

4-18-06

1 **1.14.2.3.3 Final Clean Package Insert (USPI)**

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.**)

33 **DESCRIPTION**

34 AVASTIN[®] (Bevacizumab) is a recombinant humanized monoclonal
35 IgG1 antibody that binds to and inhibits the biologic activity of human
36 vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay
37 systems. Bevacizumab contains human framework regions and the
38 complementarity-determining regions of a murine antibody that binds to
39 VEGF (1). Bevacizumab is produced in a Chinese Hamster Ovary
40 mammalian cell expression system in a nutrient medium containing the
41 antibiotic gentamicin and has a molecular weight of approximately
42 149 kilodaltons. AVASTIN is a clear to slightly opalescent, colorless to
43 pale brown, sterile, pH 6.2 solution for intravenous (IV) infusion.

44 AVASTIN is supplied in 100 mg and 400 mg preservative-free, single-use
45 vials to deliver 4 mL or 16 mL of AVASTIN (25 mg/mL). The 100 mg
46 product is formulated in 240 mg α,α -trehalose dihydrate, 23.2 mg sodium
47 phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic,
48 anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The
49 400 mg product is formulated in 960 mg α,α -trehalose dihydrate, 92.8 mg
50 sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate
51 (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water for Injection,
52 USP.

53 **CLINICAL PHARMACOLOGY**

54 **Mechanism of Action**

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

62 **Pharmacokinetics**

63 The pharmacokinetic profile of Bevacizumab was assessed using an assay
64 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.

93 **CLINICAL STUDIES**

94 The safety and efficacy of AVASTIN in the initial treatment of patients
95 with metastatic carcinoma of the colon or rectum were studied in two
96 randomized, controlled clinical trials in combination with intravenous
97 5-fluorouracil-based chemotherapy. The activity of AVASTIN in patients
98 with refractory metastatic colorectal cancer was evaluated in a third, open-
99 access trial in combination with intravenous 5-fluorouracil-based
100 chemotherapy.

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

102 Study 1 was a randomized, double-blind, active-controlled clinical trial
103 evaluating AVASTIN as first-line treatment of metastatic carcinoma of the
104 colon or rectum. Patients were randomized to bolus-IFL (irinotecan
105 125 mg/m² IV, 5-fluorouracil 500 mg/m² IV, and leucovorin 20 mg/m² IV
106 given once weekly for 4 weeks every 6 weeks) plus placebo (Arm 1),
107 bolus-IFL plus AVASTIN (5 mg/kg every 2 weeks) (Arm 2), or 5-FU/LV
108 plus AVASTIN (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3
109 was discontinued, as pre-specified, when the toxicity of AVASTIN in
110 combination with the bolus-IFL regimen was deemed acceptable.

111 Of the 813 patients randomized to Arms 1 and 2, the median age was 60,
112 40% were female, and 79% were Caucasian. Fifty-seven percent had an
113 ECOG performance status of 0. Twenty-one percent had a rectal primary
114 and 28% received prior adjuvant chemotherapy. In the majority of
115 patients, 56%, the dominant site of disease was extra-abdominal, while the
116 liver was the dominant site in 38% of patients. The patient characteristics
117 were similar across the study arms. The primary endpoint of this trial was
118 overall survival. Results are presented in Table 1 and Figure 1.

