

1 **1.14.1.3 Draft Labeling Text**

2 **Avastin®**
3 **(Bevacizumab)**

4 **For Intravenous Use**

5 **WARNINGS**

6 **Gastrointestinal Perforations**

7 Avastin administration can result in the development of
8 gastrointestinal perforation, in some instances resulting in fatality.
9 Gastrointestinal perforation, sometimes associated with
10 intra-abdominal abscess, occurred throughout treatment with Avastin
11 (i.e., was not correlated to duration of exposure). The incidence of
12 gastrointestinal perforation (gastrointestinal perforation, fistula
13 formation, and/or intra-abdominal abscess) in patients with colorectal
14 cancer and in patients with non-small cell lung cancer (NSCLC)
15 receiving Avastin was 2.4% and 0.9%, respectively. The typical
16 presentation was reported as abdominal pain associated with
17 symptoms such as constipation and vomiting. Gastrointestinal
18 perforation should be included in the differential diagnosis of patients
19 presenting with abdominal pain on Avastin. Avastin therapy should be
20 permanently discontinued in patients with gastrointestinal perforation.
21 (See **WARNINGS: Gastrointestinal Perforations** and **DOSAGE**
22 **AND ADMINISTRATION: Dose Modifications.**)

23 **Wound Healing Complications**

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

33 **Hemorrhage**

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

42 **DESCRIPTION**

43 Avastin[®] (Bevacizumab) is a recombinant humanized monoclonal
44 IgG1 antibody that binds to and inhibits the biologic activity of human
45 vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay
46 systems. Bevacizumab contains human framework regions and the
47 complementarity-determining regions of a murine antibody that binds
48 to VEGF (1). Bevacizumab is produced in a Chinese Hamster Ovary
49 mammalian cell expression system in a nutrient medium containing
50 the antibiotic gentamicin and has a molecular weight of approximately
51 149 kilodaltons. Avastin is a clear to slightly opalescent, colorless to
52 pale brown, sterile, pH 6.2 solution for intravenous (IV) infusion.
53 Avastin is supplied in 100 mg and 400 mg preservative-free,
54 single-use vials to deliver 4 mL or 16 mL of Avastin (25 mg/mL). The
55 100 mg product is formulated in 240 mg α, α -trehalose dihydrate,
56 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium
57 phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for
58 Injection, USP. The 400 mg product is formulated in 960 mg
59 α, α -trehalose dihydrate, 92.8 mg sodium phosphate (monobasic,
60 monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous),
61 6.4 mg polysorbate 20, and Water for Injection, USP.

62 **CLINICAL PHARMACOLOGY**

63 **Mechanism of Action**

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

71 **Pharmacokinetics**

72 The pharmacokinetic profile of Bevacizumab was assessed using an
73 assay that measures total serum Bevacizumab concentrations (i.e., the
74 assay did not distinguish between free Bevacizumab and Bevacizumab
75 bound to VEGF ligand). Based on a population pharmacokinetic
76 analysis of 491 patients who received 1 to 20 mg/kg of Avastin
77 weekly, every 2 weeks, or every 3 weeks, the estimated half-life of
78 Bevacizumab was approximately 20 days (range 11–50 days). The
79 predicted time to reach steady state was 100 days. The accumulation
80 ratio following a dose of 10 mg/kg of Bevacizumab every 2 weeks was
81 2.8.

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

94 **Special Populations**

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

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

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

103 **CLINICAL STUDIES**

104 **Avastin[®] In Metastatic Colorectal Cancer (mCRC)**

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

113 **Avastin in Combination with Bolus-IFL**

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

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

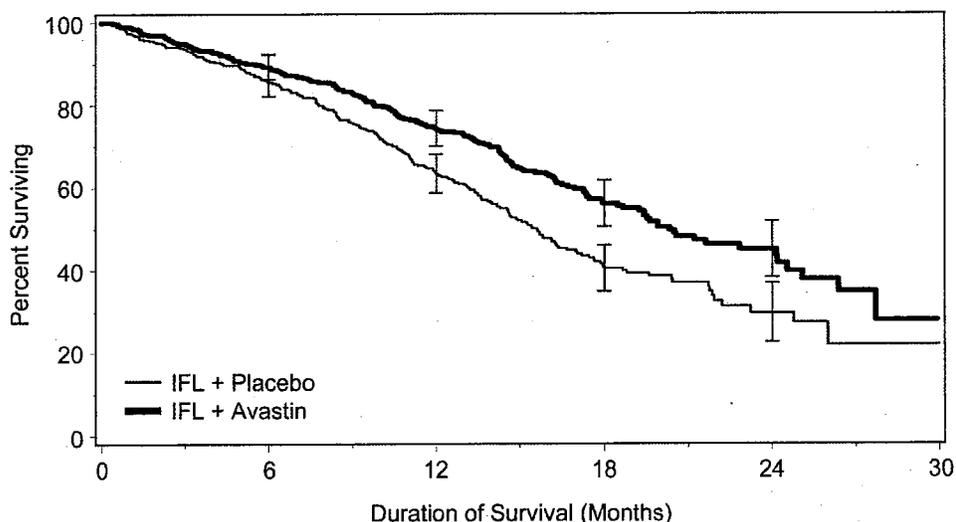
^ap < 0.001 by stratified logrank test.

^bp < 0.01 by χ^2 test.

131

132
133

Figure 1
Duration of Survival in Study 1



134

135 Error bars represent 95% confidence intervals.

136

137 The clinical benefit of Avastin, as measured by survival in the two
138 principal arms, was seen in the subgroups defined by age (<65 yrs,
139 ≥65 yrs) and gender.

140 Among the 110 patients enrolled in Arm 3, median overall survival
141 was 18.3 months, median progression-free survival was 8.8 months,
142 overall response rate was 39%, and median duration of response was
143 8.5 months.

144 **Avastin in Combination with 5-FU/LV Chemotherapy**

145 Study 2 was a randomized, active-controlled clinical trial testing
146 Avastin in combination with 5-FU/LV as first-line treatment of
147 metastatic colorectal cancer. Patients were randomized to receive
148 5-FU/LV (5-fluorouracil 500 mg/m², leucovorin 500 mg/m² weekly
149 for 6 weeks every 8 weeks) or 5-FU/LV plus Avastin (5 mg/kg every
150 2 weeks) or 5-FU/LV plus Avastin (10 mg/kg every 2 weeks).

151 The primary endpoints of the trial were objective response rate and
152 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

153

154 Progression-free survival was significantly longer in patients receiving
155 5-FU/LV plus Avastin at 5 mg/kg when compared to those not
156 receiving Avastin. However, overall survival and overall response rate
157 were not significantly different. Outcomes for patients receiving
158 5-FU/LV plus Avastin at 10 mg/kg were not significantly different
159 than for patients who did not receive Avastin.

160 **Avastin in Combination with 5-FU/LV and Oxaliplatin**
161 **Chemotherapy**

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

175 the FOLFOX4 plus Avastin arm, prior to the FOLFOX4 chemotherapy
176 on Day 1.

177 Of the 829 patients randomized to the three arms, the median age was
178 61 years, 40% were female, 87% were Caucasian, and 49% had an
179 ECOG performance status of 0. Twenty-six percent had received prior
180 radiation therapy, and 80% received prior adjuvant chemotherapy.
181 Ninety-nine percent received prior irinotecan, with or without 5-FU for
182 metastatic colorectal cancer, and 1% received prior irinotecan and
183 5-FU as adjuvant therapy.

