFL plus AVASTIN, and one of
178 109 (1%) patients receiving 5-FU/LV plus AVASTIN developed a wound
179 dehiscence during study treatment.

180 The appropriate interval between surgery and subsequent initiation of
181 AVASTIN required to avoid the risks of impaired wound healing has not
182 been determined. In Study 1, the clinical protocol did not permit initiation
183 of AVASTIN for at least 28 days following surgery. There was one
184 patient (among 501 patients receiving AVASTIN on Study 1) in whom an
185 anastomotic dehiscence occurred when AVASTIN was initiated per
186 protocol. In this patient, the interval between surgery and initiation of
187 AVASTIN was greater than 2 months.

188 Similarly, the appropriate interval between termination of AVASTIN and
189 subsequent elective surgery required to avoid the risks of impaired wound
190 healing has not been determined. In Study 1, 39 patients who were
191 receiving bolus-IFL plus AVASTIN underwent surgery following
192 AVASTIN therapy and, of these patients, six (15%) had wound
193 healing/bleeding complications. In the same study, 25 patients in the
194 bolus-IFL arm underwent surgery and, of these patients, one of 25 (4%)
195 had wound healing/bleeding complications. The longest interval between
196 last dose of study drug and dehiscence was 56 days; this occurred in a
197 patient on the bolus-IFL plus AVASTIN arm. The interval between
198 termination of AVASTIN and subsequent elective surgery should take into
199 consideration the calculated half-life of AVASTIN (approximately
200 20 days).

201 AVASTIN therapy should be discontinued in patients with gastrointestinal
202 perforation or wound dehiscence requiring medical intervention.

203 **Hemorrhage (See DOSAGE AND ADMINISTRATION: Dose**
204 **Modifications)**

205 Two distinct patterns of bleeding have occurred in patients receiving
206 AVASTIN. The first is minor hemorrhage, most commonly Grade 1
207 epistaxis. The second is serious, and in some cases fatal, hemorrhagic
208 events. Serious hemorrhagic events occurred primarily in patients with
209 non-small cell lung cancer, an indication for which AVASTIN is not
210 approved. In a randomized study in patients with non-small cell lung
211 cancer receiving chemotherapy with or without AVASTIN, four of 13
212 (31%) AVASTIN-treated patients with squamous cell histology and two
213 of 53 (4%) AVASTIN-treated patients with non-squamous histology
214 experienced life-threatening or fatal pulmonary hemorrhage as compared
215 to none of the 32 (0%) patients receiving chemotherapy alone. Of the
216 patients experiencing events of life-threatening pulmonary hemorrhage,
217 many had cavitation and/or necrosis of the tumor, either pre-existing or
218 developing during AVASTIN therapy. These serious hemorrhagic events
219 occurred suddenly and presented as major or massive hemoptysis.

220 The risk of central nervous system (CNS) bleeding in patients with CNS
221 metastases receiving AVASTIN has not been evaluated because these
222 patients were excluded from Genentech-sponsored studies following
223 development of CNS hemorrhage in a patient with a CNS metastasis in
224 Phase 1 studies.

225 Other serious bleeding events reported in patients receiving AVASTIN
226 were uncommon and included gastrointestinal hemorrhage, subarachnoid
227 hemorrhage, and hemorrhagic stroke.

228 Patients with serious hemorrhage i.e., requiring medical intervention,
229 should have AVASTIN treatment discontinued and receive aggressive
230 medical management. Patients with recent hemoptysis should not receive
231 AVASTIN.

232 **Hypertension (See DOSAGE AND ADMINISTRATION: Dose**
233 **Modifications)**

234 The incidence of hypertension and severe hypertension was increased in
235 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.

236
237 Among patients with severe hypertension in the AVASTIN arms, slightly
238 over half the patients (51%) had a diastolic reading greater than 110
239 associated with a systolic reading less than 200.

