

Final Draft  
3-1-06

1 **ERBITUX<sup>®</sup>**

Rx only

2 (Cetuximab)

3 For intravenous use only.

4 **WARNING**

5 **Infusion Reactions:** Severe infusion reactions occurred with the administration of  
6 ERBITUX in approximately 3% of patients, rarely with fatal outcome (<1 in 1000).  
7 Approximately 90% of severe infusion reactions were associated with the first infusion of  
8 ERBITUX. Severe infusion reactions are characterized by rapid onset of airway  
9 obstruction (bronchospasm, stridor, hoarseness), urticaria, hypotension and/or cardiac  
10 arrest (see **WARNINGS** and **ADVERSE REACTIONS**). Severe infusion reactions  
11 require immediate interruption of the ERBITUX infusion and permanent discontinuation  
12 from further treatment. (See **WARNINGS: Infusion Reactions** and **DOSAGE AND**  
13 **ADMINISTRATION: Dose Modifications.**)

14 **Cardiopulmonary Arrest:** Cardiopulmonary arrest and/or sudden death occurred in 2%  
15 (4/208) of patients with squamous cell carcinoma of the head and neck treated with  
16 radiation therapy and ERBITUX as compared to none of 212 patients treated with  
17 radiation therapy alone. Fatal events occurred within 1 to 43 days after the last  
18 ERBITUX treatment. ERBITUX in combination with radiation therapy should be used  
19 with caution in head and neck cancer patients with known coronary artery disease,  
20 congestive heart failure, and arrhythmias. Although the etiology of these events is  
21 unknown, close monitoring of serum electrolytes, including serum magnesium,  
22 potassium, and calcium, during and after ERBITUX therapy is recommended. (See  
23 **WARNINGS: Cardiopulmonary Arrest**, **PRECAUTIONS: Laboratory Tests:**  
24 **Electrolyte Monitoring**, and **ADVERSE REACTIONS: Electrolyte Depletion.**)

25 **DESCRIPTION**

26 ERBITUX<sup>®</sup> (Cetuximab) is a recombinant, human/mouse chimeric monoclonal antibody  
27 that binds specifically to the extracellular domain of the human epidermal growth factor  
28 receptor (EGFR). Cetuximab is composed of the Fv regions of a murine anti-EGFR  
29 antibody with human IgG1 heavy and kappa light chain constant regions and has an  
30 approximate molecular weight of 152 kDa. Cetuximab is produced in mammalian  
31 (murine myeloma) cell culture.

32 ERBITUX is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small  
33 amount of easily visible, white, amorphous, Cetuximab particulates. Each single-use,  
34 50-mL vial contains 100 mg of Cetuximab at a concentration of 2 mg/mL and is  
35 formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride,  
36 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.41 mg/mL sodium phosphate  
37 monobasic monohydrate, and Water for Injection, USP.

## 38 **CLINICAL PHARMACOLOGY**

### 39 **General**

40 The epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) is a transmembrane  
41 glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including  
42 EGFR, HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal  
43 epithelial tissues, including the skin and hair follicle. Expression of EGFR is also  
44 detected in many human cancers including those of the head and neck, colon, and rectum.

45 Cetuximab binds specifically to the EGFR on both normal and tumor cells, and  
46 competitively inhibits the binding of epidermal growth factor (EGF) and other ligands,  
47 such as transforming growth factor- $\alpha$ . *In vitro* assays and *in vivo* animal studies have  
48 shown that binding of Cetuximab to the EGFR blocks phosphorylation and activation of  
49 receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis,  
50 and decreased matrix metalloproteinase and vascular endothelial growth factor  
51 production. *In vitro*, Cetuximab can mediate antibody-dependent cellular cytotoxicity  
52 (ADCC) against certain human tumor types. While the mechanism of Cetuximab's anti-  
53 tumor effect(s) *in vivo* is unknown, all of these processes may contribute to the overall  
54 therapeutic effect of Cetuximab.

55 *In vitro* assays and *in vivo* animal studies have shown that Cetuximab inhibits the growth  
56 and survival of tumor cells that express the EGFR. No anti-tumor effects of Cetuximab  
57 were observed in human tumor xenografts lacking EGFR expression. The addition of  
58 Cetuximab to radiation therapy, irinotecan, or irinotecan plus 5-fluorouracil in human  
59 tumor xenograft models in mice resulted in an increase in anti-tumor effects compared to  
60 radiation therapy or chemotherapy alone.

### 61 **Human Pharmacokinetics**

62 ERBITUX administered as monotherapy or in combination with concomitant  
63 chemotherapy or radiation therapy exhibits nonlinear pharmacokinetics. The

64 pharmacokinetics of Cetuximab were similar in patients with squamous cell carcinoma of  
65 the head and neck (SCCHN) and those with colorectal cancer. The area under the  
66 concentration time curve (AUC) increased in a greater than dose proportional manner as  
67 the dose increased from 20 to 400 mg/m<sup>2</sup>. Clearance of Cetuximab decreased from 0.08  
68 to 0.02 L/h/m<sup>2</sup> as the dose increased from 20 to 200 mg/m<sup>2</sup>, and at doses >200 mg/m<sup>2</sup>, it  
69 appeared to plateau. The volume of the distribution for Cetuximab appeared to be  
70 independent of dose and approximated the vascular space of 2-3 L/m<sup>2</sup>.

71 Following a 2-hour infusion of 400 mg/m<sup>2</sup> of ERBITUX, the maximum mean serum  
72 concentration (C<sub>max</sub>) was 199 µg/mL (range: 70-380 µg/mL) and the mean elimination  
73 half-life was 97 hours (range 41-213 hours). A 1-hour infusion of 250 mg/m<sup>2</sup> produced a  
74 mean C<sub>max</sub> of 168 µg/mL (range 69-404 µg/mL). Following the recommended dose  
75 regimen (400 mg/m<sup>2</sup> initial dose/250 mg/m<sup>2</sup> weekly dose), concentrations of Cetuximab  
76 reached steady-state levels by the third weekly infusion with mean peak and trough  
77 concentrations across studies ranging from 168 to 235 and 41 to 85 µg/mL, respectively.  
78 The mean half-life of Cetuximab was approximately 112 hours (range 63-230 hours).

## 79 **Special Populations**

80 A population pharmacokinetic analysis was performed to explore the potential effects of  
81 selected covariates including body surface area (BSA), age, gender, race, and hepatic and  
82 renal function on the pharmacokinetics of Cetuximab.

83 Clearance of Cetuximab increased 1.8-fold as BSA increased from 1.3 to 2.3 m<sup>2</sup> (1.8-  
84 fold). This finding supports the recommended dosing of Cetuximab on a mg/m<sup>2</sup> basis.