Table 1
Study 1 Efficacy Results

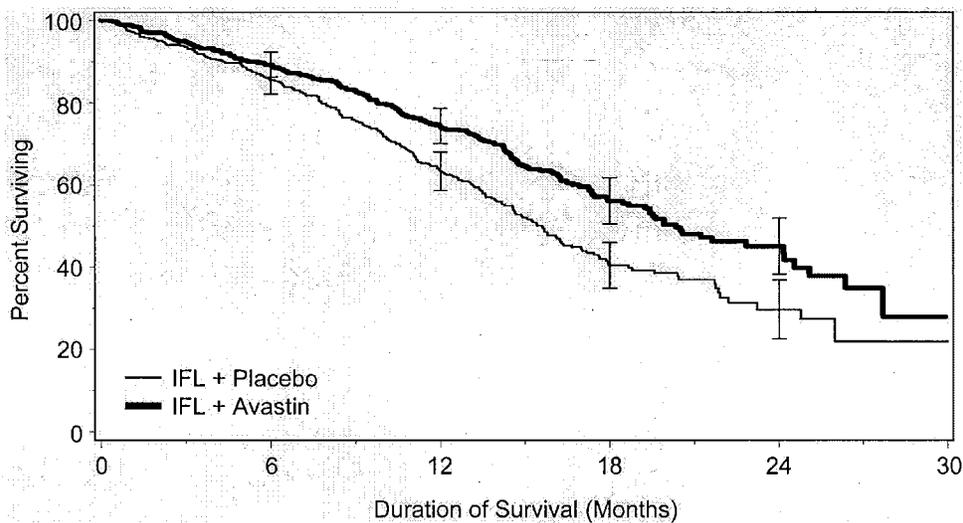
	IFL + Placebo	IFL + AVASTIN 5 mg/kg q 2 wks
Number of Patients	411	402
<u>Overall Survival^a</u>		
Median (months)	15.6	20.3
Hazard ratio		0.66
<u>Progression-Free Survival^a</u>		
Median (months)	6.2	10.6
Hazard ratio		0.54
<u>Overall Response Rate^b</u>		
Rate (percent)	35%	45%
<u>Duration of Response</u>		
Median (months)	7.1	10.4

^a p < 0.001 by stratified logrank test.

^b p < 0.01 by χ^2 test.

119
120
121

Figure 1
Duration of Survival in Study 1



122
123
124

Error bars represent 95% confidence intervals.

125 The clinical benefit of AVASTIN, as measured by survival in the two
126 principal arms, was seen in all subgroups tested. The subgroups examined
127 were based on age, sex, race, ECOG performance status, location of
128 primary tumor, prior adjuvant therapy, number of metastatic sites, and
129 tumor burden.

130 Among the 110 patients enrolled in Arm 3, median overall survival was
131 18.3 months, median progression-free survival was 8.8 months, overall
132 response rate was 39%, and median duration of response was 8.5 months.

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

134 Study 2 was a randomized, active-controlled clinical trial testing
135 AVASTIN in combination with 5-FU/LV as first-line treatment of
136 metastatic colorectal cancer. Patients were randomized to receive
137 5-FU/LV (5-fluorouracil 500 mg/m², leucovorin 500 mg/m² weekly for
138 6 weeks every 8 weeks) or 5-FU/LV plus AVASTIN (5 mg/kg every
139 2 weeks) or 5-FU/LV plus AVASTIN (10 mg/kg every 2 weeks). Patients
140 were treated until disease progression. The primary endpoints of the trial
141 were objective response rate and progression-free survival. Results are
142 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

143

144 Progression-free survival was significantly better in patients receiving
145 5-FU/LV plus AVASTIN at 5 mg/kg when compared to those not
146 receiving AVASTIN. However, overall survival and overall response rate
147 were not significantly different. Outcomes for patients receiving 5-FU/LV
148 plus AVASTIN at 10 mg/kg were not significantly different than for
149 patients who did not receive AVASTIN.

150 **AVASTIN in Refractory Metastatic Colorectal Cancer**

151 Study 3 was a multi-center, single arm study that evaluated the activity of
152 AVASTIN in combination with 5-FU/LV in 339 patients with metastatic
153 colorectal cancer with disease progression following both irinotecan- and
154 oxaliplatin-containing chemotherapy regimens. The majority (73%) of
155 patients received concurrent 5-FU/LV according to a bolus regimen. There
156 was one objective partial response in the first 100 evaluable patients, for
157 an overall response rate of 1% (95% CI 0–5.5%). The nature and severity
158 of the adverse events observed in this trial were similar to that seen in the
159 controlled clinical trials of AVASTIN.

160 **AVASTIN as a Single Agent**

161 The efficacy of AVASTIN as a single agent in colorectal cancer has not
162 been established. However, in an ongoing, randomized study of patients
163 with metastatic colorectal cancer that had progressed following a
164 5-fluorouracil and irinotecan-based regimen, the arm in which patients
165 were treated with single-agent AVASTIN was closed early due to
166 evidence of an inferior survival in that arm as compared with patients
167 treated with the FOLFOX regimen of 5-fluorouracil, leucovorin, and
168 oxaliplatin.

