

1 **ERBITUX<sup>TM</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, and hypotension (see  
10 **WARNINGS** and **ADVERSE REACTIONS**). Severe infusion reactions require  
11 immediate interruption of the ERBITUX infusion and permanent discontinuation from  
12 further treatment. (See **WARNINGS: Infusion Reactions** and **DOSAGE AND**  
13 **ADMINISTRATION: Dose Modifications**.)

#### 14 **DESCRIPTION**

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

21 ERBITUX is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small  
22 amount of easily visible, white, amorphous, Cetuximab particulates. Each single-use,  
23 50-mL vial contains 100 mg of Cetuximab at a concentration of 2 mg/mL and is  
24 formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride,  
25 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42 mg/mL sodium phosphate  
26 monobasic monohydrate, and Water for Injection, USP.

## 27 CLINICAL PHARMACOLOGY

### 28 General

29 ERBITUX binds specifically to the epidermal growth factor receptor (EGFR, HER1,  
30 c-ErbB-1) on both normal and tumor cells, and competitively inhibits the binding of  
31 epidermal growth factor (EGF) and other ligands, such as transforming growth factor-  
32 alpha. Binding of ERBITUX to the EGFR blocks phosphorylation and activation of  
33 receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis,  
34 and decreased matrix metalloproteinase and vascular endothelial growth factor  
35 production. The EGFR is a transmembrane glycoprotein that is a member of a subfamily  
36 of type I receptor tyrosine kinases including EGFR (HER1), HER2, HER3, and HER4.  
37 The EGFR is constitutively expressed in many normal epithelial tissues, including the  
38 skin and hair follicle. Over-expression of EGFR is also detected in many human cancers  
39 including those of the colon and rectum.

40 *In vitro* assays and *in vivo* animal studies have shown that ERBITUX inhibits the growth  
41 and survival of tumor cells that over-express the EGFR. No anti-tumor effects of  
42 ERBITUX were observed in human tumor xenografts lacking EGFR expression. The  
43 addition of ERBITUX to irinotecan or irinotecan plus 5-fluorouracil in animal studies  
44 resulted in an increase in anti-tumor effects compared to chemotherapy alone.

### 45 Human Pharmacokinetics

46 ERBITUX administered as monotherapy or in combination with concomitant  
47 chemotherapy or radiotherapy exhibits nonlinear pharmacokinetics. The area under the  
48 concentration time curve (AUC) increased in a greater than dose proportional manner as  
49 the dose increased from 20 to 400 mg/m<sup>2</sup>. ERBITUX clearance (CL) decreased from 0.08  
50 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  
51 appeared to plateau. The volume of the distribution (Vd) for ERBITUX appeared to be  
52 independent of dose and approximated the vascular space of 2-3 L/m<sup>2</sup>.

53 Following a 2-hour infusion of 400 mg/m<sup>2</sup> of ERBITUX, the maximum mean serum  
54 concentration (C<sub>max</sub>) was 184 ?g/mL (range: 92-327 ?g/mL) and the mean elimination  
55 half-life was 97 hours (range 41-213 hours). A 1-hour infusion of 250 mg/m<sup>2</sup> produced a  
56 mean C<sub>max</sub> of 140 ?g/mL (range 120-170 ?g/mL). Following the recommended dose  
57 regimen (400 mg/m<sup>2</sup> initial dose/250 mg/m<sup>2</sup> weekly dose), ERBITUX concentrations  
58 reached steady-state levels by the third weekly infusion with mean peak and trough

59 concentrations across studies ranging from 168 to 235 and 41 to 85  $\mu$ g/mL, respectively.  
60 The mean half-life was 114 hours (range 75-188 hours).

## 61 **Special Populations**

62 A population pharmacokinetic analysis was performed to explore the potential effects of  
63 selected covariates including race, gender, age, and hepatic and renal function on  
64 ERBITUX pharmacokinetics.

65 Female patients had a 25% lower intrinsic ERBITUX clearance than male patients.  
66 Similar efficacy and safety were observed for female and male patients in the clinical  
67 trials; therefore, dose modification based on gender is not necessary. None of the other  
68 covariates explored appeared to have an impact on ERBITUX pharmacokinetics.