85 In patients with colorectal cancer, female patients had a 25% lower intrinsic clearance of  
86 Cetuximab than male patients. The gender differences in clearance do not necessitate any  
87 alteration of dosing because of a similar safety profile. Definitive conclusions regarding  
88 comparability in efficacy cannot be made given the small number of patients with  
89 objective tumor responses. None of the other patient population covariates explored  
90 appeared to have an impact on the pharmacokinetics of Cetuximab. Qualitatively similar,  
91 but smaller gender differences in Cetuximab clearance were observed in patients with  
92 SCCHN.

93 ERBITUX has not been studied in pediatric populations.

94 **CLINICAL STUDIES**

95 **Squamous Cell Carcinoma of the Head and Neck**

96 **Randomized Trial of Radiation Therapy plus Cetuximab vs. Radiation**  
97 **Therapy**

98 The safety and efficacy of ERBITUX were studied in combination with radiation therapy  
99 in a randomized, controlled trial of 424 patients with locally or regionally advanced  
100 squamous cell carcinoma of the head and neck (SCCHN) versus radiation therapy alone.  
101 In a multicenter, controlled clinical trial, 424 patients with Stage III/IV SCC of the  
102 oropharynx, hypopharynx, or larynx with no prior therapy were randomized (1:1) to  
103 receive either ERBITUX plus radiation therapy (211 patients) or radiation therapy alone  
104 (213 patients). Stratification factors were Karnofsky Performance Status (60-80 versus  
105 90-100), nodal stage (N0 versus N+), tumor stage (T1-3 versus T4 using American Joint  
106 Committee on Cancer 1998 staging criteria), and radiation therapy fractionation  
107 (concomitant boost versus once-daily versus twice-daily). Radiation therapy was  
108 administered for 6-7 weeks as once daily, twice daily, or concomitant boost. The planned  
109 radiation therapy regimen was chosen by the investigator prior to enrollment. For patients  
110 with  $\geq$ N1 neck disease, a post-radiation therapy neck dissection was recommended.  
111 Starting one week before radiation, ERBITUX was administered as a 400-mg/m<sup>2</sup> initial  
112 dose, followed by 250 mg/m<sup>2</sup> weekly for the duration of radiation therapy (6-7 weeks).  
113 All ERBITUX-treated patients received a 20-mg test dose on Day 1. Cetuximab was  
114 administered 1 hour prior to radiation therapy, beginning week 2.

115 Of the 424 randomized patients, 80% were male and 83% were Caucasian. The median  
116 age was 57 years (range 34–83). There were 258 patients enrolled in US sites (61%) and  
117 166 patients (39%) in non-US sites. Ninety percent of patients had baseline Karnofsky  
118 Performance Status  $\geq$ 80; 60% had oropharyngeal, 25% laryngeal, and 15%  
119 hypopharyngeal primary tumors; 28% had AJCC T4 tumor stage. The patient  
120 characteristics were similar across the study arms. Fifty-six percent of the patients  
121 received radiation therapy with concomitant boost, 26% received once-daily regimen, and  
122 18% twice-daily regimen.

123 The main outcome measure of this trial was duration of locoregional control. Overall  
124 survival was also assessed. Results are presented in Table 1.

125

**Table 1: Clinical Efficacy in Locoregionally Advanced SCCHN**

	ERBITUX + Radiation (n=211)	Radiation Alone (n=213)	Hazard Ratio (95% CI) <sup>a</sup>	Stratified Log-rank p-value
<b>Locoregional control</b>				
Median duration	24.4 mo	14.9 mo	0.68 (0.52–0.89)	0.005
<b>Overall survival</b>				
Median duration	49.0 mo	29.3 mo	0.74 (0.57–0.97)	0.03

<sup>a</sup> CI = confidence interval

126

127 **Single-Arm Trial**

128 ERBITUX alone was studied in a single-arm, multicenter clinical trial in 103 patients  
 129 with recurrent or metastatic SCCHN with documented progression within 30 days after  
 130 2–6 cycles of a platinum-based chemotherapy. Patients received a 20-mg test dose of  
 131 ERBITUX on Day 1, followed by a 400-mg/m<sup>2</sup> initial dose, and 250 mg/m<sup>2</sup> weekly until  
 132 disease progression or unacceptable toxicity. Upon progression, patients were given the  
 133 option of receiving ERBITUX plus the platinum regimen that they failed prior to  
 134 enrollment. Tumor response and progression were assessed by an Independent  
 135 Radiographic Review Committee (IRC).

136 The median age was 57 years (range 23–77), 82% were male, 100% Caucasian, and 62%  
 137 had a Karnofsky performance status of ≥80.

138 The objective response rate on the monotherapy phase was 13% (95% confidence interval  
 139 7%–21%). Median duration of response was 5.8 months (range 1.2–5.8 months).

140 **Colorectal Cancer**

141 The efficacy and safety of ERBITUX alone or in combination with irinotecan were  
 142 studied in a randomized, controlled trial (329 patients) and in combination with  
 143 irinotecan in an open-label, single-arm trial (138 patients). ERBITUX was further  
 144 evaluated as a single agent in a third clinical trial (57 patients). Safety data from 111  
 145 patients treated with single-agent ERBITUX was also evaluated. All trials studied  
 146 patients with EGFR-expressing, metastatic colorectal cancer, whose disease had  
 147 progressed after receiving an irinotecan-containing regimen.

148 **Randomized Trial of Monotherapy vs. Combination Therapy**

149 A multicenter, randomized, controlled clinical trial was conducted in 329 patients  
150 randomized to receive either ERBITUX plus irinotecan (218 patients) or ERBITUX  
151 monotherapy (111 patients). In both arms of the study, ERBITUX was administered as a  
152 400-mg/m<sup>2</sup> initial dose, followed by 250 mg/m<sup>2</sup> weekly until disease progression or  
153 unacceptable toxicity. All patients received a 20-mg test dose on Day 1. In the  
154 ERBITUX plus irinotecan arm, irinotecan was added to ERBITUX using the same dose  
155 and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan  
156 schedules were 350 mg/m<sup>2</sup> every 3 weeks, 180 mg/m<sup>2</sup> every 2 weeks, or 125 mg/m<sup>2</sup>  
157 weekly times four doses every 6 weeks. An IRC, blinded to the treatment arms, assessed  
158 both the progression on prior irinotecan and the response to protocol treatment for all  
159 patients.

160 Of the 329 randomized patients, 206 (63%) were male. The median age was 59 years  
161 (range 26-84), and the majority was Caucasian (323, 98%). Eighty-eight percent of  
162 patients had baseline Karnofsky Performance Status ≥80. Fifty-eight percent of patients  
163 had colon cancer and 40% rectal cancer. Approximately two-thirds (63%) of patients had  
164 previously failed oxaliplatin treatment.

165 The efficacy of ERBITUX plus irinotecan or ERBITUX monotherapy was evaluated in  
166 all randomized patients.

167 Analyses were also conducted in two pre-specified subpopulations: irinotecan refractory  
168 and irinotecan and oxaliplatin failures. The irinotecan refractory population was defined  
169 as randomized patients who had received at least two cycles of irinotecan-based  
170 chemotherapy prior to treatment with ERBITUX, and had independent confirmation of  
171 disease progression within 30 days of completion of the last cycle of irinotecan-based  
172 chemotherapy.