169 **INDICATIONS AND USAGE**

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

173 **CONTRAINDICATIONS**

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

175 **WARNINGS**

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

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

182 In Study 1, one of 396 (0.3%) patients receiving bolus-IFL plus placebo,
183 six of 392 (2%) patients receiving bolus-IFL plus AVASTIN, and four of
184 109 (4%) patients receiving 5-FU/LV plus AVASTIN developed
185 gastrointestinal perforation, in some instances with fatal outcome. These
186 episodes occurred with or without intra-abdominal abscesses and at
187 various time points during treatment. The typical presentation was
188 reported as abdominal pain associated with symptoms such as constipation
189 and vomiting.

190 In postmarketing clinical studies and reports, gastrointestinal perforation,
191 fistula and/or intra-abdominal abscess occurred in patients receiving
192 AVASTIN for colorectal and for other types of cancer. The overall
193 incidence in clinical studies was 1%, but may be higher in some cancer
194 settings. Of the reported events, approximately 30% were fatal. Patients
195 with gastrointestinal perforation, regardless of underlying cancer, typically
196 present with abdominal pain, nausea and fever. Events were reported at
197 various time points during treatment ranging from one week to greater
198 than 1 year from initiation of AVASTIN, with most events occurring
199 within the first 50 days.

200 In addition, two of 396 (0.5%) patients receiving bolus-IFL plus placebo,
201 four of 392 (1%) patients receiving bolus-IFL plus AVASTIN, and one of
202 109 (1%) patients receiving 5-FU/LV plus AVASTIN developed a wound
203 dehiscence during study treatment.

204 The appropriate interval between surgery and subsequent initiation of
205 AVASTIN required to avoid the risks of impaired wound healing has not
206 been determined. In Study 1, the clinical protocol did not permit initiation
207 of AVASTIN for at least 28 days following surgery. There was one
208 patient (among 501 patients receiving AVASTIN on Study 1) in whom an
209 anastomotic dehiscence occurred when AVASTIN was initiated per
210 protocol. In this patient, the interval between surgery and initiation of
211 AVASTIN was greater than 2 months.

212 Similarly, the appropriate interval between termination of AVASTIN and
213 subsequent elective surgery required to avoid the risks of impaired wound
214 healing has not been determined. In Study 1, 39 patients who were
215 receiving bolus-IFL plus AVASTIN underwent surgery following
216 AVASTIN therapy and, of these patients, six (15%) had wound
217 healing/bleeding complications. In the same study, 25 patients in the
218 bolus-IFL arm underwent surgery and, of these patients, one of 25 (4%)
219 had wound healing/bleeding complications. The longest interval between
220 last dose of study drug and dehiscence was 56 days; this occurred in a
221 patient on the bolus-IFL plus AVASTIN arm. The interval between
222 termination of AVASTIN and subsequent elective surgery should take into
223 consideration the calculated half-life of AVASTIN (approximately
224 20 days).

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

227 **Hemorrhage (See DOSAGE AND ADMINISTRATION: Dose**
228 **Modifications)**

229 Two distinct patterns of bleeding have occurred in patients receiving
230 AVASTIN. The first is minor hemorrhage, most commonly Grade 1
231 epistaxis. The second is serious, and in some cases fatal, hemorrhagic
232 events. Serious hemorrhagic events occurred primarily in patients with
233 non-small cell lung cancer, an indication for which AVASTIN is not
234 approved. In a randomized study in patients with non-small cell lung

235 cancer receiving chemotherapy with or without AVASTIN, four of
236 13 (31%) AVASTIN-treated patients with squamous cell histology and
237 two of 53 (4%) AVASTIN-treated patients with non-squamous histology
238 experienced life-threatening or fatal pulmonary hemorrhage as compared
239 to none of the 32 (0%) patients receiving chemotherapy alone. Of the
240 patients experiencing events of life-threatening pulmonary hemorrhage,
241 many had cavitation and/or necrosis of the tumor, either pre-existing or
242 developing during AVASTIN therapy. These serious hemorrhagic events
243 occurred suddenly and presented as major or massive hemoptysis.

244 The risk of central nervous system (CNS) bleeding in patients with CNS
245 metastases receiving AVASTIN has not been evaluated because these
246 patients were excluded from Genentech-sponsored studies following
247 development of CNS hemorrhage in a patient with a CNS metastasis in
248 Phase 1 studies.