69 ERBITUX has not been studied in pediatric populations.

## 70 **CLINICAL STUDIES**

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

### 78 **Randomized, Controlled Trial**

79 A multicenter, randomized, controlled clinical trial was conducted in 329 patients  
80 randomized to receive either ERBITUX plus irinotecan (218 patients) or ERBITUX  
81 monotherapy (111 patients). In both arms of the study, ERBITUX was administered as a  
82 400 mg/m<sup>2</sup> initial dose, followed by 250 mg/m<sup>2</sup> weekly until disease progression or  
83 unacceptable toxicity. All patients received a 20-mg test dose on Day 1. In the  
84 ERBITUX plus irinotecan arm, irinotecan was added to ERBITUX using the same dose  
85 and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan  
86 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>  
87 weekly times four doses every 6 weeks. An Independent Radiographic Review  
88 Committee (IRC), blinded to the treatment arms, assessed both the progression on prior  
89 irinotecan and the response to protocol treatment for all patients.

90 Of the 329 randomized patients, 206 (63%) were male. The median age was 59 years  
 91 (range 26-84), and the majority was Caucasian (323, 98%). Eighty-eight percent of  
 92 patients had baseline Karnofsky Performance Status  $\geq$ 80. Fifty-eight percent of patients  
 93 had colon cancer and 40% rectal cancer. Approximately two-thirds (63%) of patients had  
 94 previously failed oxaliplatin treatment.

95 The efficacy of ERBITUX plus irinotecan or ERBITUX monotherapy was evaluated in  
 96 all randomized patients.

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

103 The irinotecan and oxaliplatin failure population was defined as irinotecan refractory  
 104 patients who had previously been treated with and failed an oxaliplatin-containing  
 105 regimen.

106 The objective response rates (ORR) in these populations are presented in Table 1.

**Table 1: 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>
<b>All Patients</b>	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

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

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

109

110 The median duration of response in the overall population was 5.7 months in the  
 111 combination arm and 4.2 months in the monotherapy arm. Compared with patients  
 112 randomized to ERBITUX alone, patients randomized to ERBITUX and irinotecan  
 113 experienced a significantly longer median time to disease progression (see Table 2).

**Table 2: Time to Progression per Independent Review**

Populations	ERBITUX + Irinotecan (median)	ERBITUX Monotherapy (median)	Hazard Ratio (95% CI <sup>a</sup> )	Log-rank p-value
<b>All Patients</b>	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

114 <sup>a</sup>Hazard ratio of ERBITUX + irinotecan: ERBITUX monotherapy with 95% confidence interval.  
115 .

## 116 Single-Arm Trials

117 ERBITUX, in combination with irinotecan, was studied in a single-arm, multicenter,  
118 open-label clinical trial in 138 patients with EGFR-expressing metastatic colorectal  
119 cancer who had progressed following an irinotecan containing regimen. Patients received  
120 a 20-mg test dose of ERBITUX on day 1, followed by a 400-mg/m<sup>2</sup> initial dose, and  
121 250 mg/m<sup>2</sup> weekly until disease progression or unacceptable toxicity. Patients received  
122 the same dose and schedule for irinotecan as the patient had previously failed. Acceptable  
123 irinotecan schedules were 350 mg/m<sup>2</sup> every 3 weeks or 125 mg/m<sup>2</sup> weekly times four  
124 doses every 6 weeks. Of 138 patients enrolled, 74 patients had documented progression  
125 to irinotecan as determined by an IRC. The overall response rate was 15% for the overall  
126 population and 12% for the irinotecan failure population. The median durations of  
127 response were 6.5 and 6.7 months, respectively.

128 ERBITUX was studied as a single agent in a multicenter, open-label, single-arm clinical  
129 trial in patients with EGFR-expressing metastatic colorectal cancer who progressed  
130 following an irinotecan-containing regimen. Of 57 patients enrolled, 28 patients had  
131 documented progression to irinotecan. The overall response rate was 9% for the all  
132 treated group and 14% for the irinotecan failure group. The median times to progression  
133 were 1.4 and 1.3 months, respectively. The median duration of response was 4.2 months  
134 for both groups.