173 The irinotecan and oxaliplatin failure population was defined as irinotecan refractory  
174 patients who had previously been treated with and failed an oxaliplatin-containing  
175 regimen.

176 The objective response rates (ORR) in these populations are presented in Table 2.

**Table 2 : Objective Response Rates per Independent Review**

Populations	ERBITUX + Irinotecan		ERBITUX Monotherapy		Difference (95% CI <sup>a</sup> )	
	n	ORR (%)	N	ORR (%)	%	p-value CMH <sup>b</sup>
All Patients	218	22.9	111	10.8	12.1 (4.1 - 20.2)	0.007
• Irinotecan-Oxaliplatin Failure	80	23.8	44	11.4	12.4 (-0.8 - 25.6)	0.09
• Irinotecan Refractory	132	25.8	69	14.5	11.3 (0.1 - 22.4)	0.07

177 <sup>a</sup>95% confidence interval for the difference in objective response rates.

178 <sup>b</sup>Cochran-Mantel-Haenszel test.

179

180 The median duration of response in the overall population was 5.7 months in the  
 181 combination arm and 4.2 months in the monotherapy arm. Compared with patients  
 182 randomized to ERBITUX alone, patients randomized to ERBITUX and irinotecan  
 183 experienced a significantly longer median time to disease progression (see Table 3).

**Table 3: Time to Progression per Independent Review**

Populations	ERBITUX + Irinotecan (median)	ERBITUX Monotherapy (median)	Hazard Ratio (95% CI <sup>a</sup> )	Log-rank p-value
All Patients	4.1 mo	1.5 mo	0.54 (0.42 - 0.71)	<0.001
• Irinotecan-Oxaliplatin Failure	2.9 mo	1.5 mo	0.48 (0.31 - 0.72)	<0.001
• Irinotecan Refractory	4.0 mo	1.5 mo	0.52 (0.37 - 0.73)	<0.001

184 <sup>a</sup>Hazard ratio of ERBITUX + irinotecan: ERBITUX monotherapy with 95% confidence interval.

185

186 **Single-Arm Trials**

187 ERBITUX, in combination with irinotecan, was also studied in a single-arm, multicenter,  
 188 open-label clinical trial in 138 patients with EGFR-expressing metastatic colorectal  
 189 cancer who had progressed following an irinotecan-containing regimen using the same  
 190 dose and schedule of ERBITUX as in the randomized trial (above). Patients received the  
 191 same dose and schedule for irinotecan as the patient had previously failed. Of 138

192 patients enrolled, 74 patients had documented progression to irinotecan as determined by  
193 an IRC. The overall response rate was 15% for the overall population and 12% for the  
194 irinotecan-failure population. The median durations of response were 6.5 and 6.7  
195 months, respectively.

196 ERBITUX was also studied as a single agent in a multicenter, open-label, single-arm  
197 clinical trial in patients with EGFR-expressing, metastatic colorectal cancer who  
198 progressed following an irinotecan-containing regimen. Of 57 patients enrolled, 28  
199 patients had documented progression to irinotecan. The overall response rate was 9% for  
200 the all-treated group and 14% for the irinotecan-failure group. The median duration of  
201 response was 4.2 months for both groups.

## 202 **EGFR Expression and Response**

203 Since expression of EGFR has been detected in nearly all patients with head and neck  
204 cancer, patients enrolled in the head and neck cancer clinical studies were not required to  
205 have immunohistochemical evidence of EGFR expression prior to study entry.

206 Patients enrolled in the colorectal cancer clinical studies were required to have  
207 immunohistochemical evidence of EGFR expression. Primary tumor or tumor from a  
208 metastatic site was tested with the DakoCytomation EGFR pharmDx<sup>TM</sup> test kit.  
209 Specimens were scored based on the percentage of cells expressing EGFR and intensity  
210 (barely/faint, weak to moderate, and strong). Response rate did not correlate with either  
211 the percentage of positive cells or the intensity of EGFR expression.

## 212 **INDICATIONS AND USAGE**

### 213 **Head and Neck Cancer**

214 ERBITUX, in combination with radiation therapy, is indicated for the treatment of locally  
215 or regionally advanced squamous cell carcinoma of the head and neck.

216 ERBITUX as a single agent is indicated for the treatment of patients with recurrent or  
217 metastatic squamous cell carcinoma of the head and neck for whom prior platinum-based  
218 therapy has failed.

### 219 **Colorectal Cancer**

220 ERBITUX, used in combination with irinotecan, is indicated for the treatment of EGFR-  
221 expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-  
222 based chemotherapy.

223 ERBITUX administered as a single agent is indicated for the treatment of EGFR-  
224 expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-  
225 based chemotherapy.

226 The effectiveness of ERBITUX for the treatment of EGFR-expressing, metastatic  
227 colorectal carcinoma is based on objective response rates (see **CLINICAL STUDIES**).  
228 Currently, no data are available that demonstrate an improvement in disease-related  
229 symptoms or increased survival with ERBITUX for the treatment of EGFR-expressing,  
230 metastatic colorectal carcinoma.

### 231 **CONTRAINDICATIONS**

232 None.

### 233 **WARNINGS**

#### 234 **Infusion Reactions (See **BOXED WARNING: Infusion Reactions,**** 235 **ADVERSE REACTIONS: Infusion Reactions, and **DOSAGE AND**** 236 **ADMINISTRATION: Dose Modifications.**)

237 Severe infusion reactions occurred with the administration of ERBITUX in  
238 approximately 3% (46/1485) of patients, rarely with fatal outcome (<1 in 1000).  
239 Approximately 90% of severe infusion reactions were associated with the first infusion of  
240 ERBITUX despite the use of prophylactic antihistamines. These reactions were  
241 characterized by the rapid onset of airway obstruction (bronchospasm, stridor,  
242 hoarseness), urticaria, hypotension, and/or cardiac arrest. Caution must be exercised with  
243 every ERBITUX infusion, as there were patients who experienced their first severe  
244 infusion reaction during later infusions. A 1-hour observation period is recommended  
245 following the ERBITUX infusion. Longer observation periods may be required in  
246 patients who experience infusion reactions.

247 Severe infusion reactions require the immediate interruption of ERBITUX therapy and  
248 permanent discontinuation from further treatment. Appropriate medical therapy including  
249 epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen  
250 should be available for use in the treatment of such reactions. Patients should be carefully  
251 observed until the complete resolution of all signs and symptoms.

252 In clinical trials, mild to moderate infusion reactions were managed by slowing the  
253 infusion rate of ERBITUX and by continued use of antihistamine medications (eg,

254 diphenhydramine) in subsequent doses (see **DOSAGE AND ADMINISTRATION:**  
255 **Dose Modifications**).