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

198 **Avastin in Third-Line Metastatic Colorectal Cancer**

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

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

207 **Avastin® In Unresectable Non-Squamous, Non-Small Cell**
208 **Lung Cancer (NSCLC)**

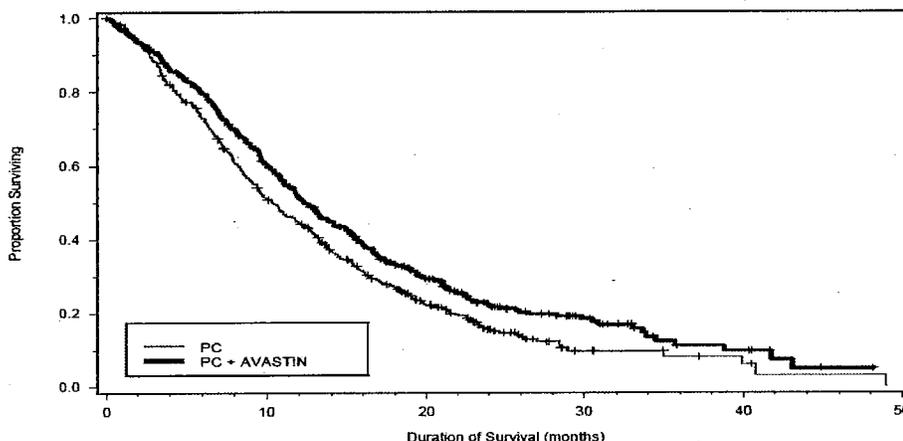
209 The safety and efficacy of Avastin as first-line treatment of patients
210 with locally advanced, metastatic, or recurrent non-squamous, NSCLC
211 was studied in a single, large, randomized, active-controlled,
212 open-label, multicenter study (Study 5, n=878), supported by a
213 randomized, dose ranging, active controlled Phase 2 study (Study 6,
214 n=98).

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

228 Among the 878 patients randomized to the two treatment arms, the
229 median age was 63, 46% were female, 43% were ≥ age 65, and 28%
230 had ≥5% weight loss at study entry. Eleven percent had recurrent
231 disease and of the remaining 89% with newly diagnosed NSCLC, 12%
232 had Stage IIIB with malignant pleural effusion and 76% had Stage IV
233 disease. The survival curves are presented in Figure 2. Overall
234 survival was statistically significantly higher among patients receiving
235 PC plus Avastin compared with those receiving PC alone; median OS

236 was 12.3 mos vs. 10.3 mos (hazard ratio 0.80 [repeated 95% CI 0.68,
237 0.94], final p-value 0.013, stratified log-rank test). Based on
238 investigator assessment which was not independently verified, patients
239 were reported to have longer progression-free survival with Avastin in
240 combination with PC compared to PC alone.

241 **Figure 2**
242 Duration of Survival in Study 5



243
244

245 In an exploratory analyses across patient subgroups, the impact of
246 Avastin on overall survival was less robust in the following: women
247 [HR=0.99 (95% CI: 0.79, 1.25)], age \geq 65 years [HR=0.91 (95% CI:
248 0.72, 1.14)] and patients with \geq 5% weight loss at study entry
249 [HR=0.96 (95% CI: 0.73, 1.26)].

250 **Avastin in Metastatic Breast Cancer**

251 The efficacy and safety of Avastin as first-line treatment of patients
252 with metastatic breast cancer was studied in a single, open-label,
253 randomized, multicenter study (Study 7, N=722). The efficacy and
254 safety of Avastin as second- and third-line treatment of patients with
255 metastatic breast cancer was studied in a single open-label randomized
256 study (Study 8, N= 462).

257

258 *Study 7*

259 In Study 7, patients who had not received chemotherapy for locally
260 recurrent or metastatic breast cancer were randomized (1:1) to receive
261 paclitaxel (90 mg/m² IV once weekly for 3 out of 4 weeks) alone or in
262 combination with Avastin (10 mg/kg IV infusion every 2 weeks).
263 Patients were treated until disease progression or unacceptable
264 toxicity. In situations where paclitaxel was discontinued or held,
265 treatment with Avastin alone could be continued until disease
266 progression. Patients with breast cancer overexpressing HER2 were
267 not eligible unless they had received prior therapy with Herceptin[®].
268 Prior hormonal therapy for the treatment of metastatic disease was
269 allowed, as was prior adjuvant chemo or hormonal therapy. Adjuvant
270 taxane therapy, if received, must have been completed 12 or more
271 months prior to study entry. Patients with central nervous system
272 metastasis were excluded. The main outcome measure of the study
273 was progression-free survival (PFS), as assessed by an independent
274 review facility (IRF). Secondary outcome measures were overall
275 survival and objective response rate.

276 Of the 722 patients randomized to the two treatment arms, the median
277 age was 55 years (range 27 - 85), 76% were white, 55.3% were
278 postmenopausal, and 64% were ER and/or PR positive. The patient
279 characteristics were similar across the treatment arms. Thirty-six
280 percent had received prior hormonal therapy for advanced disease, and
281 66% had received adjuvant chemotherapy, including 20% with prior
282 taxane use and 50% with prior anthracycline use. Efficacy results are
283 summarized in Table 3.

284

285

Table 3.

286

Avastin Efficacy Results from Study 7

Efficacy Parameter	Avastin + Paclitaxel (n=368)	Paclitaxel alone (n=354)	p-value	HR (95% CI)
Progression-free Survival [median, months (95% CI)]	11.3 (10.5, 13.3)	5.8 (5.4, 8.2)	<0.0001	0.48 (0.39, 0.61)
Overall Survival [median, months (95% CI)]	26.5 (23.7, 29.2)	24.8 (21.4, 27.4)	0.14	0.87 (0.72, 1.05)
Partial Response Rate ¹ (PR)	48.9% ²	22.2%	<0.001	

287

¹Includes only patients with measurable disease

288

² The difference in partial response rates is 26.7% with a 95% CI (18.4%, 35.0%).

289

The addition of Avastin to paclitaxel resulted in an improvement in

290

PFS with no significant improvement in overall survival. Partial

291

response rates in patients with measurable disease were higher with

292

Avastin plus paclitaxel. No complete responses were observed.

293

Thirty-four percent of the patients had incomplete follow-up for

294

disease progression, therefore, an exploratory analysis was performed

295

providing a hazard ratio of 0.57.

296

Study 8

297

In Study 8, patients who had received prior anthracycline and taxane

298

therapy in the adjuvant setting or for their metastatic breast cancer

299

were randomized (1:1) to receive capecitabine alone or in combination

300

with Avastin. The study enrolled 462 patients. The median age was

301

51 years (range 29 – 78), 80.5% were white, and 50% were ER and

302

40% were PR positive. The patient characteristics were similar across

303

the treatment arms. The study failed to demonstrate a statistically

304

significant effect on PFS or overall survival. The median PFS was 4.2

305

months in the capecitabine arm and 4.9 months in the capecitabine

306

plus Avastin arm (log-rank p-value = 0.86, hazard ratio 0.98). The

307

median overall survival was 14.5 months in the capecitabine arm and

308 15.1 months in the capecitabine plus Avastin arm (hazard ratio of
309 1.08).

310

311 **INDICATIONS AND USAGE**

312 Avastin[®], in combination with intravenous 5-fluorouracil-based
313 chemotherapy, is indicated for first- or second-line treatment of
314 patients with metastatic carcinoma of the colon or rectum.