240 Medication classes used for management of patients with Grade 3
241 hypertension receiving AVASTIN included angiotensin-converting
242 enzyme inhibitors, beta blockers, diuretics, and calcium channel blockers.
243 Four months after discontinuation of therapy, persistent hypertension was
244 present in 18 of 26 patients that received bolus-IFL plus AVASTIN and
245 8 of 10 patients that received bolus-IFL plus placebo.

246 Across all clinical studies (n= 1032), development or worsening of
247 hypertension resulted in hospitalization or discontinuation of AVASTIN in
248 17 patients. Four of these 17 patients developed hypertensive
249 encephalopathy. Severe hypertension was complicated by subarachnoid
250 hemorrhage in one patient.

251 AVASTIN should be permanently discontinued in patients with
252 hypertensive crisis. Temporary suspension is recommended in patients
253 with severe hypertension that is not controlled with medical management.

254 **Proteinuria (See DOSAGE AND ADMINISTRATION: Dose**
255 **Modifications)**

256 In Study 1, both the incidence and severity of proteinuria (defined as a
257 urine dipstick reading of 1+ or greater) was increased in patients receiving
258 AVASTIN as compared to those receiving bolus-IFL plus placebo.
259 Urinary dipstick readings of 2+ or greater occurred in 14% of patients
260 receiving bolus-IFL plus placebo, 17% receiving bolus-IFL plus
261 AVASTIN, and in 28% of patients receiving 5-FU/LV plus AVASTIN.
262 Twenty-four-hour urine collections were obtained in patients with new
263 onset or worsening proteinuria. None of the 118 patients receiving
264 bolus-IFL plus placebo, three of 158 patients (2%) receiving
265 bolus-IFL plus AVASTIN, and two of 50 (4%) patients receiving
266 5-FU/LV plus AVASTIN who had a 24-hour collection experienced
267 NCI-CTC Grade 3 proteinuria (>3.5 gm protein/24 hours).

268 In a dose-ranging, placebo-controlled, randomized study of AVASTIN in
269 patients with metastatic renal cell carcinoma, an indication for which
270 AVASTIN is not approved, 24-hour urine collections were obtained in
271 approximately half the patients enrolled. Among patients in whom
272 24-hour urine collections were obtained, four of 19 (21%) patients
273 receiving AVASTIN at 10 mg/kg every two weeks, two of 14 (14%)
274 receiving AVASTIN at 3 mg/kg every two weeks, and none of the
275 15 placebo patients experienced NCI-CTC Grade 3 proteinuria (>3.5 gm
276 protein/24 hours).

277 Nephrotic syndrome occurred in five of 1032 (0.5%) patients receiving
278 AVASTIN in Genentech-sponsored studies. One patient died and one
279 required dialysis. In three patients, proteinuria decreased in severity
280 several months after discontinuation of AVASTIN. No patient had

281 normalization of urinary protein levels (by 24-hour urine) following
282 discontinuation of AVASTIN.

283 AVASTIN should be discontinued in patients with nephrotic syndrome.
284 The safety of continued AVASTIN treatment in patients with moderate to
285 severe proteinuria has not been evaluated. In most clinical studies,
286 AVASTIN was interrupted for ≥ 2 grams of proteinuria/24 hours and
287 resumed when proteinuria was < 2 gm/24 hours. Patients with moderate
288 to severe proteinuria based on 24-hour collections should be monitored
289 regularly until improvement and/or resolution is observed.

290 **Congestive Heart Failure**

291 Congestive heart failure (CHF), defined as NCI-CTC Grade 2–4 left
292 ventricular dysfunction, was reported in 22 of 1032 (2%) patients
293 receiving AVASTIN in Genentech-sponsored studies. Congestive heart
294 failure occurred in six of 44 (14%) patients receiving AVASTIN and
295 concurrent anthracyclines. Congestive heart failure occurred in 13 of 299
296 (4%) patients who received prior anthracyclines and/or left chest wall
297 irradiation. In a controlled study, the incidence was higher in patients
298 receiving AVASTIN plus chemotherapy as compared to patients receiving
299 chemotherapy alone. The safety of continuation or resumption of
300 AVASTIN in patients with cardiac dysfunction has not been studied.