256 **Cardiopulmonary Arrest (See BOXED WARNING:**  
257 **Cardiopulmonary Arrest, PRECAUTIONS: Laboratory Tests:**  
258 **Electrolyte Monitoring, and ADVERSE REACTIONS: Electrolyte**  
259 **Depletion.)**

260 In a randomized, controlled trial in patients with squamous cell carcinoma of the head  
261 and neck (SCCHN), cardiopulmonary arrest and/or sudden death occurred in 4/208  
262 patients (2%) treated with radiation therapy and ERBITUX as compared to none of 212  
263 patients treated with radiation therapy alone. Three patients with prior history of  
264 coronary artery disease died at home, with myocardial infarction as the presumed cause  
265 of death. One of these patients had arrhythmia and one had congestive heart failure.  
266 Death occurred 27, 32, and 43 days after the last dose of ERBITUX. One patient with no  
267 prior history of coronary artery disease died one day after the last dose of ERBITUX.  
268 ERBITUX in combination with radiation therapy should be used with caution in head and  
269 neck cancer patients with a history of coronary artery disease, congestive heart failure,  
270 and arrhythmias. Although the etiology of these events is unknown, close monitoring of  
271 serum electrolytes, including serum magnesium, potassium, and calcium, during and after  
272 ERBITUX therapy is recommended.

### 273 **Pulmonary Toxicity**

274 Interstitial lung disease (ILD) was reported in 3 of 774 (<0.5%) patients with advanced  
275 colorectal cancer and in 1 of 796 patients with head and neck cancer receiving ERBITUX  
276 in clinical studies. Among these four cases, interstitial pneumonitis with non-cardiogenic  
277 pulmonary edema resulting in death was reported in one patient with colon cancer. In two  
278 of the remaining cases, the patients had pre-existing fibrotic lung disease and experienced  
279 an acute exacerbation of their disease while receiving ERBITUX in combination with  
280 irinotecan. The onset of symptoms occurred between the fourth and eleventh doses of  
281 treatment in all reported cases.

282 In the event of acute onset or worsening pulmonary symptoms, ERBITUX therapy should  
283 be interrupted and a prompt investigation of these symptoms should occur. If ILD is  
284 confirmed, ERBITUX should be discontinued and the patient should be treated  
285 appropriately.

286 **Dermatologic Toxicity (See ADVERSE REACTIONS:**  
287 **Dermatologic Toxicity and DOSAGE AND ADMINISTRATION:**  
288 **Dose Modifications.)**

289 In cynomolgus monkeys, Cetuximab, when administered at doses of approximately 0.4 to  
290 4 times the weekly human exposure (based on total body surface area), resulted in  
291 dermatologic findings, including inflammation at the injection site and desquamation of  
292 the external integument. At the highest dose level, the epithelial mucosa of the nasal  
293 passage, esophagus, and tongue were similarly affected, and degenerative changes in the  
294 renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of  
295 the animals at the highest dose level beginning after approximately 13 weeks of  
296 treatment.

297 In clinical studies of ERBITUX, dermatologic toxicities, including acneform rash, skin  
298 drying and fissuring, and inflammatory and infectious sequelae (eg, blepharitis, cheilitis,  
299 cellulitis, cyst) were reported. In patients with head and neck cancer treated with  
300 ERBITUX plus radiation, acneform rash was reported in 87% as compared with 10% in  
301 patients treated with radiation therapy alone. The incidence of severe acneform rash was  
302 markedly increased in the ERBITUX plus radiation arm (17% versus 1%). In patients  
303 with head and neck cancer treated with ERBITUX monotherapy, acneform rash was  
304 reported in 76% of patients and was severe in 1%. In patients with advanced colorectal  
305 cancer, acneform rash was reported in 89% (686/774) of all treated patients, and was  
306 severe in 11% (84/774). Subsequent to the development of severe dermatologic toxicities,  
307 complications including *S. aureus* sepsis and abscesses requiring incision and drainage  
308 were reported.

309 Patients developing dermatologic toxicities while receiving ERBITUX should be  
310 monitored for the development of inflammatory or infectious sequelae, and appropriate  
311 treatment of these symptoms initiated. Dose modifications of any future ERBITUX  
312 infusions should be instituted in case of severe acneform rash (see **DOSAGE AND**  
313 **ADMINISTRATION**, Table 6). Treatment with topical and/or oral antibiotics should be  
314 considered; topical corticosteroids are not recommended.

315 **Use of ERBITUX in Combination With Radiation and Cisplatin**

316 The safety of ERBITUX in combination with radiation therapy and cisplatin has not been  
317 established. Death and serious cardiotoxicity were observed in a single-arm trial with  
318 ERBITUX, delayed, accelerated (concomitant boost) fractionation radiation therapy, and

319 cisplatin (100 mg/m<sup>2</sup>) conducted in patients with locally advanced squamous cell  
320 carcinoma of the head and neck. Two of 21 patients died, one as a result of pneumonia  
321 and one of an unknown cause. Four patients discontinued treatment due to adverse  
322 events. Two of these discontinuations were due to cardiac events (myocardial infarction  
323 in one patient and arrhythmia, diminished cardiac output, and hypotension in the other  
324 patient).

## 325 **PRECAUTIONS**

### 326 **General**

327 ERBITUX therapy should be used with caution in patients with known hypersensitivity  
328 to Cetuximab, murine proteins, or any component of this product.

329 It is recommended that patients wear sunscreen and hats and limit sun exposure while  
330 receiving ERBITUX as sunlight can exacerbate any skin reactions that may occur.

### 331 **Use of ERBITUX in Combination with Radiation Therapy**

332 ERBITUX plus radiation therapy should be used with caution in patients with a known  
333 history of coronary artery disease, arrhythmias and congestive heart failure. Close  
334 monitoring of serum electrolytes, including serum magnesium, potassium, and calcium,  
335 during and after ERBITUX therapy is recommended. (See **BOXED WARNING**,  
336 **WARNINGS: Cardiopulmonary Arrest**, and **PRECAUTIONS: Laboratory Tests:**  
337 **Electrolyte Monitoring**.)

### 338 **EGF Receptor Testing**

#### 339 **Head and Neck Cancer**

340 Pretreatment assessment for evidence of EGFR expression is not required for patients  
341 with squamous cell carcinoma of the head and neck (SCCHN).

#### 342 **Colorectal Cancer**

343 Patients enrolled in the colorectal cancer clinical studies were required to have  
344 immunohistochemical evidence of EGFR expression using the DakoCytomation EGFR  
345 pharmDx™ test kit. Assessment for EGFR expression should be performed by  
346 laboratories with demonstrated proficiency in the specific technology being utilized.  
347 Improper assay performance, including use of suboptimally fixed tissue, failure to utilize  
348 specified reagents, deviation from specific assay instructions, and failure to include

349 appropriate controls for assay validation, can lead to unreliable results. Refer to the  
350 DakoCytomation test kit package insert for full instructions on assay performance. (See  
351 **CLINICAL STUDIES: EGFR Expression and Response.**)

### 352 **Laboratory Tests: Electrolyte Monitoring**

353 Patients should be periodically monitored for hypomagnesemia, and accompanying  
354 hypocalcemia and hypokalemia, during and following the completion of ERBITUX  
355 therapy. Monitoring should continue for a period of time commensurate with the half-life  
356 and persistence of the product; ie, 8 weeks. (See **ADVERSE REACTIONS: Electrolyte**  
357 **Depletion.**)

### 358 **Drug Interactions**

359 A drug interaction study was performed in which ERBITUX was administered in  
360 combination with irinotecan. There was no evidence of any pharmacokinetic interactions  
361 between ERBITUX and irinotecan.