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

318 Avastin[®], in combination with paclitaxel is indicated for the treatment
319 of patients who have not received chemotherapy for metastatic HER2
320 negative breast cancer.

321 The effectiveness of Avastin in metastatic breast cancer is based on an
322 improvement in progression free survival. Avastin is not indicated for
323 patients with breast cancer that has progressed following anthracycline
324 and taxane chemotherapy administered for metastatic disease.

325 Currently, no data are available that demonstrate an improvement in
326 disease-related symptoms or increased survival with Avastin in breast
327 cancer. (See CLINICAL STUDIES.)

328 **CONTRAINDICATIONS**

329 None.

330 **WARNINGS**

331 **Gastrointestinal Perforations (See DOSAGE AND** 332 **ADMINISTRATION: Dose Modifications)**

333 Gastrointestinal perforation complicated by intra-abdominal abscesses
334 or fistula formation and in some instances with fatal outcome, occurs

335 at an increased incidence in patients receiving Avastin as compared to
336 controls. In Studies 1, 2, and 3, the incidence of gastrointestinal
337 perforation (gastrointestinal perforation, fistula formation, and/or
338 intra-abdominal abscess) in patients receiving Avastin was 2.4%.
339 These episodes occurred with or without intra-abdominal abscesses
340 and at various time points during treatment. The typical presentation
341 was reported as abdominal pain associated with symptoms such as
342 constipation and emesis.

343 In post-marketing clinical studies and reports, gastrointestinal
344 perforation, fistula formation in the gastrointestinal tract
345 (eg. gastrointestinal, enterocutaneous, esophageal, duodenal, rectal),
346 and/or intra-abdominal abscess occurred in patients receiving Avastin
347 for colorectal and for other types of cancer. The overall incidence in
348 clinical studies was 1%, but may be higher in some cancer settings. Of
349 the reported events, approximately 30% were fatal. Patients with
350 gastrointestinal perforation, regardless of underlying cancer, typically
351 present with abdominal pain, nausea and fever. Events were reported
352 at various time points during treatment ranging from one week to
353 greater than 1 year from initiation of Avastin, with most events
354 occurring within the first 50 days.

355 Permanently discontinue Avastin in patients with gastrointestinal
356 perforation (gastrointestinal perforation, fistula formation, and/or
357 intra-abdominal abscess).

358 **Non-Gastrointestinal Fistula Formation (See DOSAGE AND**
359 **ADMINISTRATION: Dose Modifications)**

360 Non-gastrointestinal fistula formation has been reported in patients
361 treated with Avastin in controlled clinical studies (with an incidence of
362 < 0.3%) and in post-marketing experience, in some cases with fatal
363 outcome. Fistula formation involving the following areas of the body
364 other than the gastrointestinal tract have been reported:
365 tracheo-esophageal, bronchopleural, biliary, vagina and bladder.

366 Events were reported throughout treatment with Avastin, with most
367 events occurring within the first 6 months.

368 Permanently discontinue Avastin in patients with fistula formation
369 involving an internal organ.

370 **Wound Healing Complications (See DOSAGE AND**
371 **ADMINISTRATION: Dose Modifications)**

372 Avastin impairs wound healing in animal models. In clinical studies
373 of Avastin, patients were not allowed to receive Avastin until at least
374 28 days had elapsed following surgery. In clinical studies of Avastin
375 in combination with chemotherapy, there were 6 instances of
376 dehiscence among 788 patients (0.8%).

377 The appropriate interval between discontinuation of Avastin and
378 subsequent elective surgery required to avoid the risks of impaired
379 wound healing has not been determined. In Study 1, 39 patients who
380 received bolus-IFL plus Avastin underwent surgery following Avastin
381 therapy; of these patients, six (15%) had wound healing/bleeding
382 complications. In the same study, 25 patients in the bolus-IFL arm
383 underwent surgery; of these patients, one of 25 (4%) had wound
384 healing/bleeding complications. The longest interval between last
385 dose of study drug and dehiscence was 56 days; this occurred in a
386 patient on the bolus-IFL plus Avastin arm.

387 The interval between termination of Avastin and subsequent elective
388 surgery should take into consideration the calculated half-life of
389 Avastin (approximately 20 days).

390 Discontinue Avastin in patients with wound healing complications
391 requiring medical intervention.

392 **Hemorrhage (See DOSAGE AND ADMINISTRATION:**
393 **Dose Modifications)**

394 Two distinct patterns of bleeding have occurred in patients receiving
395 Avastin. The first is minor hemorrhage, most commonly NCI-CTC
396 Grade 1 epistaxis. The second is serious, and in some cases fatal,
397 hemorrhagic events.

398 In Study 6, four of 13 (31%) Avastin-treated patients with squamous
399 cell histology and two of 53 (4%) Avastin-treated patients with
400 histology other than squamous cell, experienced serious or fatal
401 pulmonary hemorrhage as compared to none of the 32 (0%) patients
402 receiving chemotherapy alone. Of the patients experiencing
403 pulmonary hemorrhage requiring medical intervention, many had
404 cavitation and/or necrosis of the tumor, either pre-existing or
405 developing during Avastin therapy. In Study 5, the rate of pulmonary
406 hemorrhage requiring medical intervention for the PC plus Avastin
407 arm was 2.3% (10 of 427) compared to 0.5% (2 of 441) for the PC
408 alone arm. There were seven deaths due to pulmonary hemorrhage
409 reported by investigators in the PC plus Avastin arm as compared to
410 one in the PC alone arm. Generally, these serious hemorrhagic events
411 presented as major or massive hemoptysis without an antecedent
412 history of minor hemoptysis during Avastin therapy. Do not
413 administer Avastin to patients with recent history of hemoptysis of
414 $\geq 1/2$ tsp of red blood. Other serious bleeding events occurring in
415 patients receiving Avastin across all indications include
416 gastrointestinal hemorrhage, subarachnoid hemorrhage, and
417 hemorrhagic stroke. Some of these events were fatal. (See **ADVERSE**
418 **REACTIONS: Hemorrhage.**)

419 The risk of central nervous system (CNS) bleeding in patients with
420 CNS metastases receiving Avastin has not been evaluated because
421 these patients were excluded from late stage clinical studies following
422 development of CNS hemorrhage in a patient with a CNS metastasis in
423 a Phase 1 study.

424 Discontinue Avastin in patients with serious hemorrhage
425 (i.e., requiring medical intervention) and initiate aggressive medical
426 management. (See **ADVERSE REACTIONS: Hemorrhage.**)

427 **Arterial Thromboembolic Events (see DOSAGE AND**
428 **ADMINISTRATION: Dose Modifications and**
429 **PRECAUTIONS: Geriatric Use)**

430 Arterial thromboembolic events (ATE) occurred at a higher incidence
431 in patients receiving Avastin in combination with chemotherapy as
432 compared to those receiving chemotherapy alone. ATE included
433 cerebral infarction, transient ischemic attacks (TIAs), myocardial
434 infarction (MI), angina, and a variety of other ATE. These events
435 were fatal in some instances.