301 **PRECAUTIONS**

302 **General**

303 AVASTIN should be used with caution in patients with known
304 hypersensitivity to AVASTIN or any component of this drug product.

305 **Infusion Reactions**

306 Infusion reactions with the first dose of AVASTIN were uncommon
307 ($< 3\%$). Severe reactions during the infusion of AVASTIN occurred in
308 two patients. One patient developed stridor and wheezing during their
309 first dose. A second patient, receiving paclitaxel followed by AVASTIN,
310 developed a Grade 3 hypersensitivity reaction requiring hospitalization

311 during their third infusion of AVASTIN. Both patients responded to
312 medical management. Information on rechallenge is not available.

313 AVASTIN infusion should be interrupted in all patients with severe
314 infusion reactions and appropriate medical therapy administered.

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

318 **Surgery**

319 AVASTIN therapy should not be initiated for at least 28 days following
320 major surgery. The surgical incision should be fully healed prior to
321 initiation of AVASTIN. Because of the potential for impaired wound
322 healing, AVASTIN should be suspended prior to elective surgery. The
323 appropriate interval between the last dose of AVASTIN and elective
324 surgery is unknown; however, the half-life of AVASTIN is estimated to be
325 20 days (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**) and
326 the interval chosen should take into consideration the half-life of the drug.
327 (See **WARNINGS: Gastrointestinal Perforations/Wound Healing**
328 **Complications.**)

329 **Cardiovascular Disease**

330 Patients were excluded from participation in AVASTIN clinical trials if, in
331 the previous year, they had experienced clinically significant
332 cardiovascular disease. Thus, the safety of AVASTIN in patients with
333 clinically significant cardiovascular disease has not been adequately
334 evaluated.

335 **Immunogenicity**

336 As with all therapeutic proteins, there is a potential for immunogenicity.
337 The incidence of antibody development in patients receiving AVASTIN
338 has not been adequately determined because the assay sensitivity was
339 inadequate to reliably detect lower titers. Enzyme-linked immunosorbant
340 assays (ELISAs) were performed on sera from approximately 500 patients

341 treated with AVASTIN, primarily in combination with chemotherapy.

342 High titer human anti-AVASTIN antibodies were not detected.

343 Immunogenicity data are highly dependent on the sensitivity and
344 specificity of the assay. Additionally, the observed incidence of antibody
345 positivity in an assay may be influenced by several factors, including
346 sample handling, timing of sample collection, concomitant medications,
347 and underlying disease. For these reasons, comparison of the incidence of
348 antibodies to AVASTIN with the incidence of antibodies to other products
349 may be misleading.

350 **Laboratory Tests**

351 Blood pressure monitoring should be conducted every two to three weeks
352 during treatment with AVASTIN. Patients who develop hypertension on
353 AVASTIN may require blood pressure monitoring at more frequent
354 intervals. Patients with AVASTIN-induced or -exacerbated hypertension
355 who discontinue AVASTIN should continue to have their blood pressure
356 monitored at regular intervals.

357 Patients receiving AVASTIN should be monitored for the development or
358 worsening of proteinuria with serial urinalyses. Patients with a 2+ or
359 greater urine dipstick reading should undergo further assessment, e.g., a
360 24-hour urine collection. (See **WARNINGS: Proteinuria** and **DOSAGE**
361 **AND ADMINISTRATION: Dose Modifications**.)

362 **Drug Interactions**

363 No formal drug interaction studies with anti-neoplastic agents have been
364 conducted. In Study 1, patients with colorectal cancer were given
365 irinotecan/5-FU/leucovorin (bolus-IFL) with or without AVASTIN.
366 Irinotecan concentrations were similar in patients receiving bolus-IFL
367 alone and in combination with AVASTIN. The concentrations of SN38,
368 the active metabolite of irinotecan, were on average 33% higher in patients
369 receiving bolus-IFL in combination with AVASTIN when compared with
370 bolus-IFL alone. In Study 1, patients receiving bolus-IFL plus AVASTIN

371 had a higher incidence of Grade 3–4 diarrhea and neutropenia. Due to
372 high inter-patient variability and limited sampling, the extent of the
373 increase in SN38 levels in patients receiving concurrent irinotecan and
374 AVASTIN is uncertain.