### 362 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

363 Long-term animal studies have not been performed to test Cetuximab for carcinogenic  
364 potential. No mutagenic or clastogenic potential of Cetuximab was observed in the  
365 *Salmonella-Escherichia coli* (Ames) assay or in the *in vivo* rat micronucleus test. A 39-  
366 week toxicity study in cynomolgus monkeys receiving 0.4 to 4 times the human dose of  
367 Cetuximab (based on total body surface area) revealed a tendency for impairment of  
368 menstrual cycling in treated female monkeys, including increased incidences of  
369 irregularity or absence of cycles, when compared to control animals, and beginning from  
370 week 25 of treatment and continuing through the 6-week recovery period. Serum  
371 testosterone levels and analysis of sperm counts, viability, and motility were not  
372 remarkably different between Cetuximab-treated and control male monkeys. It is not  
373 known if Cetuximab can impair fertility in humans.

### 374 **Pregnancy Category C**

375 Animal reproduction studies have not been conducted with Cetuximab. However, the  
376 EGFR has been implicated in the control of prenatal development and may be essential  
377 for normal organogenesis, proliferation, and differentiation in the developing embryo. In  
378 addition, human IgG1 is known to cross the placental barrier; therefore Cetuximab has  
379 the potential to be transmitted from the mother to the developing fetus. It is not known  
380 whether ERBITUX can cause fetal harm when administered to a pregnant woman or

381 whether ERBITUX can affect reproductive capacity. There are no adequate and well-  
382 controlled studies of ERBITUX in pregnant women. ERBITUX should only be given to  
383 a pregnant woman, or any woman not employing adequate contraception if the potential  
384 benefit justifies the potential risk to the fetus. All patients should be counseled regarding  
385 the potential risk of ERBITUX treatment to the developing fetus prior to initiation of  
386 therapy. If the patient becomes pregnant while receiving this drug, she should be  
387 apprised of the potential hazard to the fetus and/or the potential risk for loss of the  
388 pregnancy.

### 389 **Nursing Mothers**

390 It is not known whether ERBITUX is secreted in human milk. Because human IgG is  
391 secreted in human milk, the potential for absorption and harm to the infant after ingestion  
392 exists. Based on the mean half-life of Cetuximab after multiple dosing of 114 hours  
393 [range 75-188 hours] (see **CLINICAL PHARMACOLOGY: Human**  
394 **Pharmacokinetics**), women should be advised to discontinue nursing during treatment  
395 with ERBITUX and for 60 days following the last dose of ERBITUX.

### 396 **Pediatric Use**

397 The safety and effectiveness of ERBITUX in pediatric patients have not been established.

### 398 **Geriatric Use**

399 Of the 424 patients with head and neck cancer who received ERBITUX with radiation  
400 therapy or radiation therapy alone, 110 patients were 65 years of age or older [65 (30%)  
401 in the radiation therapy alone arm, 45 (21%) in the radiation and ERBITUX arm]. In a  
402 subgroup analysis of patients less than 65 years of age, the hazard ratio of the radiation  
403 and ERBITUX arm versus radiation therapy alone arm for duration of locoregional  
404 control was 0.68 (95% confidence interval 0.50–0.93), and in patients age 65 years and  
405 older the hazard ratio was 0.87 (95% confidence interval 0.56–1.37). For overall  
406 survival, the hazard ratio in patients less than 65 years of age was 0.68 (95% confidence  
407 interval 0.49–0.94), and in patients age 65 years and older the hazard ratio was 1.15 (95%  
408 confidence interval 0.72–1.84).

409 Of the 774 patients who received ERBITUX with irinotecan or ERBITUX monotherapy  
410 in four advanced colorectal cancer studies, 253 patients (33%) were 65 years of age or  
411 older. No overall differences in safety or efficacy were observed between these patients  
412 and younger patients.

## 413 **ADVERSE REACTIONS**

414 Because clinical trials are conducted under widely varying conditions, adverse reaction  
415 rates observed in the clinical trials of a drug cannot be directly compared to rates in the  
416 clinical trials of another drug and may not reflect the rates observed in practice. The  
417 adverse reaction information from clinical trials does, however, provide a basis for  
418 identifying the adverse events that appear to be related to drug use and for approximating  
419 rates.

## 420 **Immunogenicity**

421 As with all therapeutic proteins, there is potential for immunogenicity. Potential  
422 immunogenic responses to Cetuximab were assessed using either a double antigen  
423 radiometric assay or an enzyme-linked immunosorbant assay. Due to limitations in assay  
424 performance and sampling timing, the incidence of antibody development in patients  
425 receiving ERBITUX has not been adequately determined. The incidence of antibodies to  
426 Cetuximab was measured by collecting and analyzing serum pre-study, prior to selected  
427 infusions and during treatment follow-up. Patients were considered evaluable if they had  
428 a negative pre-treatment sample and a post-treatment sample. Non-neutralizing anti-  
429 Cetuximab antibodies were detected in 5% (49 of 1001) of evaluable patients. In patients  
430 positive for anti-Cetuximab antibody, the median time to onset was 44 days (range 8-281  
431 days). Although the number of sero-positive patients is limited, there does not appear to  
432 be any relationship between the appearance of antibodies to Cetuximab and the safety or  
433 antitumor activity of ERBITUX.

434 The observed incidence of anti-Cetuximab antibody responses may be influenced by the  
435 low sensitivity of available assays, inadequate to reliably detect lower antibody titers.  
436 Other factors which might influence the incidence of anti-Cetuximab antibody response  
437 include sample handling, timing of sample collection, concomitant medications, and  
438 underlying disease. For these reasons, comparison of the incidence of antibodies to  
439 Cetuximab with the incidence of antibodies to other products may be misleading.