436 In a pooled analysis of randomized, controlled clinical trials involving
437 1745 patients, the incidence of ATE was 4.4% among patients treated
438 with Avastin in combination with chemotherapy and 1.9%
439 among patients receiving chemotherapy alone. Fatal outcomes for
440 these events occurred in 7 of 963 patients (0.7%) who were treated
441 with Avastin in combination with chemotherapy, compared to 3 of
442 782 patients (0.4%) who were treated with chemotherapy alone. The
443 incidences of both cerebrovascular arterial events (1.9% vs. 0.5%) and
444 cardiovascular arterial events (2.1% vs. 1.0%) were increased in
445 patients receiving Avastin compared to chemotherapy alone. The
446 relative risk of ATE was greater in patients 65 and over (8.5% vs.
447 2.9%) as compared to those less than 65 (2.1% vs. 1.4%).
448 (See **PRECAUTIONS: Geriatric Use.**)

449 The safety of resumption of Avastin therapy after resolution of an
450 ATE has not been studied. Permanently discontinue Avastin in
451 patients who experience a severe ATE during treatment. (See
452 **DOSAGE AND ADMINISTRATION: Dose Modifications and**
453 **PRECAUTIONS: Geriatric Use.**)

454 **Hypertension (See DOSAGE AND ADMINISTRATION:**
455 **Dose Modifications)**

456 The incidence of severe hypertension was increased in patients
457 receiving Avastin as compared to controls. Across clinical studies the
458 incidence of NCI-CTC Grade 3 or 4 hypertension ranged from 8-18%.

459 Medication classes used for management of patients with NCI-CTC
460 Grade 3 hypertension receiving Avastin included
461 angiotensin-converting enzyme inhibitors, beta blockers, diuretics, and
462 calcium channel blockers. Development or worsening of hypertension
463 can require hospitalization or require discontinuation of Avastin in up
464 to 1.7% of patients. Hypertension can persist after discontinuation of
465 Avastin. Complications can include hypertensive encephalopathy
466 (in some cases fatal) and CNS hemorrhage.

467 In the post-marketing experience, acute increases in blood pressure
468 associated with initial or subsequent infusions of Avastin have been
469 reported (see **PRECAUTIONS: Infusion Reactions**). Some cases
470 were serious and associated with clinical sequelae.

471 Permanently discontinue Avastin in patients with hypertensive crisis or
472 hypertensive encephalopathy. Temporarily suspend Avastin in
473 patients with severe hypertension that is not controlled with medical
474 management. (See **DOSAGE AND ADMINISTRATION: Dose**
475 **Modifications.**)

476 **Reversible Posterior Leukoencephalopathy Syndrome**
477 **(RPLS) (See DOSAGE AND ADMINISTRATION:**
478 **Dose Modifications)**

479 RPLS has been reported in clinical studies (with an incidence of
480 <0.1%) and in post-marketing experience. RPLS is a neurological
481 disorder which can present with headache, seizure, lethargy,
482 confusion, blindness and other visual and neurologic disturbances.
483 Mild to severe hypertension may be present, but is not necessary for
484 diagnosis of RPLS. Magnetic Resonance Imaging (MRI) is necessary

485 to confirm the diagnosis of RPLS. The onset of symptoms has been
486 reported to occur from 16 hours to 1 year after initiation of Avastin.

487 In patients developing RPLS, discontinue Avastin and initiate
488 treatment of hypertension, if present. Symptoms usually resolve or
489 improve within days, although some patients have experienced
490 ongoing neurologic sequelae. The safety of reinitiating Avastin
491 therapy in patients previously experiencing RPLS is not known.

492 **Neutropenia and Infection (See PRECAUTIONS: Geriatric**
493 **Use and ADVERSE REACTIONS: Neutropenia and Infection)**

494 Increased rates of severe neutropenia, febrile neutropenia, and
495 infection with severe neutropenia (including some fatalities) have been
496 observed in patients treated with myelosuppressive chemotherapy plus
497 Avastin. (See **PRECAUTIONS: Geriatric Use and ADVERSE**
498 **REACTIONS: Neutropenia and Infection.**)

499 **Proteinuria (See DOSAGE AND ADMINISTRATION:**
500 **Dose Modifications)**

501 The incidence and severity of proteinuria is increased in patients
502 receiving Avastin as compared to control. In Studies 1, 3 and 5 the
503 incidence of NCI-CTC Grade 3 and 4 proteinuria, characterized as
504 >3.5 gm/24 hours, ranged up to 3.0% in Avastin-treated patients.

505 Nephrotic syndrome occurred in seven of 1459 (0.5%) patients
506 receiving Avastin in clinical studies. One patient died and one
507 required dialysis. In three patients, proteinuria decreased in severity
508 several months after discontinuation of Avastin. No patient had
509 normalization of urinary protein levels (by 24-hour urine) following
510 discontinuation of Avastin.

511 The highest incidence of proteinuria was observed in a dose-ranging,
512 placebo-controlled, randomized study of Avastin in patients with
513 metastatic renal cell carcinoma, an indication for which Avastin is not
514 approved, 24-hour urine collections were obtained in approximately

515 half the patients enrolled. Among patients in whom 24-hour urine
516 collections were obtained, four of 19 (21%) patients receiving Avastin
517 at 10 mg/kg every two weeks, two of 14 (14%) patients receiving
518 Avastin at 3 mg/kg every two weeks, and none of the 15 placebo
519 patients experienced NCI-CTC Grade 3 proteinuria (>3.5 gm
520 protein/24 hours).

521 Discontinue Avastin in patients with nephrotic syndrome. The safety
522 of continued Avastin treatment in patients with moderate to severe
523 proteinuria has not been evaluated. In most clinical studies, Avastin
524 was interrupted for ≥ 2 grams of proteinuria/24 hours and resumed
525 when proteinuria was <2 gm/24 hours. Patients with moderate to
526 severe proteinuria based on 24-hour collections should be monitored
527 regularly until improvement and/or resolution is observed. (See
528 **DOSAGE AND ADMINISTRATION: Dose Modifications.**)

529 **Congestive Heart Failure**

530 NCI-CTC Grade 2–4 left ventricular dysfunction, was reported in 25
531 of 1459 (1.7%) patients receiving Avastin in clinical studies. In Study
532 7, the rate of congestive heart failure (defined as NCI-CTC Grade 3
533 and 4) in the Avastin plus paclitaxel arm was 2.2 % versus 0.3% in the
534 control arm. Among patients receiving anthracyclines, the rate of CHF
535 was 3.8% for Avastin treated patients and 0.6 % for patients receiving
536 paclitaxel alone. Congestive heart failure occurred in six of 44 (14%)
537 patients with relapsed acute leukemia (an unlabelled indication)
538 receiving Avastin and concurrent anthracyclines in a single arm study.

539 The safety of continuation or resumption of Avastin in patients with
540 cardiac dysfunction has not been studied.

541 **PRECAUTIONS**

542 **General**

543 Use Avastin with caution in patients with known hypersensitivity to
544 Avastin or any component of this drug product.

545 **Infusion Reactions**

546 In clinical studies, infusion reactions with the first dose of Avastin
547 were uncommon (<3%) and severe reactions occurred in 0.2% of
548 patients. Infusion reactions reported in the clinical trials and post-
549 marketing experience include hypertension, hypertensive crises
550 associated with neurologic signs and symptoms, wheezing, oxygen
551 desaturation, NCI-CTC Grade 3 hypersensitivity, chest pain,
552 headaches, rigors, and diaphoresis. Adequate information on
553 rechallenge is not available. Avastin infusion should be interrupted in
554 all patients with severe infusion reactions and appropriate medical
555 therapy administered.

556 There are no data regarding the most appropriate method of
557 identification of patients who may safely be retreated with Avastin
558 after experiencing a severe infusion reaction.