## 135 EGFR Expression and Response

136 Patients enrolled in the clinical studies were required to have immunohistochemical  
137 evidence of positive EGFR expression. Primary tumor or tumor from a metastatic site  
138 was tested with the DakoCytomation EGFR pharmDx<sup>TM</sup> test kit. Specimens were scored

139 based on the percentage of cells expressing EGFR and intensity (barely/faint, weak to  
140 moderate, and strong). Response rate did not correlate with either the percentage of  
141 positive cells or the intensity of EGFR expression.

## 142 **INDICATIONS AND USAGE**

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

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

149 The effectiveness of ERBITUX is based on objective response rates (see **CLINICAL**  
150 **STUDIES**). Currently, no data are available that demonstrate an improvement in disease-  
151 related symptoms or increased survival with ERBITUX.

## 152 **CONTRAINDICATIONS**

153 None.

## 154 **WARNINGS**

### 155 **Infusion Reactions (See BOXED WARNINGS: Infusion** 156 **Reactions, ADVERSE REACTIONS: Infusion Reactions, and** 157 **DOSAGE AND ADMINISTRATION: Dose Modifications)**

158 Severe infusion reactions occurred with the administration of ERBITUX in  
159 approximately 3% (17/633) of patients, rarely with fatal outcome (<1 in 1000).  
160 Approximately 90% of severe infusion reactions were associated with the first infusion of  
161 ERBITUX despite the use of prophylactic antihistamines. These reactions were  
162 characterized by the rapid onset of airway obstruction (bronchospasm, stridor,  
163 hoarseness), urticaria, and/or hypotension. Caution must be exercised with every  
164 ERBITUX infusion, as there were patients who experienced their first severe infusion  
165 reaction during later infusions.

166 Severe infusion reactions require the immediate interruption of ERBITUX therapy and  
167 permanent discontinuation from further treatment. Appropriate medical therapy

168 including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and  
169 oxygen should be available for use in the treatment of such reactions. Patients should be  
170 carefully observed until the complete resolution of all signs and symptoms.

171 In clinical trials, mild to moderate infusion reactions were managed by slowing the  
172 infusion rate of ERBITUX and by continued use of antihistamine medications (eg,  
173 diphenhydramine) in subsequent doses (see **DOSAGE AND ADMINISTRATION:**  
174 **Dose Modifications**).

## 175 **Pulmonary Toxicity**

176 Interstitial lung disease (ILD) was reported in 3 of 633 (<0.5%) patients with advanced  
177 colorectal cancer receiving ERBITUX. Interstitial pneumonitis with non-cardiogenic  
178 pulmonary edema resulting in death was reported in one case. Two patients had pre-  
179 existing fibrotic lung disease and experienced an acute exacerbation of their disease while  
180 receiving ERBITUX in combination with irinotecan. In the clinical investigational  
181 program, an additional case of interstitial pneumonitis was reported in a patient with head  
182 and neck cancer treated with ERBITUX and cisplatin. The onset of symptoms occurred  
183 between the fourth and eleventh doses of treatment in all reported cases.

184 In the event of acute onset or worsening pulmonary symptoms, ERBITUX therapy should  
185 be interrupted and a prompt investigation of these symptoms should occur. If ILD is  
186 confirmed, ERBITUX should be discontinued and the patient should be treated  
187 appropriately.

## 188 **Dermatologic Toxicity (See ADVERSE REACTIONS:** 189 **Dermatologic Toxicity and DOSAGE AND ADMINISTRATION:** 190 **Dose Modifications)**

191 In cynomolgus monkeys, ERBITUX, when administered at doses of approximately 0.4 to  
192 4 times the weekly human exposure (based on total body surface area), resulted in  
193 dermatologic findings, including inflammation at the injection site and desquamation of  
194 the external integument. At the highest dose level, the epithelial mucosa of the nasal  
195 passage, esophagus, and tongue were similarly affected, and degenerative changes in the  
196 renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of  
197 the animals at the highest dose level beginning after approximately 13 weeks of  
198 treatment.

199 In clinical studies of ERBITUX, dermatologic toxicities, including acneform rash, skin  
200 drying and fissuring, and inflammatory and infectious sequelae (eg, blepharitis, cheilitis,  
201 cellulitis, cyst) were reported. In patients with advanced colorectal cancer, acneform rash  
202 was reported in 88% (560/633) of all treated patients, and was severe (Grade 3 or 4) in  
203 12% (79/633) of these patients. Subsequent to the development of severe dermatologic  
204 toxicities, complications including *S. aureus* sepsis and abscesses requiring incision and  
205 drainage were reported.