249 Other serious bleeding events reported in patients receiving AVASTIN
250 were uncommon and included gastrointestinal hemorrhage, subarachnoid
251 hemorrhage, and hemorrhagic stroke.

252 Patients with serious hemorrhage i.e., requiring medical intervention,
253 should have AVASTIN treatment discontinued and receive aggressive
254 medical management. Patients with recent hemoptysis should not receive
255 AVASTIN.

256 **Arterial Thromboembolic Events (see DOSAGE AND**
257 **ADMINISTRATION: Dose Modifications, and PRECAUTIONS:**
258 **Geriatric Use)**

259 Arterial thromboembolic events occurred at a higher incidence in patients
260 receiving AVASTIN in combination with chemotherapy as compared to
261 those receiving chemotherapy alone. Arterial thromboembolic events
262 included cerebral infarction, transient ischemic attacks (TIAs), myocardial
263 infarction (MI), angina, and a variety of other arterial thromboembolic
264 events. These events were fatal in some instances.

265 In an exploratory analysis pooling the data from five randomized,
 266 controlled, clinical trials involving 1745 patients, the overall incidence of
 267 arterial thromboembolic events was increased (4.4% vs. 1.9%) among the
 268 963 patients treated with AVASTIN in combination with chemotherapy as
 269 compared to 782 patients treated with chemotherapy alone. Fatal outcomes
 270 from arterial thromboembolic events occurred in 7 of 963 patients (0.7%)
 271 who were treated with AVASTIN in combination with chemotherapy,
 272 compared to 3 of 782 patients (0.4%) who were treated with chemotherapy
 273 alone. The incidences of both cerebrovascular arterial events (1.9% vs.
 274 0.5%) and cardiovascular arterial events (2.1% vs. 1.0%) were increased
 275 in patients receiving AVASTIN. In addition, there was a correlation
 276 between age (65 years and over) and the increase in risk of
 277 thromboembolic events (See PRECAUTIONS: Geriatric Use).

278 The safety of resumption of AVASTIN therapy after resolution of an
 279 arterial thromboembolic event has not been studied. AVASTIN therapy
 280 should be permanently discontinued in patients who experience a severe
 281 arterial thromboembolic event during treatment.

282 **Hypertension (See DOSAGE AND ADMINISTRATION: Dose**
 283 **Modifications)**

284 The incidence of hypertension and severe hypertension was increased in
 285 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.

286

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

290 Medication classes used for management of patients with Grade 3
291 hypertension receiving AVASTIN included angiotensin-converting
292 enzyme inhibitors, beta blockers, diuretics, and calcium channel blockers.
293 Four months after discontinuation of therapy, persistent hypertension was
294 present in 18 of 26 patients that received bolus-IFL plus AVASTIN and
295 8 of 10 patients that received bolus-IFL plus placebo.

296 Across pooled clinical studies (n=1032), development or worsening of
297 hypertension resulted in hospitalization or discontinuation of AVASTIN in
298 17 patients. Four of these 17 patients developed hypertensive
299 encephalopathy. Severe hypertension was complicated by subarachnoid
300 hemorrhage in one patient.

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

305 AVASTIN should be permanently discontinued in patients with
306 hypertensive crisis. Temporary suspension is recommended in patients
307 with severe hypertension that is not controlled with medical management.

308 **Proteinuria (See DOSAGE AND ADMINISTRATION: Dose**
309 **Modifications)**

310 In Study 1, both the incidence and severity of proteinuria (defined as a
311 urine dipstick reading of 1+ or greater) was increased in patients receiving
312 AVASTIN as compared to those receiving bolus-IFL plus placebo.
313 Urinary dipstick readings of 2+ or greater occurred in 14% of patients
314 receiving bolus-IFL plus placebo, 17% receiving bolus-IFL plus
315 AVASTIN, and in 28% of patients receiving 5-FU/LV plus AVASTIN.

316 Twenty-four-hour urine collections were obtained in patients with new
317 onset or worsening proteinuria. None of the 118 patients receiving
318 bolus-IFL plus placebo, three of 158 patients (2%) receiving
319 bolus-IFL plus AVASTIN, and two of 50 (4%) patients receiving
320 5-FU/LV plus AVASTIN who had a 24-hour collection experienced
321 NCI-CTC Grade 3 proteinuria (>3.5 gm protein/24 hours).