559 **Surgery**

560 Avastin therapy should not be initiated for at least 28 days following
561 major surgery. The surgical incision should be fully healed prior to
562 initiation of Avastin. Because of the potential for impaired wound
563 healing, Avastin should be suspended prior to elective surgery.

564 The appropriate interval between the last dose of Avastin and elective
565 surgery is unknown; however, the half-life of Avastin is estimated to
566 be 20 days (see **CLINICAL PHARMACOLOGY:**

567 **Pharmacokinetics**) and the interval chosen should take into
568 consideration the half-life of the drug. (See **WARNINGS:**
569 **Gastrointestinal Perforations and Wound Healing Complications.**)

570 **Cardiovascular Disease**

571 Patients were excluded from participation in Avastin clinical trials if,
572 in the previous year, they had experienced clinically significant
573 cardiovascular disease. In an exploratory analysis pooling the data
574 from five randomized, placebo-controlled, clinical trials conducted in
575 patients without a recent history of clinically significant cardiovascular

576 disease, the overall incidence of arterial thromboembolic events, the
577 incidence of fatal arterial thromboembolic events, and the incidence of
578 cardiovascular thromboembolic events were increased in patients
579 receiving Avastin plus chemotherapy as compared to chemotherapy
580 alone.

581 **Laboratory Tests**

582 Blood pressure monitoring should be conducted every two to
583 three weeks during treatment with Avastin. Patients who develop
584 hypertension on Avastin may require blood pressure monitoring at
585 more frequent intervals. Patients with Avastin-induced or
586 -exacerbated hypertension who discontinue Avastin should continue to
587 have their blood pressure monitored at regular intervals.

588 Patients receiving Avastin should be monitored for the development or
589 worsening of proteinuria with serial urinalyses. Patients with a 2+ or
590 greater urine dipstick reading should undergo further assessment,
591 e.g., a 24-hour urine collection. (See **WARNINGS: Proteinuria** and
592 **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

593 **Drug Interactions**

594 No formal drug interaction studies with anti-neoplastic agents have
595 been conducted. In Study 1, patients with colorectal cancer were
596 given irinotecan/5-FU/leucovorin (bolus-IFL) with or without Avastin.
597 Irinotecan concentrations were similar in patients receiving bolus-IFL
598 alone and in combination with Avastin. The concentrations of SN38,
599 the active metabolite of irinotecan, were on average 33% higher in
600 patients receiving bolus-IFL in combination with Avastin when
601 compared with bolus-IFL alone. In Study 1, patients receiving
602 bolus-IFL plus Avastin had a higher incidence of NCI-CTC Grade 3–4
603 diarrhea and neutropenia. Due to high inter-patient variability and
604 limited sampling, the extent of the increase in SN38 levels in patients
605 receiving concurrent irinotecan and Avastin is uncertain.

606 In Study 6, based on limited data, there did not appear to be a
607 difference in the mean exposure of either carboplatin or paclitaxel
608 when each was administered alone or in combination with Avastin.
609 However, 3 of the 8 patients receiving Avastin plus
610 paclitaxel/carboplatin had substantially lower paclitaxel exposure after
611 four cycles of treatment (at Day 63) than those at Day 0, while patients
612 receiving paclitaxel/carboplatin without Avastin had a greater
613 paclitaxel exposure at Day 63 than at Day 0.

614 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

615 No carcinogenicity data are available for Avastin in animals or
616 humans.

617 Avastin may impair fertility. Dose-related decreases in ovarian and
618 uterine weights, endometrial proliferation, number of menstrual cycles,
619 and arrested follicular development or absent corpora lutea were
620 observed in female cynomolgus monkeys treated with 10 or 50 mg/kg
621 of Avastin for 13 or 26 weeks. Following a 4- or 12-week recovery
622 period, which examined only the high-dose group, trends suggestive
623 of reversibility were noted in the two females for each regimen that
624 were assigned to recover. After the 12-week recovery period,
625 follicular maturation arrest was no longer observed, but ovarian
626 weights were still moderately decreased. Reduced endometrial
627 proliferation was no longer observed at the 12-week recovery time
628 point, but uterine weight decreases were still notable, corpora lutea
629 were absent in 1 out of 2 animals, and the number of menstrual cycles
630 remained reduced (67%).

631 **Pregnancy Category C**

632 Avastin has been shown to be teratogenic in rabbits when administered
633 in doses that approximate the human dose on a mg/kg basis. Observed
634 effects included decreases in maternal and fetal body weights, an
635 increased number of fetal resorptions, and an increased incidence of

636 specific gross and skeletal fetal alterations. Adverse fetal outcomes
637 were observed at all doses tested.

638 Angiogenesis is critical to fetal development and the inhibition of
639 angiogenesis following administration of Avastin is likely to result in
640 adverse effects on pregnancy. There are no adequate and
641 well-controlled studies in pregnant women. Avastin should be used
642 during pregnancy or in any woman not employing adequate
643 contraception only if the potential benefit justifies the potential risk to
644 the fetus. All patients should be counseled regarding the potential risk
645 of Avastin to the developing fetus prior to initiation of therapy. If the
646 patient becomes pregnant while receiving Avastin, she should be
647 apprised of the potential hazard to the fetus and/or the potential risk of
648 loss of pregnancy. Patients who discontinue Avastin should also be
649 counseled concerning the prolonged exposure following
650 discontinuation of therapy (half-life of approximately 20 days) and the
651 possible effects of Avastin on fetal development.

652 **Nursing Mothers**

653 It is not known whether Avastin is secreted in human milk. Because
654 human IgG1 is secreted into human milk, the potential for absorption
655 and harm to the infant after ingestion is unknown. Women should be
656 advised to discontinue nursing during treatment with Avastin and for a
657 prolonged period following the use of Avastin, taking into account the
658 half-life of the product, approximately 20 days [range 11–50 days].
659 (See **CLINICAL PHARMACOLOGY: Pharmacokinetics.**)

660 **Pediatric Use**

661 The safety and effectiveness of Avastin in pediatric patients has not
662 been studied. However, physeal dysplasia was observed in juvenile
663 cynomolgus monkeys with open growth plates treated for four weeks
664 with doses that were less than the recommended human dose based on
665 mg/kg and exposure. The incidence and severity of physeal dysplasia

666 were dose-related and were at least partially reversible upon cessation
667 of treatment.

668 **Geriatric Use**

669 In Study 1, NCI-CTC Grade 3–4 adverse events were collected in all
670 patients receiving study drug (396 bolus-IFL plus placebo;
671 392 bolus-IFL plus Avastin; 109 5-FU/LV plus Avastin), while
672 NCI-CTC Grade 1 and 2 adverse events were collected in a subset of
673 309 patients. There were insufficient numbers of patients 65 years and
674 older in the subset in which NCI-CTC Grade 1-4 adverse events were
675 collected to determine whether the overall adverse event profile was
676 different in the elderly as compared to younger patients. Among the
677 392 patients receiving bolus-IFL plus Avastin, 126 were at least
678 65 years of age. Severe adverse events that occurred at a higher
679 incidence ($\geq 2\%$) in the elderly when compared to those less than
680 65 years were asthenia, sepsis, deep thrombophlebitis, hypertension,
681 hypotension, myocardial infarction, congestive heart failure, diarrhea,
682 constipation, anorexia, leukopenia, anemia, dehydration, hypokalemia,
683 and hyponatremia. The effect of Avastin on overall survival was
684 similar in elderly patients as compared to younger patients.