## 440 **Electrolyte Depletion**

441 In 244 patients evaluated in ongoing, controlled clinical trials, the incidence of  
442 hypomagnesemia, both overall and severe (NCI-CTC Grades 3 and 4), was increased in  
443 patients receiving ERBITUX alone or in combination with chemotherapy as compared to  
444 those receiving best supportive care or chemotherapy alone. Approximately one-half of  
445 these patients receiving ERBITUX experienced hypomagnesemia and 10-15%

446 experienced severe hypomagnesemia. The onset of electrolyte abnormalities has been  
447 reported to occur from days to months after initiation of ERBITUX. Electrolyte repletion  
448 was necessary in some patients and in severe cases, intravenous replacement was  
449 required. The time to resolution of electrolyte abnormalities is not well known, hence  
450 monitoring during and after ERBITUX treatment is recommended. (See  
451 **PRECAUTIONS: Laboratory Tests: Electrolyte Monitoring.**)

#### 452 **Infusion Reactions (see **BOXED WARNING: Infusion Reactions**)**

453 In clinical trials, severe, potentially fatal infusion reactions were reported. These events  
454 include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness),  
455 urticaria, and/or hypotension. In major clinical studies in advanced SCCHN, severe  
456 infusion reactions (Grade 3 or 4) were observed in 3% of patients receiving ERBITUX  
457 plus radiation and 4% of patients receiving ERBITUX monotherapy. In studies in  
458 advanced colorectal cancer, severe infusion reactions were observed in 3% of patients  
459 receiving ERBITUX plus irinotecan and 2% of patients receiving ERBITUX  
460 monotherapy. Grade 1 and 2 infusion reactions, including chills, fever, and dyspnea  
461 usually occurring on the first day of initial dosing, were observed in 16% of patients  
462 receiving ERBITUX plus irinotecan and 19% of patients receiving ERBITUX  
463 monotherapy. (See **WARNINGS: Infusion Reactions** and **DOSAGE AND**  
464 **ADMINISTRATION: Dose Modifications.**)

465 In the clinical studies described above, a 20-mg test dose was administered intravenously  
466 over 10 minutes prior to the loading dose to all patients. The test dose did not reliably  
467 identify patients at risk for severe allergic reactions.

#### 468 **Head and Neck Cancer**

469 Except where indicated, the data described below reflect exposure to ERBITUX in 208  
470 patients with locally or regionally advanced SCCHN who received ERBITUX in  
471 combination with radiation and as monotherapy in 103 patients with recurrent or  
472 metastatic SCCHN. Of the 103 patients receiving ERBITUX monotherapy, 53 continued  
473 to a second phase with the combination of ERBITUX plus chemotherapy.

474 Patients receiving ERBITUX plus radiation therapy received a median of 8 doses (range  
475 1-11 infusions). The population had a median age of 56; 81% were male and 84%  
476 Caucasian.

477 Patients receiving ERBITUX monotherapy, received a median of 11 doses (range 1–45  
478 infusions). The population had a median age of 57; 82% were male and 100%  
479 Caucasian.

480 The most **serious adverse reactions** associated with ERBITUX in combination with  
481 radiation therapy in patients with head and neck cancer were:

- 482 • Infusion reaction (3%) (see **BOXED WARNINGS, WARNINGS, and**  
483 **DOSAGE AND ADMINISTRATION: Dose Modifications**);
- 484 • Cardiopulmonary arrest (2%) (see **BOXED WARNINGS, WARNINGS**);
- 485 • Dermatologic toxicity (2.5%) (see **WARNINGS and DOSAGE AND**  
486 **ADMINISTRATION: Dose Modifications**);
- 487 • Mucositis (6%);
- 488 • Radiation dermatitis (3%);
- 489 • Confusion (2%);
- 490 • Diarrhea (2%).

491

492 Fourteen (7%) patients receiving ERBITUX plus radiation therapy and 5 (5%) patients  
493 receiving ERBITUX monotherapy, discontinued treatment primarily because of adverse  
494 events.

495 The most common adverse events seen in 208 patients receiving ERBITUX in  
496 combination with radiation therapy were acneform rash (87%), mucositis (86%),  
497 radiation dermatitis (86%), weight loss (84%), xerostomia (72%), dysphagia (65%),  
498 asthenia (56%), nausea (49%), constipation (35%), and vomiting (29%).

499 The most common adverse events seen in 103 patients receiving ERBITUX monotherapy  
500 were acneform rash (76%), asthenia (45%), pain (28%), fever (27%), and weight loss  
501 (27%).

502 The data in Table 4 are based on the experience of 208 patients with locoregionally  
503 advanced SCCHN treated with ERBITUX plus radiation therapy compared to 212  
504 patients treated with radiation therapy alone.

**Table 4: Incidence of Selected Adverse Events (≥10%) in Patients with Locoregionally Advanced SCCN**

Body System Preferred Term	ERBITUX plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
% of Patients				
<b>Body as a Whole</b>				
Asthenia	56	4	49	5
Fever <sup>1</sup>	29	1	13	1
Headache	19	<1	8	<1
Infusion Reaction <sup>2</sup>	15	3	2	0
Infection	13	1	9	1
Chills <sup>1</sup>	16	0	5	0
<b>Digestive</b>				
Mucositis/Stomatitis	93	56	94	52
Xerostomia	72	5	71	3
Dysphagia	65	26	63	30
Nausea	49	2	37	2
Constipation	35	5	30	5
Vomiting	29	2	23	4
Anorexia	27	2	23	2
Diarrhea	19	2	13	1
Dyspepsia	14	0	9	1
<b>Metabolic/Nutritional</b>				
Weight Loss	84	11	72	7
Dehydration	25	6	19	8

**Table 4: Incidence of Selected Adverse Events (≥10%) in Patients with Locoregionally Advanced SCCHN**

Body System Preferred Term	ERBITUX plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
% of Patients				
<b>Respiratory</b>				
Pharyngitis	26	3	19	4
Cough Increased	20	<1	19	0
<b>Skin/Appendages</b>				
Acneform Rash <sup>3</sup>	87	17	10	1
Radiation Dermatitis	86	23	90	18
Application Site Reaction	18	0	12	1
Pruritus	16	0	4	0

<sup>1</sup> Includes cases also reported as infusion reaction.

<sup>2</sup> Infusion reaction is defined as any event described at any time during the clinical study as “allergic reaction” or “anaphylactoid reaction”, or any event occurring on the first day of dosing described as “allergic reaction”, “anaphylactoid reaction”, “fever”, “chills”, “chills and fever”, or “dyspnea”.

<sup>3</sup> Acneform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.

505

## 506 **Late Radiation Toxicity**

507 The overall incidence of late radiation toxicities (any grade) was higher in ERBITUX in  
508 combination with radiation therapy compared with radiation therapy alone. The following  
509 sites were affected: salivary glands (65% versus 56%), larynx (52% versus 36%),  
510 subcutaneous tissue (49% versus 45%), mucous membrane (48% versus 39%), esophagus  
511 (44% versus 35%), skin (42% versus 33%), brain (11% versus 9%), lung (11% versus  
512 8%), spinal cord (4% versus 3%), and bone (4% versus 5%). The incidence of Grade 3 or  
513 4 late radiation toxicities were generally similar between the radiation therapy alone and  
514 the ERBITUX plus radiation treatment groups.