375 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

376 No carcinogenicity data are available for AVASTIN in animals or
377 humans.

378 AVASTIN may impair fertility. Dose-related decreases in ovarian and
379 uterine weights, endometrial proliferation, number of menstrual cycles, and
380 arrested follicular development or absent corpora lutea were observed in
381 female cynomolgus monkeys treated with 10 or 50 mg/kg of AVASTIN for
382 13 or 26 weeks. Following a 4- or 12-week recovery period, which
383 examined only the high-dose group, trends suggestive of reversibility were
384 noted in the two females for each regimen that were assigned to recover.
385 After the 12-week recovery period, follicular maturation arrest was no
386 longer observed, but ovarian weights were still moderately decreased.
387 Reduced endometrial proliferation was no longer observed at the 12-week
388 recovery time point, but uterine weight decreases were still notable,
389 corpora lutea were absent in 1 out of 2 animals, and the number of
390 menstrual cycles remained reduced (67%).

391 **Pregnancy Category C**

392 AVASTIN has been shown to be teratogenic in rabbits when administered
393 in doses that are two-fold greater than the recommended human dose on a
394 mg/kg basis. Observed effects included decreases in maternal and fetal
395 body weights, an increased number of fetal resorptions, and an increased
396 incidence of specific gross and skeletal fetal alterations. Adverse fetal
397 outcomes were observed at all doses tested.

398 Angiogenesis is critical to fetal development and the inhibition of
399 angiogenesis following administration of AVASTIN is likely to result in
400 adverse effects on pregnancy. There are no adequate and well-controlled

401 studies in pregnant women. AVASTIN should be used during pregnancy
402 or in any woman not employing adequate contraception only if the
403 potential benefit justifies the potential risk to the fetus. All patients should
404 be counseled regarding the potential risk of AVASTIN to the developing
405 fetus prior to initiation of therapy. If the patient becomes pregnant while
406 receiving AVASTIN, she should be apprised of the potential hazard to the
407 fetus and/or the potential risk of loss of pregnancy. Patients who
408 discontinue AVASTIN should also be counseled concerning the prolonged
409 exposure following discontinuation of therapy (half-life of approximately
410 20 days) and the possible effects of AVASTIN on fetal development.

411 **Nursing Mothers**

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

419 **Pediatric Use**

420 The safety and effectiveness of AVASTIN in pediatric patients has not
421 been studied. However, physcal dysplasia was observed in juvenile
422 cynomolgus monkeys with open growth plates treated for four weeks with
423 doses that were less than the recommended human dose based on mg/kg
424 and exposure. The incidence and severity of physcal dysplasia were
425 dose-related and were at least partially reversible upon cessation of
426 treatment.

427 **Geriatric Use**

428 In Study 1, NCI-CTC Grade 3-4 adverse events were collected in all
429 patients receiving study drug (396 bolus-IFL plus placebo; 392 bolus-IFL
430 plus AVASTIN; 109 5-FU/LV plus AVASTIN), while NCI-CTC Grade 1
431 and 2 adverse events were collected in a subset of 309 patients. There

432 were insufficient numbers of patients 65 years and older in the subset in
433 which Grade 1-4 adverse events were collected to determine whether the
434 overall adverse event profile was different in the elderly as compared to
435 younger patients. Among the 392 patients receiving bolus-IFL plus
436 AVASTIN, 126 were at least 65 years of age. Severe adverse events that
437 occurred at a higher incidence ($\geq 2\%$) in the elderly when compared to
438 those less than 65 years were asthenia, sepsis, deep thrombophlebitis,
439 hypertension, hypotension, myocardial infarction, congestive heart failure,
440 diarrhea, constipation, anorexia, leukopenia, anemia, dehydration,
441 hypokalemia, and hyponatremia. The effect of AVASTIN on overall
442 survival was similar in elderly patients as compared to younger patients.