322 In a dose-ranging, placebo-controlled, randomized study of AVASTIN in
323 patients with metastatic renal cell carcinoma, an indication for which
324 AVASTIN is not approved, 24-hour urine collections were obtained in
325 approximately half the patients enrolled. Among patients in whom
326 24-hour urine collections were obtained, four of 19 (21%) patients
327 receiving AVASTIN at 10 mg/kg every two weeks, two of 14 (14%)
328 receiving AVASTIN at 3 mg/kg every two weeks, and none of the
329 15 placebo patients experienced NCI-CTC Grade 3 proteinuria (>3.5 gm
330 protein/24 hours).

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

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

344 **Congestive Heart Failure**

345 Congestive heart failure (CHF), defined as NCI-CTC Grade 2–4 left
346 ventricular dysfunction, was reported in 22 of 1032 (2%) patients
347 receiving AVASTIN in Genentech-sponsored studies. Congestive heart
348 failure occurred in six of 44 (14%) patients receiving AVASTIN and
349 concurrent anthracyclines. Congestive heart failure occurred in 13 of 299
350 (4%) patients who received prior anthracyclines and/or left chest wall
351 irradiation. In a controlled study, the incidence was higher in patients
352 receiving AVASTIN plus chemotherapy as compared to patients receiving
353 chemotherapy alone. The safety of continuation or resumption of
354 AVASTIN in patients with cardiac dysfunction has not been studied.

355 **PRECAUTIONS**

356 **General**

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

359 **Infusion Reactions**

360 In clinical studies, infusion reactions with the first dose of AVASTIN
361 were uncommon (< 3%) and severe reactions occurred in 0.2% of patients.
362 Infusion reactions reported in the clinical trials and postmarketing
363 experience include hypertension, hypertensive crises associated with
364 neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3
365 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. Adequate
366 information on rechallenge is not available. AVASTIN infusion should be
367 interrupted in all patients with severe infusion reactions and appropriate
368 medical therapy administered.

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

372 **Surgery**

373 AVASTIN therapy should not be initiated for at least 28 days following
374 major surgery. The surgical incision should be fully healed prior to

375 initiation of AVASTIN. Because of the potential for impaired wound
376 healing, AVASTIN should be suspended prior to elective surgery. The
377 appropriate interval between the last dose of AVASTIN and elective
378 surgery is unknown; however, the half-life of AVASTIN is estimated to be
379 20 days (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**) and
380 the interval chosen should take into consideration the half-life of the drug.
381 (See **WARNINGS: Gastrointestinal Perforations/Wound Healing**
382 **Complications.**)

383 **Cardiovascular Disease**

384 Patients were excluded from participation in AVASTIN clinical trials if, in
385 the previous year, they had experienced clinically significant
386 cardiovascular disease. In an exploratory analysis pooling the data from
387 five randomized, placebo-controlled, clinical trials conducted in patients
388 without a recent history of clinically significant cardiovascular disease, the
389 overall incidence of arterial thromboembolic events, the incidence of fatal
390 arterial thromboembolic events, and the incidence of cardiovascular
391 thromboembolic events were increased in patients receiving AVASTIN
392 plus chemotherapy as compared to chemotherapy alone.

393 **Immunogenicity**

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

401 Immunogenicity data are highly dependent on the sensitivity and
402 specificity of the assay. Additionally, the observed incidence of antibody
403 positivity in an assay may be influenced by several factors, including
404 sample handling, timing of sample collection, concomitant medications,
405 and underlying disease. For these reasons, comparison of the incidence of

406 antibodies to AVASTIN with the incidence of antibodies to other products
407 may be misleading.

408 **Laboratory Tests**

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

415 Patients receiving AVASTIN should be monitored for the development or
416 worsening of proteinuria with serial urinalyses. Patients with a 2+ or
417 greater urine dipstick reading should undergo further assessment, e.g., a
418 24-hour urine collection. (See **WARNINGS: Proteinuria** and **DOSAGE**
419 **AND ADMINISTRATION: Dose Modifications**.)

420 **Drug Interactions**

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

433 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

434 No carcinogenicity data are available for AVASTIN in animals or
435 humans.

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

449 **Pregnancy Category C**

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

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

467 exposure following discontinuation of therapy (half-life of approximately
468 20 days) and the possible effects of AVASTIN on fetal development.