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

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

691 In Study 7, there were insufficient numbers of patients ≥ 65 years old
692 to determine whether the overall adverse event profile was different in
693 the elderly as compared with younger patients.

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

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

701 In an exploratory, pooled analysis of 1745 patients treated in
702 five randomized, controlled studies, there were 618 (35%) patients age
703 65 or older and 1127 patients less than 65 years of age. The overall
704 incidence of arterial thromboembolic events was increased in all
705 patients receiving Avastin with chemotherapy as compared to those
706 receiving chemotherapy alone, regardless of age. However, the
707 increase in arterial thromboembolic events incidence was greater in
708 patients 65 and over (8.5% vs. 2.9%) as compared to those less than 65
709 (2.1% vs. 1.4%). (See **WARNINGS: Arterial Thromboembolic**
710 **Events.**)

711 **ADVERSE REACTIONS**

712 The most serious adverse reactions in patients receiving Avastin were:

- 713 • Gastrointestinal Perforations (see **WARNINGS**)
- 714 • Non-Gastrointestinal Fistula Formation (see **WARNINGS**)
- 715 • Wound Healing Complications (see **WARNINGS**)
- 716 • Hemorrhage (see **WARNINGS**)
- 717 • Arterial Thromboembolic Events (see **WARNINGS**)
- 718 • Hypertensive Crises (see **WARNINGS: Hypertension**)
- 719 • Reversible Posterior Leukoencephalopathy Syndrome
720 (see **WARNINGS**)
- 721 • Neutropenia and Infection (see **WARNINGS**)
- 722 • Nephrotic Syndrome (see **WARNINGS: Proteinuria**)
- 723 • Congestive Heart Failure (see **WARNINGS**)

724

725 **Adverse Reactions in Clinical Trials**

726 Because clinical trials are conducted under widely varying conditions,
727 adverse reaction rates observed in the clinical trials of a drug cannot be
728 directly compared to rates in the clinical trials of another drug and may
729 not reflect the rates observed in practice. The adverse reaction
730 information from clinical trials does, however, provide a basis for
731 identifying the adverse events that appear to be related to drug use and
732 for approximating rates.

733 The data described below reflect exposure to Avastin in 1529 patients,
734 including 665 receiving Avastin for at least 6 months and
735 199 receiving Avastin for at least one year. Avastin was studied
736 primarily in placebo- and active-controlled trials (n= 501, and
737 n= 1028, respectively).

738 **Gastrointestinal Perforation**

739 The incidence of gastrointestinal perforation across all studies ranged
740 from 0–3.7%. The incidence of gastrointestinal perforation, in some
741 cases fatal, in patients with mCRC receiving Avastin alone or in
742 combination with chemotherapy was 2.4% compared to 0.3% in
743 patients receiving only chemotherapy. The incidence of
744 gastrointestinal perforation in NSCLC patients receiving Avastin was
745 0.9% compared to 0% in patients receiving only chemotherapy. (See
746 **WARNINGS: Gastrointestinal Perforations** and **DOSAGE AND**
747 **ADMINISTRATION: Dose Modifications.**)

748 **Non-Gastrointestinal Fistula Formation**

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

751 **Wound Healing Complications**

752 The incidence of post-operative wound healing and/or bleeding
753 complications was increased in patients with mCRC receiving Avastin
754 as compared to patients receiving only chemotherapy. Among patients

755 requiring surgery on or within 60 days of receiving study treatment,
756 wound healing and/or bleeding complications occurred in 15% (6/39)
757 of patients receiving bolus-IFL plus Avastin as compared to 4% (1/25)
758 of patients who received bolus-IFL alone. In the same study, the
759 incidence of wound dehiscence was also higher in the Avastin-treated
760 patients (1% vs. 0.5%).

761 Hemorrhage

762 Severe or fatal hemorrhages, including hemoptysis, gastrointestinal
763 bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal
764 bleeding occurred up to five-fold more frequently in Avastin-treated
765 patients compared to patients treated with chemotherapy alone.
766 NCI-CTC Grade 3–5 hemorrhagic events occurred in 4.7% of NSCLC
767 patients and 5.2% of mCRC patients receiving Avastin compared to
768 1.1% and 0.7% for the control groups respectively. (See
769 **WARNINGS: Hemorrhage.**)

770 The incidence of epistaxis was higher (35% vs. 10%) in patients with
771 mCRC receiving bolus-IFL plus Avastin compared with patients
772 receiving bolus-IFL plus placebo. These events were generally mild in
773 severity (NCI-CTC Grade 1) and resolved without medical
774 intervention. Additional mild to moderate hemorrhagic events
775 reported more frequently in patients receiving bolus-IFL plus Avastin
776 when compared to those receiving bolus-IFL plus placebo included
777 gastrointestinal hemorrhage (24% vs. 6%), minor gum bleeding (2%
778 vs. 0), and vaginal hemorrhage (4% vs. 2%). (See **WARNINGS:**
779 **Hemorrhage** and **DOSAGE AND ADMINISTRATION: Dose**
780 **Modifications.**)

781 Arterial Thromboembolic Events

782 The incidence of arterial thromboembolic events was increased in
783 NSCLC patients receiving PC plus Avastin (3.0%) compared with
784 patients receiving PC alone (1.4%). Five events were fatal in the PC
785 plus Avastin arm, compared with 1 event in the PC alone arm. This

786 increased risk is consistent with that observed in patients with mCRC.
787 (See **WARNINGS: Arterial Thromboembolic Events, DOSAGE**
788 **AND ADMINISTRATION: Dose Modifications, and**
789 **PRECAUTIONS: Geriatric Use.**)

790 Venous Thromboembolic Events

791 The incidence of NCI-CTC Grade 3–4 venous thromboembolic events
792 was higher in patients with mCRC or NSCLC receiving Avastin with
793 chemotherapy as compared to those receiving chemotherapy alone. In
794 addition, in patients with mCRC the risk of developing a second
795 subsequent thromboembolic event in patients receiving Avastin and
796 chemotherapy is increased compared to patients receiving
797 chemotherapy alone. In Study 1, 53 patients (14%) on the bolus-IFL
798 plus Avastin arm and 30 patients (8%) on the bolus-IFL plus placebo
799 arm received full dose warfarin following a venous thromboembolic
800 event. Among these patients, an additional thromboembolic event
801 occurred in 21% (11/53) of patients receiving bolus-IFL plus Avastin
802 and 3% (1/30) of patients receiving bolus-IFL alone.

803 The overall incidence of NCI-CTC Grade 3–4 venous thromboembolic
804 events in Study 1 was 15.1% in patients receiving bolus-IFL plus
805 Avastin and 13.6% in patients receiving bolus-IFL plus placebo.
806 In Study 1, the incidence of the following NCI-CTC Grade 3 and 4
807 venous thromboembolic events was higher in patients receiving
808 bolus-IFL plus Avastin as compared to patients receiving bolus-IFL
809 plus placebo: deep venous thrombosis (34 vs. 19 patients) and
810 intra-abdominal venous thrombosis (10 vs. 5 patients).

811 Hypertension

812 Fatal CNS hemorrhage complicating Avastin induced hypertension
813 can occur.

814 In Study 1, the incidences of hypertension and of severe hypertension
 815 were increased in patients with mCRC receiving Avastin compared to
 816 those receiving chemotherapy alone (see Table 3).

Table 4
 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.