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

450 **ADVERSE EVENTS**

451 The most serious adverse events associated with AVASTIN were:

- 452 • Gastrointestinal Perforations/Wound Healing Complications (see
453 **WARNINGS**)
- 454 • Hemorrhage (see **WARNINGS**)
- 455 • Hypertensive Crises (see **WARNINGS**)
- 456 • Nephrotic Syndrome (see **WARNINGS**)
- 457 • Congestive Heart Failure (see **WARNINGS**)

458 The most common severe (NCI-CTC Grade 3-4) adverse events among
459 1032 patients receiving AVASTIN in Genentech-sponsored studies were
460 asthenia, pain, hypertension, diarrhea, and leukopenia.

461 The most common adverse events of any severity among the 742 patients
462 receiving AVASTIN in Genentech-sponsored studies were asthenia, pain,
463 abdominal pain, headache, hypertension, diarrhea, nausea, vomiting,
464 anorexia, stomatitis, constipation, upper respiratory infection, epistaxis,
465 dyspnea, exfoliative dermatitis, and proteinuria.

466 Because clinical trials are conducted under widely varying conditions,
467 adverse reaction rates observed in the clinical trials of a drug cannot be
468 directly compared to rates in the clinical trials of another drug and may not
469 reflect the rates observed in practice. The adverse reaction information
470 from clinical trials does, however, provide a basis for identifying the
471 adverse events that appear to be related to drug use and for approximating
472 rates.

473 A total of 1032 patients with metastatic colorectal cancer (n=568) and
474 with other cancers (n=464) received AVASTIN either as a single agent
475 (n=157) or in combination with chemotherapy (n=875) in
476 Genentech-sponsored clinical trials. All adverse events were collected in
477 742 of the 1032 patients; for the remaining 290, all NCI-CTC Grade 3
478 and 4 adverse events and only selected Grade 1 and 2 adverse events
479 (hypertension, proteinuria, thromboembolic events) were collected.
480 Adverse events across all Genentech-sponsored studies were used to
481 further characterize specific adverse events. (See **WARNINGS:**
482 **Hemorrhage, Hypertension, Proteinuria, Congestive Heart Failure**
483 **and PRECAUTIONS: Geriatric Use.**)

484 Comparative data on adverse experiences, except where indicated, are
485 limited to Study 1, a randomized, active-controlled study in 897 patients
486 receiving initial treatment for metastatic colorectal cancer. All NCI-CTC
487 Grade 3 and 4 adverse events and selected Grade 1 and 2 adverse events
488 (hypertension, proteinuria, thromboembolic events) were reported for the
489 overall study population. In Study 1, the median age was 60, 60% were
490 male, 78% had colon primary lesion, and 29% had prior adjuvant or
491 neoadjuvant chemotherapy. The median duration of exposure to

AVASTIN in Study 1 was 8 months in Arm 2 and 7 months in Arm 3. All adverse events, including all NCI-CTC Grade 1 and 2 events, were reported in a subset of 309 patients. The baseline entry characteristics in the 309 patient safety subset were similar to the overall study population and well-balanced across the three study arms.

Severe and life-threatening (NCI-CTC Grade 3 and 4) adverse events, which occurred at a higher incidence ($\geq 2\%$) in patients receiving bolus-IFL plus AVASTIN as compared to bolus-IFL plus placebo, are presented in Table 4.

Table 4
NCI-CTC Grade 3 and 4 Adverse Events in Study 1
(Occurring at Higher Incidence ($\geq 2\%$) in 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>		
Deep Vein Thrombosis	19 (5%)	34 (9%)
Hypertension	10 (2%)	46 (12%)
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.

502 Adverse events of any severity, which occurred at a higher incidence
503 ($\geq 5\%$) in the initial phase of the study in patients receiving AVASTIN
504 (bolus-IFL plus AVASTIN or 5-FU/LV plus AVASTIN) as compared to
505 the bolus-IFL plus placebo arm, are presented in Table 5.