206 Patients developing dermatologic toxicities while receiving ERBITUX should be  
207 monitored for the development of inflammatory or infectious sequelae, and appropriate  
208 treatment of these symptoms initiated. Dose modifications of any future ERBITUX  
209 infusions should be instituted in case of severe acneform rash (see **DOSAGE AND**  
210 **ADMINISTRATION**, Table 4). Treatment with topical and/or oral antibiotics should be  
211 considered; topical corticosteroids are not recommended.

## 212 **PRECAUTIONS**

### 213 **General**

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

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

### 218 **EGF Receptor Testing**

219 Patients enrolled in the clinical studies were required to have immunohistochemical  
220 evidence of positive EGFR expression using the DakoCytomation EGFR pharmDx™ test  
221 kit. Assessment for EGFR expression should be performed by laboratories with  
222 demonstrated proficiency in the specific technology being utilized. Improper assay  
223 performance, including use of suboptimally fixed tissue, failure to utilize specified  
224 reagents, deviation from specific assay instructions, and failure to include appropriate  
225 controls for assay validation, can lead to unreliable results. Refer to the DakoCytomation  
226 test kit package insert for full instructions on assay performance. (See **CLINICAL**  
227 **STUDIES: EGFR Expression and Response**.)



## 228 **Drug Interactions**

229 A drug interaction study was performed in which ERBITUX was administered in  
230 combination with irinotecan. There was no evidence of any pharmacokinetic interactions  
231 between ERBITUX and irinotecan.

## 232 **Immunogenicity**

233 As with all therapeutic proteins, there is potential for immunogenicity. Potential  
234 immunogenic responses to ERBITUX were assessed using either a double antigen  
235 radiometric assay or an enzyme-linked immunosorbant assay. Due to limitations in assay  
236 performance and sample timing, the incidence of antibody development in patients  
237 receiving ERBITUX has not been adequately determined. The incidence of antibodies to  
238 ERBITUX was measured by collecting and analyzing serum pre-study, prior to selected  
239 infusions and during treatment follow-up. Patients were considered evaluable if they had  
240 a negative pre-treatment sample and a post-treatment sample. Non-neutralizing anti-  
241 ERBITUX antibodies were detected in 5% (28 of 530) of evaluable patients. In patients  
242 positive for anti-ERBITUX antibody, the median time to onset was 44 days (range 8-281  
243 days). Although the number of sero-positive patients is limited, there does not appear to  
244 be any relationship between the appearance of antibodies to ERBITUX and the safety or  
245 antitumor activity of the molecule.

246 The observed incidence of anti-ERBITUX antibody responses may be influenced by the  
247 low sensitivity of available assays, inadequate to reliably detect lower antibody titers.  
248 Other factors which might influence the incidence of anti-ERBITUX antibody response  
249 include sample handling, timing of sample collection, concomitant medications, and  
250 underlying disease. For these reasons, comparison of the incidence of antibodies to  
251 ERBITUX with the incidence of antibodies to other products may be misleading.

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

253 Long-term animal studies have not been performed to test ERBITUX for carcinogenic  
254 potential. No mutagenic or clastogenic potential of ERBITUX was observed in the  
255 *Salmonella-Escherichia coli* (Ames) assay or in the *in vivo* rat micronucleus test. A 39-  
256 week toxicity study in cynomolgus monkeys receiving 0.4 to 4 times the human dose of  
257 ERBITUX (based on total body surface area) revealed a tendency for impairment of  
258 menstrual cycling in treated female monkeys, including increased incidences of  
259 irregularity or absence of cycles, when compared to control animals, and beginning from

260 week 25 of treatment and continuing through the 6 week recovery period. Serum  
261 testosterone levels and analysis of sperm counts, viability, and motility were not  
262 remarkably different between ERBITUX-treated and control male monkeys. It is not  
263 known if ERBITUX can impair fertility in humans.