817
 818 Among patients with severe hypertension in the Avastin arms, slightly
 819 over half the patients (51%) had a diastolic reading greater than
 820 110 mmHg associated with a systolic reading less than 200 mmHg.

821 Similar results were seen in patients receiving Avastin alone or in
 822 combination with FOLFOX4 or carboplatin and paclitaxel.
 823 (See **WARNINGS: Hypertension and DOSAGE AND**
 824 **ADMINISTRATION: Dose Modifications.**)

825 **Neutropenia and Infection**

826 An increased incidence of neutropenia has been reported in patients
 827 receiving Avastin and chemotherapy compared to chemotherapy alone.
 828 In Study 1, the incidence of NCI-CTC Grade 3 or 4 neutropenia was
 829 increased in patients with mCRC receiving IFL+Avastin (21%)
 830 compared to patients receiving IFL alone (14%). In Study 5, the
 831 incidence of NCI-CTC Grade 4 neutropenia was increased in patients
 832 with NSCLC receiving PC plus Avastin (26.2%) compared with
 833 patients receiving PC alone (17.2%). Febrile neutropenia was also
 834 increased (5.4% for PC plus Avastin vs. 1.8% for PC alone). There

835 were 19 (4.5%) infections with NCI-CTC Grade 3 or 4 neutropenia in
836 the PC plus Avastin arm of which 3 were fatal compared to 9 (2%)
837 neutropenic infections in patients receiving PC alone, of which none
838 were fatal. During the first 6 cycles of treatment the incidence of
839 serious infections including pneumonia, febrile neutropenia, catheter
840 infections and wound infections was increased in the PC plus Avastin
841 arm [58 patients (13.6%)] compared to the PC alone arm [29 patients
842 (6.6%)].

843 Proteinuria

844 (See **WARNINGS: Proteinuria, DOSAGE AND**
845 **ADMINISTRATION: Dose Modifications, and PRECAUTIONS:**
846 **Geriatric Use.**)

847 Immunogenicity

848 As with all therapeutic proteins, there is a potential for
849 immunogenicity. The incidence of antibody development in patients
850 receiving Avastin has not been adequately determined because the
851 assay sensitivity was inadequate to reliably detect lower titers.
852 Enzyme-linked immunosorbent assays (ELISAs) were performed on
853 sera from approximately 500 patients treated with Avastin, primarily
854 in combination with chemotherapy. High titer human anti-Avastin
855 antibodies were not detected.

856 Immunogenicity data are highly dependent on the sensitivity and
857 specificity of the assay. Additionally, the observed incidence of
858 antibody positivity in an assay may be influenced by several factors,
859 including sample handling, timing of sample collection, concomitant
860 medications, and underlying disease. For these reasons, comparison of
861 the incidence of antibodies to Avastin with the incidence of antibodies
862 to other products may be misleading.

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

864 The data in Tables 5 and 6 were obtained in Study 1. All NCI-CTC
865 Grade 3 and 4 adverse events and selected NCI-CTC Grade 1 and 2
866 adverse events (hypertension, proteinuria, thromboembolic events)
867 were reported for the overall study population. The median age was
868 60, 60% were male, 79% were Caucasian, 78% had a colon primary
869 lesion, 56% had extra-abdominal disease, 29% had prior adjuvant or
870 neoadjuvant chemotherapy, and 57% had ECOG performance status
871 of 0. The median duration of exposure to Avastin was 8 months in
872 Arm 2 and 7 months in Arm 3. Severe and life-threatening (NCI-CTC
873 Grade 3 and 4) adverse events, which occurred at a higher incidence
874 ($\geq 2\%$) in patients receiving bolus-IFL plus Avastin as compared to
875 bolus-IFL plus placebo, are presented in Table 5.

Table 5
 NCI-CTC Grade 3 and 4 Adverse Events in Study 1
 (Occurring at Higher Incidence ($\geq 2\%$) Avastin vs. Control)

	Arm 1 IFL+Placebo (n=396)	Arm 2 IFL+Avastin (n=392)
NCI-CTC Grade 3–4 Events	295 (74%)	340 (87%)
<u>Body as a Whole</u>		
Asthenia	28 (7%)	38 (10%)
Abdominal Pain	20 (5%)	32 (8%)
Pain	21 (5%)	30 (8%)
<u>Cardiovascular</u>		
Hypertension	10 (2%)	46 (12%)
Deep Vein Thrombosis	19 (5%)	34 (9%)
Intra-Abdominal Thrombosis	5 (1%)	13 (3%)
Syncope	4 (1%)	11 (3%)
<u>Digestive</u>		
Diarrhea	99 (25%)	133 (34%)
Constipation	9 (2%)	14 (4%)
<u>Hemic/Lymphatic</u>		
Leukopenia	122 (31%)	145 (37%)
Neutropenia ^a	41 (14%)	58 (21%)

^a Central laboratories were collected on Days 1 and 21 of each cycle.
 Neutrophil counts are available in 303 patients in Arm 1 and 276 in Arm 2.

876

877 NCI-CTC Grade 1–4 adverse events which occurred at a higher
 878 incidence ($\geq 5\%$) in patients receiving bolus-IFL plus Avastin as
 879 compared to the bolus-IFL plus placebo arm, are presented in Table 6.

Table 6
 NCI-CTC Grade 1–4 Adverse Events in Study 1
 (Occurring at Higher Incidence (≥5%) in IFL+Avastin vs. IFL)

	Arm 1 IFL+Placebo (n=98)	Arm 2 IFL+ Avastin (n=102)	Arm 3 5-FU/LV+Avastin (n=109)
<u>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%)

880

Table 6 (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%)

881

882 The data in Table 7 were obtained in Study 3. Only NCI-CTC
 883 Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse
 884 events related to treatment were reported. The median age was a
 885 61 years, 40% were female, 87% were Caucasian, 99% received prior
 886 chemotherapy for metastatic colorectal cancer, 26% had received prior
 887 radiation therapy, and the 49% had an ECOG performance status of 0.
 888 Selected NCI-CTC Grade 3–5 non-hematologic and Grade 4–5
 889 hematologic adverse events which occurred at a higher incidence in
 890 patients receiving FOLFOX4 plus Avastin as compared to those who
 891 received FOLFOX4 alone, are presented in Table 7. These data are
 892 likely to under-estimate the true adverse event rates due to the
 893 reporting mechanisms used in Study 3.

Table 7
 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%)

894

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

896 The data in Table 8 were obtained in Study 5. Only NCI-CTC

897 Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse

898 events were reported. The median age was 63, 46% were female, no

899 patients had received prior chemotherapy, 76% had Stage IV disease,

900 12% had Stage IIIB disease with malignant pleural effusion, 11% had

901 recurrent disease, and 40% had an ECOG performance status of 0.
902 The median duration of exposure to Avastin was 4.9 months.
903 NCI-CTC Grade 3, 4, and 5 adverse events that occurred at a $\geq 2\%$
904 higher incidence in patients receiving PC plus Avastin as compared
905 with PC alone are presented in Table 8.