515 **Colorectal Cancer**

516 Except where indicated, the data described below reflect exposure to ERBITUX in 774  
517 patients with advanced metastatic colorectal cancer. ERBITUX was studied in  
518 combination with irinotecan (n=354) or as monotherapy (n=420). Patients receiving  
519 ERBITUX plus irinotecan received a median of 12 doses [with 88/354 (25%) treated for  
520 over 6 months], and patients receiving ERBITUX monotherapy received a median of 7  
521 doses [with 36/420 (9%) treated for over 6 months]. The population had a median age of  
522 59 and was 59% male and 91% Caucasian. The range of dosing for patients receiving  
523 ERBITUX plus irinotecan was 1-84 infusions, and the range of dosing for patients  
524 receiving ERBITUX monotherapy was 1-63 infusions.

525 The most **serious adverse reactions** associated with ERBITUX were:

- 526 • Infusion reaction (3%) (see **BOXED WARNING, WARNINGS, and DOSAGE**  
527 **AND ADMINISTRATION: Dose Modifications**);
- 528 • Dermatologic toxicity (1%) (see **WARNINGS and DOSAGE AND**  
529 **ADMINISTRATION: Dose Modifications**);
- 530 • Interstitial lung disease (0.4%) (see **WARNINGS**);
- 531 • Fever (5%);
- 532 • Sepsis (3%);
- 533 • Kidney failure (2%);
- 534 • Pulmonary embolus (1%);
- 535 • Dehydration (5%) in patients receiving ERBITUX plus irinotecan, 2% in patients  
536 receiving ERBITUX monotherapy;
- 537 • Diarrhea (6%) in patients receiving ERBITUX plus irinotecan, 0.2% in patients  
538 receiving ERBITUX monotherapy.

539 Thirty-seven (10%) patients receiving ERBITUX plus irinotecan and 17 (4%) patients  
540 receiving ERBITUX monotherapy discontinued treatment primarily because of adverse  
541 events.

542 The most common adverse events seen in 354 patients receiving ERBITUX plus  
543 irinotecan were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), nausea  
544 (55%), abdominal pain (45%), and vomiting (41%).

545 The most common adverse events seen in 420 patients receiving ERBITUX monotherapy  
546 were acneform rash (90%), asthenia/malaise (48%), nausea (29%), fever (27%),  
547 constipation (26%), abdominal pain (26%), headache (26%), and diarrhea (25%).

548 Data in patients with advanced colorectal carcinoma in Table 5 are based on the  
 549 experience of 354 patients treated with ERBITUX plus irinotecan and 420 patients  
 550 treated with ERBITUX monotherapy.

**Table 5: Incidence of Adverse Events (≥10%) in Patients with Advanced Colorectal Carcinoma**

Body System Preferred Term <sup>1</sup>	ERBITUX plus Irinotecan (n=354)		ERBITUX Monotherapy (n=420)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
	% of Patients			
<b>Body as a Whole</b>				
Asthenia/Malaise <sup>2</sup>	73	16	48	10
Abdominal Pain	45	8	26	9
Fever <sup>3</sup>	34	4	27	<1
Pain	23	6	17	5
Infusion Reaction <sup>4</sup>	19	3	21	2
Infection	16	1	14	1
Back Pain	16	3	10	2
Headache	14	2	26	2
<b>Digestive</b>				
Diarrhea	72	22	25	2
Nausea	55	6	29	2
Vomiting	41	7	25	3
Anorexia	36	4	23	2
Constipation	30	2	26	2
Stomatitis	26	2	10	<1
Dyspepsia	14	0	6	0
<b>Hematic/Lymphatic</b>				
Leukopenia	25	17	<1	0
Anemia	16	5	9	3
<b>Metabolic/Nutritional</b>				
Weight Loss	21	0	7	1
Peripheral Edema	16	1	10	1
Dehydration	15	6	10	3
<b>Nervous</b>				
Insomnia	12	0	10	<1
Depression	10	0	7	0
<b>Respiratory</b>				
Dyspnea <sup>3</sup>	23	2	17	7
Cough Increased	20	0	11	1

**Table 5: Incidence of Adverse Events (≥10%) in Patients with Advanced Colorectal Carcinoma**

Body System Preferred Term <sup>1</sup>	ERBITUX plus Irinotecan (n=354)		ERBITUX Monotherapy (n=420)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
	% of Patients			
<b>Skin/Appendages</b>				
Acneform Rash <sup>5</sup>	88	14	90	8
Alopecia	21	0	4	0
Skin Disorder	15	1	4	0
Nail Disorder	12	<1	16	<1
Pruritus	10	1	11	<1
Conjunctivitis	14	1	7	<1

<sup>1</sup> Adverse events that occurred (toxicity Grades 1 through 4) in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX plus irinotecan or in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX monotherapy.

<sup>2</sup> Asthenia/malaise is defined as any event described as “asthenia”, “malaise”, or “somnolence”.

<sup>3</sup> Includes cases also reported as infusion reaction.

<sup>4</sup> Infusion reaction is defined as any event described at any time during the clinical study as “allergic reaction” or “anaphylactoid reaction”, or any event occurring on the first day of dosing described as “allergic reaction”, “anaphylactoid reaction”, “fever”, “chills”, “chills and fever”, or “dyspnea”.

<sup>5</sup> Acneform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.

## 551 Dermatologic Toxicity and Related Disorders

552 Non-suppurative acneform rash described as “acne”, “rash”, “maculopapular rash”,  
553 “pustular rash”, “dry skin”, or “exfoliative dermatitis” was observed in patients receiving  
554 ERBITUX plus radiation, ERBITUX plus irinotecan, or ERBITUX monotherapy. One or  
555 more of the dermatological adverse events were reported in 87% (17% Grade 3 or 4) of  
556 patients receiving ERBITUX plus radiation and in 76% (1% Grade 3 or 4) receiving  
557 ERBITUX monotherapy during treatment for advanced SCCHN. In studies of advanced  
558 colorectal cancer, dermatological adverse events were reported in 88% (14% Grade 3) of  
559 patients receiving ERBITUX plus irinotecan and in 90% (8% Grade 3) of patients  
560 receiving ERBITUX monotherapy. Acneform rash most commonly occurred on the face,  
561 upper chest, and back, but could extend to the extremities and was characterized by  
562 multiple follicular- or pustular-appearing lesions. Skin drying and fissuring were  
563 common in some instances, and were associated with inflammatory and infectious

564 sequelae (eg, blepharitis, cellulitis, cyst). Two cases of *S. aureus* sepsis were reported.  
565 The onset of acneform rash was generally within the first two weeks of therapy. Although  
566 in a majority of the patients the event resolved following cessation of treatment, in nearly  
567 half of the cases, the event continued beyond 28 days. (See **WARNINGS:**  
568 **Dermatologic Toxicity** and **DOSAGE AND ADMINISTRATION: Dose**  
569 **Modifications.**)

570 A related nail disorder, occurring in 12% of patients (0.4% Grade 3), was characterized  
571 as a paronychia inflammation with associated swelling of the lateral nail folds of the toes  
572 and fingers, with the great toes and thumbs as the most commonly affected digits.