## 264 **Pregnancy Category C**

265 Animal reproduction studies have not been conducted with ERBITUX. However, the  
266 EGFR has been implicated in the control of prenatal development and may be essential  
267 for normal organogenesis, proliferation, and differentiation in the developing embryo. In  
268 addition, human IgG1 is known to cross the placental barrier; therefore ERBITUX has  
269 the potential to be transmitted from the mother to the developing fetus. It is not known  
270 whether ERBITUX can cause fetal harm when administered to a pregnant woman or  
271 whether ERBITUX can affect reproductive capacity. There are no adequate and well-  
272 controlled studies of ERBITUX in pregnant women. ERBITUX should only be given to  
273 a pregnant woman, or any woman not employing adequate contraception if the potential  
274 benefit justifies the potential risk to the fetus. All patients should be counseled regarding  
275 the potential risk of ERBITUX treatment to the developing fetus prior to initiation of  
276 therapy. If the patient becomes pregnant while receiving this drug, she should be  
277 apprised of the potential hazard to the fetus and/or the potential risk for loss of the  
278 pregnancy.

## 279 **Nursing Mothers**

280 It is not known whether ERBITUX is secreted in human milk. Since human IgG1 is  
281 secreted in human milk, the potential for absorption and harm to the infant after ingestion  
282 is unknown. Based on the mean half-life of ERBITUX after multiple dosing of 114 hours  
283 [range 75-188 hours] (see **CLINICAL PHARMACOLOGY: Human**  
284 **Pharmacokinetics**), women should be advised to discontinue nursing during treatment  
285 with ERBITUX and for 60 days following the last dose of ERBITUX.

## 286 **Pediatric Use**

287 The safety and effectiveness of ERBITUX in pediatric patients has not been established.

## 288 **Geriatric Use**

289 Of the 633 patients who received ERBITUX with irinotecan or ERBITUX monotherapy  
290 in four advanced colorectal cancer studies, 206 patients (33%) were 65 years of age or

291 older. No overall differences in safety or efficacy were observed between these patients  
292 and younger patients.

## 293 **ADVERSE REACTIONS**

294 Except where indicated, the data described below reflect exposure to ERBITUX in 633  
295 patients with advanced metastatic colorectal cancer. ERBITUX was studied in  
296 combination with irinotecan (n=354) or as monotherapy (n=279). Patients receiving  
297 ERBITUX plus irinotecan received a median of 12 doses (with 88/354 [25%] treated for  
298 over 6 months), and patients receiving ERBITUX monotherapy received a median of 7  
299 doses (with 26/279 [9%] treated for over 6 months). The population had a median age of  
300 59 and was 60% male and 91% Caucasian. The range of dosing for patients receiving  
301 ERBITUX plus irinotecan was 1-84 infusions, and the range of dosing for patients  
302 receiving ERBITUX monotherapy was 1-63 infusions.

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

- 304 ? Infusion reaction (3%) (See **BOXED WARNINGS, WARNINGS, and**  
305 **DOSAGE AND ADMINISTRATION: Dose Modifications**);
- 306 ? Dermatologic toxicity (1%) (See **WARNINGS and DOSAGE AND**  
307 **ADMINISTRATION: Dose Modifications**);
- 308 ? Interstitial lung disease (0.5%) (See **WARNINGS**);
- 309 ? Fever (5%);
- 310 ? Sepsis (3%);
- 311 ? Kidney failure (2%);
- 312 ? Pulmonary embolus (1%);
- 313 ? Dehydration (5%) in patients receiving ERBITUX plus irinotecan, 2% in patients  
314 receiving ERBITUX monotherapy;
- 315 ? Diarrhea (6%) in patients receiving ERBITUX plus irinotecan, 0% in patients  
316 receiving ERBITUX monotherapy.

317 Thirty-seven (10%) patients receiving ERBITUX plus irinotecan and 14 (5%) patients  
318 receiving ERBITUX monotherapy discontinued treatment primarily because of adverse  
319 events.

320 The most common adverse events seen in 354 patients receiving ERBITUX plus  
 321 irinotecan were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), nausea  
 322 (55%), abdominal pain (45%), and vomiting (41%).

323 The most common adverse events seen in 279 patients receiving ERBITUX monotherapy  
 324 were acneform rash (90%), asthenia/malaise (49%), fever (33%), nausea (29%),  
 325 constipation (28%), and diarrhea (28%).

326 Because clinical trials are conducted under widely varying conditions, adverse reaction  
 327 rates observed in the clinical trials of a drug cannot be directly compared to rates in the  
 328 clinical trials of another drug and may not reflect the rates observed in practice. The  
 329 adverse reaction information from clinical trials does, however, provide a basis for  
 330 identifying the adverse events that appear to be related to drug use and for approximating  
 331 rates.