Table 8
 NCI-CTC Grade 3–5 Non-Hematologic and
 Grade 4 and 5 Hematologic Adverse Events in Study 5
 (Occurring at a $\geq 2\%$ Higher Incidence in
 Avastin-Treated Patients Compared with Control)

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

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

906

907 **Metastatic Breast Cancer**

908 The data in Table 9 were obtained in Study 7. Only NCI-CTC
 909 Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse
 910 events were reported. The median age was 55 years (range 27 - 85);

911 76% were white; 36% had received prior hormonal therapy for
912 advanced disease, and 66% had received adjuvant chemotherapy,
913 including 20% with prior taxane use and 50% with prior
914 anthracyclines use. The median duration of exposure was 9 months
915 with Avastin plus paclitaxel and 5 months for patients receiving
916 paclitaxel alone

917 Severe and life-threatening (NCI-CTC Grade 3 and 4) adverse events
918 that occurred at a higher incidence ($\geq 2\%$) in patients receiving
919 paclitaxel plus Avastin compared with paclitaxel alone, are presented
920 in Table 9.

Table 9
 NCI-CTC Grade 3–5 Non-Hematologic and
 Grade 4 and 5 Hematologic Adverse Events in
 Study 7 (Occurring at Higher Incidence ($\geq 2\%$) in
 Paclitaxel + Avastin vs. Paclitaxel alone)

NCI-CTC Terminology	Paclitaxel (n = 348)	Paclitaxel + Avastin (n = 363)
Patients with at least one event	176 (50.6%)	258 (71.1%)
Neuropathy—sensory	61 (17.5%)	88 (24.2%)
Cerebrovascular ischemia	0 (0%)	9 (2.5%)
Hypertension	5 (1.4%)	58 (16.0%)
Headache	2 (0.6%)	13 (3.6%)
Bone pain	6 (1.7%)	14 (3.9%)
Nausea	5 (1.4%)	15 (4.1%)
Vomiting	8 (2.3%)	20 (5.5%)
Diarrhea	5 (1.4%)	17 (4.7%)
Dehydration	3 (0.9%)	12 (3.3%)
Fatigue	18 (5.2%)	39 (10.7%)
Infection w/o neutropenia	16 (4.6%)	33 (9.1%)
Infection w/ unknown ANC	1 (0.3%)	11 (3.0%)
Neutrophils	11 (3.2%)	21 (5.8%)
Rash/desquamation	1 (0.3%)	9 (2.5%)
Proteinuria	0 (0.0%)	11 (3.0%)

921

922 Sensory neuropathy, hypertension, and fatigue were reported at a $\geq 5\%$
 923 higher absolute incidence in the paclitaxel+Avastin arm compared
 924 with the paclitaxel alone arm.

925 Fatal adverse reactions occurred in 6/363 (1.7%) of patients who
 926 received paclitaxel plus Avastin. Causes of death were gastrointestinal
 927 perforation (2), myocardial infarction (2), diarrhea/abdominal
 928 pain/weakness/hypotension (2).

929 **Other Serious Adverse Events**

930 The following additional serious adverse events occurred in at least
931 one subject treated with Avastin in clinical studies or post-marketing
932 experience:

933 *Body as a Whole: polyserositis*

934 **Cardiovascular: pulmonary hypertension**

935 *Digestive: intestinal necrosis, mesenteric venous occlusion,*
936 *anastomotic ulceration*

937 *Hemic and lymphatic: pancytopenia*

938 *Respiratory: nasal septum perforation*

939 **OVERDOSAGE**

940 The highest dose tested in humans (20 mg/kg IV) was associated with
941 headache in nine of 16 patients and with severe headache in three of
942 16 patients.

943 **DOSAGE AND ADMINISTRATION**

944 Do not initiate Avastin until at least 28 days following major surgery.
945 The surgical incision should be fully healed prior to initiation of
946 Avastin.

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

948 Avastin, used in combination with intravenous 5-FU-based
949 chemotherapy, is administered as an intravenous infusion (5 mg/kg or
950 10 mg/kg) every 14 days.

951 The recommended dose of Avastin, when used in combination with
952 bolus-IFL, is 5 mg/kg.

953 The recommended dose of Avastin, when used in combination with
954 FOLFOX4, is 10 mg/kg.

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

956 The recommended dose of Avastin is 15 mg/kg, as an IV infusion
957 every 3 weeks.

958 **Metastatic Breast Cancer**

959 The recommended dose of Avastin is 10 mg/kg, as an IV infusion
960 every 14 days.

961 **Dose Modifications**

962 There are no recommended dose reductions for the use of Avastin.
963 If needed, Avastin should be either discontinued or temporarily
964 suspended as described below.

965 Avastin should be permanently discontinued in patients who develop
966 gastrointestinal perforation (gastrointestinal perforation, fistula
967 formation in the gastrointestinal tract, intra-abdominal abscess), fistula
968 formation involving an internal organ, wound dehiscence requiring
969 medical intervention, serious bleeding, a severe arterial
970 thromboembolic event, nephrotic syndrome, hypertensive crisis or
971 hypertensive encephalopathy. In patients developing RPLS,
972 discontinue Avastin and initiate treatment of hypertension, if present.
973 (See **WARNINGS: Reversible Posterior Leukoencephalopathy**
974 **Syndrome.**)

975 Temporary suspension of Avastin is recommended in patients with
976 evidence of moderate to severe proteinuria pending further evaluation
977 and in patients with severe hypertension that is not controlled with
978 medical management. The risk of continuation or temporary
979 suspension of Avastin in patients with moderate to severe proteinuria
980 is unknown.

981 Avastin should be suspended at least several weeks prior to elective
982 surgery. (See **WARNINGS: Gastrointestinal Perforation** and
983 **Wound Healing Complications** and **PRECAUTIONS: Surgery.**)
984 Avastin should not be resumed until the surgical incision is fully
985 healed.

986 **Preparation for Administration**

987 Avastin should be diluted for infusion by a healthcare professional
988 using aseptic technique. Withdraw the necessary amount of Avastin to
989 obtain the required dose and dilute in a total volume of 100 mL of
990 0.9% Sodium Chloride Injection, USP. Discard any unused portion
991 left in a vial, as the product contains no preservatives. Parenteral drug
992 products should be inspected visually for particulate matter and
993 discoloration prior to administration.

994 Diluted Avastin solutions for infusion may be stored at 2°C–8°C
995 (36°F–46°F) for up to 8 hours. No incompatibilities between Avastin
996 and polyvinylchloride or polyolefin bags have been observed.

997 **Avastin infusions should not be administered or mixed with**
998 **dextrose solutions.**

999 **Administration**

1000 **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.** The initial
1001 Avastin dose should be delivered over 90 minutes as an IV infusion
1002 following chemotherapy. If the first infusion is well tolerated, the
1003 second infusion may be administered over 60 minutes. If the
1004 60-minute infusion is well tolerated, all subsequent infusions may be
1005 administered over 30 minutes.

1006 **Stability and Storage**

1007 Avastin vials must be refrigerated at 2–8°C (36–46°F). Avastin vials
1008 should be protected from light. Store in the original carton until time
1009 of use. **DO NOT FREEZE. DO NOT SHAKE.**

1010 **HOW SUPPLIED**

1011 Avastin is supplied as 4 mL and 16 mL of a sterile solution in
1012 single-use glass vials to deliver 100 and 400 mg of Bevacizumab per
1013 vial, respectively.

- 1014 Single unit 100 mg carton: Contains one 4 mL vial of Avastin
1015 (25 mg/mL). NDC 50242-060-01
- 1016 Single unit 400 mg carton: Contains one 16 mL vial of Avastin
1017 (25 mg/mL). NDC 50242-061-01

1018 **REFERENCES**

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1023

Avastin®
(Bevacizumab)

For Intravenous Use

Manufactured by: 745530X

Genentech, Inc. LV0017

1 DNA Way 483570X

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