Table 5
NCI-CTC Grade 1–4 Adverse Events in Study 1 Subset
(Occurring at Higher Incidence (≥5%) in AVASTIN vs. Control)

	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>			
Asthenia	68 (70%)	75 (74%)	80 (73%)
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%)
Weight Loss	10 (10%)	15 (15%)	18 (16%)
Flatulence	10 (10%)	11 (11%)	21 (19%)
GI Hemorrhage	6 (6%)	25 (24%)	21 (19%)
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>Metabolic/Nutrition</u>			
Hypokalemia	11 (11%)	12 (12%)	18 (16%)
Bilirubinemia	0	1 (1%)	7 (6%)
<u>Musculoskeletal</u>			
Myalgia	7 (7%)	8 (8%)	16 (15%)
<u>Nervous</u>			
Dizziness	20 (20%)	27 (26%)	21 (19%)
Confusion	1 (1%)	1 (1%)	6 (6%)
Abnormal Gait	0	1 (1%)	5 (5%)

506

Table 5 (cont'd)
NCI-CTC Grade 1–4 Adverse Events in Study 1 Subset

	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%)
Dyspnea	15 (15%)	26 (26%)	27 (25%)
Epistaxis	10 (10%)	36 (35%)	35 (32%)
Voice Alteration	2 (2%)	9 (9%)	6 (6%)
<u>Skin/Appendages</u>			
Alopecia	25 (26%)	33 (32%)	6 (6%)
Dry Skin	7 (7%)	7 (7%)	22 (20%)
Exfoliative Dermatitis	3 (3%)	3 (3%)	21 (19%)
Nail Disorder	3 (3%)	2 (2%)	9 (8%)
Skin Discoloration	3 (3%)	2 (2%)	17 (16%)
Skin Ulcer	1 (1%)	6 (6%)	7 (6%)
<u>Special Senses</u>			
Taste Disorder	9 (9%)	14 (14%)	23 (21%)
Excess Lacrimation	2 (2%)	6 (6%)	20 (18%)
<u>Urogenital</u>			
Proteinuria	24 (24%)	37 (36%)	39 (36%)
Urinary Frequency/Urgency	1 (1%)	3 (3%)	6 (6%)

507

508 **Mucocutaneous Hemorrhage**

509 In Study 1, both serious and non-serious hemorrhagic events occurred at a
510 higher incidence in patients receiving AVASTIN. (See **WARNINGS:**
511 **Hemorrhage.**) In the 309 patients in which Grade 1–4 events were
512 collected, epistaxis was common and reported in 35% of patients receiving
513 bolus-IFL plus AVASTIN compared with 10% of patients receiving
514 bolus-IFL plus placebo. These events were generally mild in severity
515 (NCI–CTC Grade 1) and resolved without medical intervention. Other
516 mild to moderate hemorrhagic events reported more frequently in patients
517 receiving bolus-IFL plus AVASTIN when compared to those receiving
518 bolus-IFL plus placebo included gastrointestinal hemorrhage (24% vs.

519 6%), minor gum bleeding (2% vs. 0), and vaginal hemorrhage (4% vs.
520 2%).

521 **Thromboembolism**

522 In Study 1, 18% of patients receiving bolus-IFL plus AVASTIN and 15%
523 of patients receiving bolus-IFL plus placebo experienced a Grade 3–4
524 thromboembolic event. The incidence of the following Grade 3 and 4
525 thromboembolic events were higher in patients receiving bolus-IFL plus
526 AVASTIN as compared to patients receiving bolus-IFL plus placebo:
527 cerebrovascular events (4 vs. 0 patients), myocardial infarction (6 vs. 3),
528 deep venous thrombosis (34 vs. 19), and intra-abdominal thrombosis (13
529 vs. 5). In contrast, the incidence of pulmonary embolism was higher in
530 patients receiving bolus-IFL plus placebo (16 vs. 20).