332 Data in patients with advanced colorectal carcinoma in Table 3 are based on the  
 333 experience of 354 patients treated with ERBITUX plus irinotecan and 279 patients  
 334 treated with ERBITUX monotherapy.

**Table 3: 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=279)	
	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	49	10
Abdominal Pain	45	8	25	7
Fever <sup>3</sup>	34	4	33	0
Pain	23	6	19	5
Infusion Reaction <sup>4</sup>	19	3	25	2
Infection	16	1	11	1
Back Pain	16	3	11	3
Headache	14	2	25	3
<b>Digestive</b>				
Diarrhea	72	22	28	2
Nausea	55	6	29	2
Vomiting	41	7	25	3
Anorexia	36	4	25	3
Constipation	30	2	28	1

**Table 3: 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=279)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
	% of Patients			
Stomatitis	26	2	11	<1
Dyspepsia	14	0	7	0
<b>Hematic/Lymphatic</b>				
Leukopenia	25	17	1	0
Anemia	16	5	10	4
<b>Metabolic/Nutritional</b>				
Weight Loss	21	0	9	1
Peripheral Edema	16	1	10	<1
Dehydration	15	6	9	2
<b>Nervous</b>				
Insomnia	12	0	10	<1
Depression	10	0	9	0
<b>Respiratory</b>				
Dyspnea <sup>3</sup>	23	2	20	7
Cough Increased	20	0	10	1
<b>Skin/Appendages</b>				
Acneform Rash <sup>5</sup>	88	14	90	10
Alopecia	21	0	5	0
Skin Disorder	15	1	5	0
Nail Disorder	12	<1	16	<1
Pruritus	10	1	10	<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 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”.

336 **Infusion Reactions (see BOXED WARNING: Infusion Reactions)**

337 In clinical trials, severe, potentially fatal infusion reactions were reported. These events  
338 include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness),  
339 urticaria, and/or hypotension. In studies in advanced colorectal cancer, severe infusion  
340 reactions were observed in 3% of patients receiving ERBITUX plus irinotecan and 2% of  
341 patients receiving ERBITUX monotherapy. Grade 1 and 2 infusion reactions, including  
342 chills, fever, and dyspnea usually occurring on the first day of initial dosing, were  
343 observed in 16% of patients receiving ERBITUX plus irinotecan and 23% of patients  
344 receiving ERBITUX monotherapy. (See **WARNINGS: Infusion Reactions** and  
345 **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

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

349 **Dermatologic Toxicity and Related Disorders**

350 Non-suppurative acneform rash described as “acne”, “rash”, “maculopapular rash”,  
351 “pustular rash”, “dry skin”, or “exfoliative dermatitis” was observed in patients receiving  
352 ERBITUX plus irinotecan or ERBITUX monotherapy. One or more of the  
353 dermatological adverse events were reported in 88% (14% Grade 3) of patients receiving  
354 ERBITUX plus irinotecan and in 90% (10% Grade 3) of patients receiving ERBITUX  
355 monotherapy. Acneform rash most commonly occurred on the face, upper chest, and  
356 back, but could extend to the extremities and was characterized by multiple follicular- or  
357 pustular-appearing lesions. Skin drying and fissuring were common in some instances,  
358 and were associated with inflammatory and infectious sequelae (eg, blepharitis, cellulitis,  
359 cyst). Two cases of *S. aureus* sepsis were reported. The onset of acneform rash was  
360 generally within the first two weeks of therapy. Although in a majority of the patients the  
361 event resolved following cessation of treatment, in nearly half of the cases, the event  
362 continued beyond 28 days. (See **WARNINGS: Dermatologic Toxicity** and **DOSAGE**  
363 **AND ADMINISTRATION: Dose Modifications**.)

364 A related nail disorder, occurring in 14% of patients (0.3% Grade 3), was characterized  
365 as a paronychia inflammation with associated swelling of the lateral nail folds of the toes  
366 and fingers, with the great toes and thumbs as the most commonly affected digits.