469 **Nursing Mothers**

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

477 **Pediatric Use**

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

485 **Geriatric Use**

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

498 diarrhea, constipation, anorexia, leukopenia, anemia, dehydration,
499 hypokalemia, and hyponatremia. The effect of AVASTIN on overall
500 survival was similar in elderly patients as compared to younger patients.

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

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

517 **ADVERSE EVENTS**

518 The most serious adverse events associated with AVASTIN were:

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

526 The most common severe (NCI-CTC Grade 3–4) adverse events among
527 1032 patients receiving AVASTIN in Genentech-sponsored studies were
528 asthenia, pain, hypertension, diarrhea, and leukopenia.

529 The most common adverse events of any severity among 742 patients
530 receiving AVASTIN in Genentech-sponsored studies were asthenia, pain,
531 abdominal pain, headache, hypertension, diarrhea, nausea, vomiting,
532 anorexia, stomatitis, constipation, upper respiratory infection, epistaxis,
533 dyspnea, exfoliative dermatitis, and proteinuria.

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

541 In pooled safety data, 1032 patients with metastatic colorectal cancer
542 (n=568) and with other cancers (n=464) received AVASTIN either as a
543 single agent (n=157) or in combination with chemotherapy (n=875) in
544 Genentech-sponsored clinical trials. All adverse events were collected in
545 742 of the 1032 patients; for the remaining 290, all NCI-CTC Grade 3
546 and 4 adverse events and only selected Grade 1 and 2 adverse events
547 (hypertension, proteinuria, thromboembolic events) were collected.
548 Adverse events across all Genentech-sponsored studies were used to
549 further characterize specific adverse events. (See **WARNINGS:**
550 **Hemorrhage, Arterial Thromboembolic Events, Hypertension,**
551 **Proteinuria, Congestive Heart Failure** and **PRECAUTIONS:**
552 **Geriatric Use.**)

553 Comparative data on adverse experiences, except where indicated, are
554 limited to Study 1, a randomized, active-controlled study in 897 patients
555 receiving initial treatment for metastatic colorectal cancer. All NCI-CTC

556 Grade 3 and 4 adverse events and selected Grade 1 and 2 adverse events
557 (hypertension, proteinuria, thromboembolic events) were reported for the
558 overall study population. In Study 1, the median age was 60, 60% were
559 male, 78% had colon primary lesion, and 29% had prior adjuvant or
560 neoadjuvant chemotherapy. The median duration of exposure to
561 AVASTIN in Study 1 was 8 months in Arm 2 and 7 months in Arm 3. All
562 adverse events, including all NCI-CTC Grade 1 and 2 events, were
563 reported in a subset of 309 patients. The baseline entry characteristics in
564 the 309 patient safety subset were similar to the overall study population
565 and well-balanced across the three study arms.

566 Severe and life-threatening (NCI-CTC Grade 3 and 4) adverse events,
567 which occurred at a higher incidence ($\geq 2\%$) in patients receiving
568 bolus-IFL plus AVASTIN as compared to bolus-IFL plus placebo, are
569 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.

570

571 Adverse events of any severity, which occurred at a higher incidence
 572 ($\geq 5\%$) in the initial phase of the study in patients receiving AVASTIN
 573 (bolus-IFL plus AVASTIN or 5-FU/LV plus AVASTIN) as compared to
 574 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 ($\geq 5\%$) 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%)

Table 5 (cont'd)
 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>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%)

576

577 **Mucocutaneous Hemorrhage**

578 In Study 1, both serious and non-serious hemorrhagic events occurred at a
 579 higher incidence in patients receiving AVASTIN. (See **WARNINGS:**
 580 **Hemorrhage**.) In the 309 patients in which Grade 1–4 events were
 581 collected, epistaxis was common and reported in 35% of patients receiving
 582 bolus-IFL plus AVASTIN compared with 10% of patients receiving
 583 bolus-IFL plus placebo. These events were generally mild in severity
 584 (NCI–CTC Grade 1) and resolved without medical intervention. Other
 585 mild to moderate hemorrhagic events reported more frequently in patients
 586 receiving bolus-IFL plus AVASTIN when compared to those receiving
 587 bolus-IFL plus placebo included gastrointestinal hemorrhage

588 (24% vs. 6%), minor gum bleeding (2% vs. 0), and vaginal hemorrhage
589 (4% vs. 2%).