### 573 **OVERDOSAGE**

574 Single doses of ERBITUX higher than 500 mg/m<sup>2</sup> have not been tested. There is no  
575 experience with overdosage in human clinical trials.

### 576 **DOSAGE AND ADMINISTRATION**

#### 577 **General**

578 Premedication with an H<sub>1</sub> antagonist (eg, 50 mg of diphenhydramine IV) is  
579 recommended. Appropriate medical resources for the treatment of severe infusion  
580 reactions should be available during ERBITUX infusions. (See **WARNINGS: Infusion**  
581 **Reactions.**)

#### 582 **Squamous Cell Carcinoma of the Head and Neck**

583 The recommended dose of ERBITUX, in combination with radiation therapy, is 400  
584 mg/m<sup>2</sup> as an initial loading dose (first infusion) administered as a 120-minute IV infusion  
585 (maximum infusion rate 5 mL/min) one week prior to initiation of a course of radiation  
586 therapy. The recommended weekly maintenance dose (all other infusions) is 250 mg/m<sup>2</sup>  
587 infused over 60 minutes (maximum infusion rate 5 mL/min) weekly for the duration of  
588 radiation therapy (6-7 weeks). In clinical studies, Cetuximab was administered 1 hour  
589 prior to radiation therapy.

590 The recommended dosing regimen for single-agent ERBITUX in the treatment of  
591 recurrent or metastatic squamous cell carcinoma of the head and neck is a 400-mg/m<sup>2</sup>  
592 initial dose followed by 250 mg/m<sup>2</sup> weekly until disease progression or unacceptable  
593 toxicity.

594 **Colorectal Cancer**

595 The recommended dose of ERBITUX, in combination with irinotecan, or as  
 596 monotherapy, is 400 mg/m<sup>2</sup> as an initial loading dose (first infusion) administered as a  
 597 120-minute IV infusion (maximum infusion rate 5 mL/min). The recommended weekly  
 598 maintenance dose (all other infusions) is 250 mg/m<sup>2</sup> infused over 60 minutes (maximum  
 599 infusion rate 5 mL/min).

600 **Dose Modifications**

601 **Infusion Reactions**

602 If the patient experiences a mild or moderate (Grade 1 or 2) infusion reaction, the  
 603 infusion rate should be permanently reduced by 50%.

604 ERBITUX should be immediately and permanently discontinued in patients who  
 605 experience severe (Grade 3 or 4) infusion reactions. (See **WARNINGS** and **ADVERSE**  
 606 **REACTIONS**.)

607 **Dermatologic Toxicity and Related Disorders**

608 Dosage modifications for dermatologic toxicity are recommended for severe acneform  
 609 rash (NCI CTC Grades 3 or 4), as specified in Table 6. ERBITUX dosage modification is  
 610 not recommended for severe radiation dermatitis. (See **WARNINGS** and **ADVERSE**  
 611 **REACTIONS**.)

**Table 6: ERBITUX Dose Modification Guidelines**

Severe Acneform Rash	ERBITUX	Outcome	ERBITUX Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 250 mg/m <sup>2</sup>
		No Improvement	Discontinue ERBITUX
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 200 mg/m <sup>2</sup>
		No Improvement	Discontinue ERBITUX
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 150 mg/m <sup>2</sup>
		No Improvement	Discontinue ERBITUX
4th occurrence	Discontinue ERBITUX		

612

613 **Preparation for Administration**

614 DO NOT ADMINISTER ERBITUX AS AN IV PUSH OR BOLUS.

615 **ERBITUX must be administered with the use of a low protein binding 0.22-**  
616 **micrometer in-line filter.**

617 ERBITUX is supplied as a 50-mL, single-use vial containing 100 mg of Cetuximab at a  
618 concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and  
619 colorless and may contain a small amount of easily visible, white, amorphous, Cetuximab  
620 particulates. **DO NOT SHAKE OR DILUTE.**

621 PREPARE INFUSION USING APPROPRIATE ASEPTIC TECHNIQUE. ERBITUX  
622 SHOULD BE ADMINISTERED VIA INFUSION PUMP OR SYRINGE PUMP.

623 **Infusion Pump:**

- 624 • Draw up the volume of a vial using a sterile syringe attached to an appropriate  
625 needle (a vented needle or pin may be used).
- 626 • Fill ERBITUX into a sterile evacuated container or bag such as glass containers,  
627 polyolefin bags (eg, Baxter Intravia), ethylene vinyl acetate bags (eg, Baxter  
628 Clintec), DEHP plasticized PVC bags (eg, Abbott Lifecare), or PVC bags.
- 629 • Repeat procedure until the calculated volume has been put into the container. Use  
630 a new needle for each vial.
- 631 • Administer through a low protein binding 0.22-micrometer in-line filter (placed as  
632 proximal to the patient as practical).
- 633 • Affix the infusion line and prime it with ERBITUX before starting the infusion.
- 634 • Maximum infusion rate should not exceed 5 mL/min.
- 635 • Use 0.9% saline solution to flush line at the end of infusion.

636 **Syringe Pump:**

- 637 • Draw up the volume of a vial using a sterile syringe attached to an appropriate  
638 needle (a vented needle or pin may be used).
- 639 • Place the syringe into the syringe driver of a syringe pump and set the rate.
- 640 • Administer through a low protein binding 0.22-micrometer in-line filter rated for  
641 syringe pump use (placed as proximal to the patient as practical).
- 642 • Connect up the infusion line and start the infusion after priming the line with  
643 ERBITUX.

- 644       • Repeat procedure until the calculated volume has been infused.  
645       • Use a new needle and filter for each vial.  
646       • Maximum infusion rate should not exceed 5 mL/min.  
647       • Use 0.9% saline solution to flush line at the end of infusion.

648       **ERBITUX should be piggybacked to the patient's infusion line.**

649       **Following the ERBITUX infusion, a 1-hour observation period is recommended.**  
650       **Longer observation periods may be required in those who experience infusion**  
651       **reactions.**

## 652       **HOW SUPPLIED**

653       ERBITUX<sup>®</sup> (Cetuximab) is supplied as a single-use, 50-mL vial containing 100 mg of  
654       Cetuximab as a sterile, preservative-free, injectable liquid. Each carton contains one  
655       ERBITUX vial (NDC 66733-948-23).

## 656       **Stability and Storage**

657       Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). **DO NOT FREEZE.**  
658       Increased particulate formation may occur at temperatures at or below 0°C. This product  
659       contains no preservatives. Preparations of ERBITUX in infusion containers are  
660       chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and  
661       up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard  
662       any remaining solution in the infusion container after 8 hours at controlled room  
663       temperature or after 12 hours at 2° to 8° C. Discard any unused portion of the vial.

664       ERBITUX<sup>®</sup> is a registered trademark of ImClone Systems Incorporated.

665       Manufactured by ImClone Systems Incorporated, Branchburg, NJ 08876

666       Distributed and Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543

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Revised \_\_\_\_\_