367 **Use with Radiation Therapy**

368 In a study of 21 patients with locally advanced squamous cell cancer of the head and  
369 neck, patients treated with ERBITUX, cisplatin, and radiation had a 95% incidence of  
370 rash (19% Grade 3). The incidence and severity of cutaneous reactions with combined  
371 modality therapy appears to be additive, particularly within the radiation port. The  
372 addition of radiation to ERBITUX therapy in patients with colorectal cancer should be  
373 done with appropriate caution.

374 **OVERDOSAGE**

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

377 **DOSAGE AND ADMINISTRATION**

378 The recommended dose of ERBITUX, in combination with irinotecan or as monotherapy,  
379 is 400 mg/m<sup>2</sup> as an initial loading dose (first infusion) administered as a 120-minute IV  
380 infusion (maximum infusion rate 5 mL/min). The recommended weekly maintenance  
381 dose (all other infusions) is 250 mg/m<sup>2</sup> infused over 60 minutes (maximum infusion rate  
382 5 mL/min). Premedication with an H<sub>1</sub> antagonist (eg, 50 mg of diphenhydramine IV) is  
383 recommended. Appropriate medical resources for the treatment of severe infusion  
384 reactions should be available during ERBITUX infusions. (See **WARNINGS: Infusion**  
385 **Reactions.**)

386 **Dose Modifications**

387 **Infusion Reactions**

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

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

393 **Dermatologic Toxicity and Related Disorders**

394 If a patient experiences severe acneform rash, ERBITUX treatment adjustments should  
395 be made according to Table 4. In patients with mild and moderate skin toxicity, treatment  
396 should continue without dose modification. (See **WARNINGS** and **ADVERSE**  
397 **REACTIONS**.)

**Table 4: ERBITUX Dose Modification Guidelines**

<b>Severe Acneform Rash</b>	<b>ERBITUX</b>	<b>Outcome</b>	<b>ERBITUX Dose Modification</b>
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		

398

399 **Preparation for Administration**

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

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

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

407 ERBITUX CAN BE ADMINISTERED VIA INFUSION PUMP OR SYRINGE PUMP.

408 **Infusion Pump:**

409 ? Draw up the volume of a vial using a sterile syringe attached to an appropriate  
410 needle (a vented spike or other appropriate transfer device may be used).



- 411 ? Fill ERBITUX into a sterile evacuated container or bag such as glass containers,  
412 polyolefin bags (eg, Baxter Intravia), ethylene vinyl acetate bags (eg, Baxter  
413 Clintec), DEHP plasticized PVC bags (eg, Abbott Lifecare), or PVC bags.
- 414 ? Repeat procedure until the calculated volume has been put in to the container.  
415 Use a new needle for each vial.
- 416 ? Administer through a low protein binding 0.22-micrometer in-line filter (placed as  
417 proximal to the patient as practical).
- 418 ? Affix the infusion line and prime it with ERBITUX before starting the infusion.
- 419 ? Maximum infusion rate should not exceed 5 mL/min.
- 420 ? Use 0.9% saline solution to flush line at the end of infusion.

421 **Syringe Pump:**

- 422 ? Draw up the volume of a vial using a sterile syringe attached to an appropriate  
423 needle (a vented spike may be used).
- 424 ? Place the syringe into the syringe driver of a syringe pump and set the rate.
- 425 ? Administer through a low protein binding 0.22-micrometer in-line filter rated for  
426 syringe pump use (placed as proximal to the patient as practical).
- 427 ? Connect up the infusion line and start the infusion after priming the line with  
428 ERBITUX.
- 429 ? Repeat procedure until the calculated volume has been infused.
- 430 ? Use a new needle and filter for each vial.
- 431 ? Maximum infusion rate should not exceed 5 mL/min.
- 432 ? Use 0.9% saline solution to flush line at the end of infusion.

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

434 **Following the ERBITUX infusion, a 1-hour observation period is recommended.**

435 **HOW SUPPLIED**

436 ERBITUX? (Cetuximab) is supplied as a single-use, 50-mL vial containing 100 mg of  
437 Cetuximab as a sterile, preservative-free, injectable liquid. Each carton contains one  
438 ERBITUX vial (NDC 66733-948-23).

439 **Stability and Storage**

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

447

448 US Patent No. 6,217,866

449 ERBITUX® is a trademark of ImClone Systems Incorporated.

450 Manufactured by ImClone Systems Incorporated, Branchburg, NJ 08876

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

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