590 **Venous Thromboembolic Events**

591 In Study 1, 15.1% of patients receiving bolus-IFL plus AVASTIN and
592 13.6% of patients receiving bolus-IFL plus placebo experienced a
593 Grade 3–4 venous thromboembolic event. The incidence of the following
594 Grade 3 and 4 venous thromboembolic events was higher in patients
595 receiving bolus-IFL plus AVASTIN as compared to patients receiving
596 bolus-IFL plus placebo: deep venous thrombosis (34 vs. 19 patients) and
597 intra-abdominal venous thrombosis (10 vs. 5 patients). The incidence of
598 pulmonary embolism was higher in patients receiving bolus-IFL plus
599 placebo (16 vs. 20 patients).

600 In Study 1, 53 of 392 (14%) patients who received bolus-IFL plus
601 AVASTIN and 30 of 396 (8%) patients who received bolus-IFL plus
602 placebo had a thromboembolic event and received full-dose warfarin.
603 Two patients in each treatment arm (four total) developed bleeding
604 complications. In the two patients treated with full-dose warfarin and
605 AVASTIN, these events were associated with marked elevations in their
606 INR. Eleven of 53 (21%) patients receiving bolus-IFL plus AVASTIN
607 and one of 30 (3%) patients receiving bolus-IFL developed an additional
608 thromboembolic event.

609 **Other Serious Adverse Events**

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

613 *Body as a Whole: polyserositis*

614 *Digestive: intestinal obstruction, intestinal necrosis, mesenteric venous*
615 *occlusion, anastomotic ulceration*

616 *Hemic and lymphatic: pancytopenia*

617 *Metabolic and nutritional disorders: hyponatremia.*

618 *Urogenital: ureteral stricture*

619 **OVERDOSAGE**

620 The maximum tolerated dose of AVASTIN has not been determined. The
621 highest dose tested in humans (20 mg/kg IV) was associated with
622 headache in nine of 16 patients and with severe headache in three of
623 16 patients.

624 **DOSAGE AND ADMINISTRATION**

625 The recommended dose of AVASTIN is 5 mg/kg given once every
626 14 days as an IV infusion until disease progression is detected.

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

630 **Dose Modifications**

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

634 AVASTIN should be permanently discontinued in patients who develop
635 gastrointestinal perforation, wound dehiscence requiring medical
636 intervention, serious bleeding, a severe arterial thromboembolic event,
637 nephrotic syndrome, or hypertensive crisis.

638 Temporary suspension of AVASTIN is recommended in patients with
639 evidence of moderate to severe proteinuria pending further evaluation and
640 in patients with severe hypertension that is not controlled with medical
641 management. The risk of continuation or temporary suspension of
642 AVASTIN in patients with moderate to severe proteinuria is unknown.

643 AVASTIN should be suspended at least several weeks prior to elective
644 surgery. (See **WARNINGS: Gastrointestinal Perforation/Wound**

645 **Healing Complications and PRECAUTIONS: Surgery.) AVASTIN**
646 should not be resumed until the surgical incision is fully healed.

647 **Preparation for Administration**

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

655 Diluted AVASTIN solutions for infusion may be stored at 2–8°C
656 (36–46°F) for up to 8 hours. No incompatibilities between AVASTIN and
657 polyvinylchloride or polyolefin bags have been observed.

658 **AVASTIN infusions should not be administered or mixed with**
659 **dextrose solutions.**

660 **Administration**

661 **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** The initial
662 AVASTIN dose should be delivered over 90 minutes as an IV infusion
663 following chemotherapy. If the first infusion is well tolerated, the second
664 infusion may be administered over 60 minutes. If the 60-minute infusion
665 is well tolerated, all subsequent infusions may be administered over
666 30 minutes.

667 **Stability and Storage**

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

671 **HOW SUPPLIED**

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

675 Single unit 100 mg carton: Contains one 4 mL vial of AVASTIN
676 (25 mg/mL). NDC 50242-060-01

677 Single unit 400 mg carton: Contains one 16 mL vial of AVASTIN
678 (25 mg/mL). NDC 50242-061-01

679 **REFERENCES**

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684

AVASTIN®

(Bevacizumab)

For Intravenous Use

Manufactured by:

Genentech, Inc.

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7455303

LV0017

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FDA Approval Date: April 2006

Code Revision Date: April 2006

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