531 In Study 1, 53 of 392 (14%) patients who received bolus-IFL plus
532 AVASTIN and 30 of 396 (8%) patients who received bolus-IFL plus
533 placebo had a thromboembolic event and received full-dose warfarin.
534 Two patients in each treatment arm (four total) developed bleeding
535 complications. In the two patients treated with full-dose warfarin and
536 AVASTIN, these events were associated with marked elevations in their
537 INR. Eleven of 53 (21%) patients receiving bolus-IFL plus AVASTIN
538 and one of 30 (3%) patients receiving bolus-IFL developed an additional
539 thromboembolic event.

540 **Other Serious Adverse Events**

541 The following other serious adverse events are considered unusual in
542 cancer patients receiving cytotoxic chemotherapy and occurred in at least
543 one subject treated with AVASTIN in clinical studies.

544 *Body as a Whole: polyserositis*

545 *Digestive: intestinal obstruction, intestinal necrosis, mesenteric venous*
546 *occlusion, anastomotic ulceration*

547 *Hemic and lymphatic: pancytopenia*

548 *Metabolic and nutritional disorders: hyponatremia.*

549 *Urogenital: ureteral stricture*

550 **OVERDOSAGE**

551 The maximum tolerated dose of AVASTIN has not been determined. The
552 highest dose tested in humans (20 mg/kg IV) was associated with
553 headache in nine of 16 patients and with severe headache in three of
554 16 patients.

555 **DOSAGE AND ADMINISTRATION**

556 The recommended dose of AVASTIN is 5 mg/kg given once every
557 14 days as an IV infusion until disease progression is detected.

558 AVASTIN therapy should not be initiated for at least 28 days following
559 major surgery. The surgical incision should be fully healed prior to
560 initiation of AVASTIN.

561 **Dose Modifications**

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

565 AVASTIN should be permanently discontinued in patients who develop
566 gastrointestinal perforation, wound dehiscence requiring medical
567 intervention, serious bleeding, nephrotic syndrome, or hypertensive crisis.

568 Temporary suspension of AVASTIN is recommended in patients with
569 evidence of moderate to severe proteinuria pending further evaluation and
570 in patients with severe hypertension that is not controlled with medical
571 management. The risk of continuation or temporary suspension of
572 AVASTIN in patients with moderate to severe proteinuria is unknown.

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

577 **Preparation for Administration**

578 AVASTIN should be diluted for infusion by a healthcare professional
579 using aseptic technique. Withdraw the necessary amount of AVASTIN
580 for a dose of 5 mg/kg and dilute in a total volume of 100 mL of 0.9%
581 Sodium Chloride Injection, USP. Discard any unused portion left in a
582 vial, as the product contains no preservatives. Parenteral drug products
583 should be inspected visually for particulate matter and discoloration prior
584 to administration.

585 Diluted AVASTIN solutions for infusion may be stored at 2–8°C
586 (36–46°F) for up to 8 hours. No incompatibilities between AVASTIN and
587 polyvinylchloride or polyolefin bags have been observed.

588 **AVASTIN infusions should not be administered or mixed with**
589 **dextrose solutions.**

590 **Administration**

591 **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** The initial
592 AVASTIN dose should be delivered over 90 minutes as an IV infusion
593 following chemotherapy. If the first infusion is well tolerated, the second
594 infusion may be administered over 60 minutes. If the 60-minute infusion
595 is well tolerated, all subsequent infusions may be administered over
596 30 minutes.

597 **Stability and Storage**

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

601 **HOW SUPPLIED**

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

- 605 Single unit 100 mg carton: Contains one 4 mL vial of AVASTIN
606 (25 mg/mL). NDC 50242-060-01
- 607 Single unit 400 mg carton: Contains one 16 mL vial of AVASTIN
608 (25 mg/mL). NDC 50242-060-02

609 **REFERENCES**

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AVASTIN™

(Bevacizumab)

For Intravenous Use

Manufactured by:

Genentech, Inc.

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G#####-R0

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