

Rx only

ERBITUX[®]

(Cetuximab)

For intravenous use only.

WARNING

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

DESCRIPTION

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

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

28 **CLINICAL PHARMACOLOGY**

29 **General**

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

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

46 **Human Pharmacokinetics**

47 ERBITUX administered as monotherapy or in combination with concomitant
48 chemotherapy or radiotherapy exhibits nonlinear pharmacokinetics. The area under the
49 concentration time curve (AUC) increased in a greater than dose proportional manner as
50 the dose increased from 20 to 400 mg/m². ERBITUX clearance (CL) decreased from 0.08
51 to 0.02 L/h/m² as the dose increased from 20 to 200 mg/m², and at doses >200 mg/m², it
52 appeared to plateau. The volume of the distribution (Vd) for ERBITUX appeared to be
53 independent of dose and approximated the vascular space of 2-3 L/m².

54 Following a 2-hour infusion of 400 mg/m² of ERBITUX, the maximum mean serum
55 concentration (C_{max}) was 184 µg/mL (range: 92-327 µg/mL) and the mean elimination
56 half-life was 97 hours (range 41-213 hours). A 1-hour infusion of 250 mg/m² produced a
57 mean C_{max} of 140 µg/mL (range 120-170 µg/mL). Following the recommended dose
58 regimen (400 mg/m² initial dose/250 mg/m² weekly dose), ERBITUX concentrations

59 reached steady-state levels by the third weekly infusion with mean peak and trough
60 concentrations across studies ranging from 168 to 235 and 41 to 85 µg/mL, respectively.
61 The mean half-life was 114 hours (range 75-188 hours).

62 **Special Populations**

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

66 Female patients had a 25% lower intrinsic ERBITUX clearance than male patients. The
67 toxicity profile was similar in males and females. Definitive conclusions regarding
68 comparability in efficacy cannot be made given the small number of patients with
69 objective tumor responses. None of the other covariates explored appeared to have an
70 impact on ERBITUX pharmacokinetics.

71 ERBITUX has not been studied in pediatric populations.

72 **CLINICAL STUDIES**

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

80 **Randomized, Controlled Trial**

81 A multicenter, randomized, controlled clinical trial was conducted in 329 patients
82 randomized to receive either ERBITUX plus irinotecan (218 patients) or ERBITUX
83 monotherapy (111 patients). In both arms of the study, ERBITUX was administered as a
84 400 mg/m² initial dose, followed by 250 mg/m² weekly until disease progression or
85 unacceptable toxicity. All patients received a 20-mg test dose on Day 1. In the
86 ERBITUX plus irinotecan arm, irinotecan was added to ERBITUX using the same dose
87 and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan
88 schedules were 350 mg/m² every 3 weeks, 180 mg/m² every 2 weeks, or 125 mg/m²
89 weekly times four doses every 6 weeks. An Independent Radiographic Review

90 Committee (IRC), blinded to the treatment arms, assessed both the progression on prior
 91 irinotecan and the response to protocol treatment for all patients.

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

97 The efficacy of ERBITUX plus irinotecan or ERBITUX monotherapy was evaluated in
 98 all randomized patients.

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

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

108 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 ^a)	
	n	ORR (%)	n	ORR (%)	%	p-value CMH ^b
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

109 ^a95% confidence interval for the difference in objective response rates.

110 ^bCochran-Mantel-Haenszel test.

111

112 The median duration of response in the overall population was 5.7 months in the
 113 combination arm and 4.2 months in the monotherapy arm. Compared with patients

114 randomized to ERBITUX alone, patients randomized to ERBITUX and irinotecan
 115 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 ^a)	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

116 ^aHazard ratio of ERBITUX + irinotecan: ERBITUX monotherapy with 95% confidence interval.
 117

118 Single-Arm Trials

119 ERBITUX, in combination with irinotecan, was studied in a single-arm, multicenter,
 120 open-label clinical trial in 138 patients with EGFR-expressing metastatic colorectal
 121 cancer who had progressed following an irinotecan-containing regimen. Patients received
 122 a 20-mg test dose of ERBITUX on day 1, followed by a 400-mg/m² initial dose, and
 123 250 mg/m² weekly until disease progression or unacceptable toxicity. Patients received
 124 the same dose and schedule for irinotecan as the patient had previously failed. Acceptable
 125 irinotecan schedules were 350 mg/m² every 3 weeks or 125 mg/m² weekly times four
 126 doses every 6 weeks. Of 138 patients enrolled, 74 patients had documented progression
 127 to irinotecan as determined by an IRC. The overall response rate was 15% for the overall
 128 population and 12% for the irinotecan-failure population. The median durations of
 129 response were 6.5 and 6.7 months, respectively.

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

137 **EGFR Expression and Response**

138 Patients enrolled in the clinical studies were required to have immunohistochemical
139 evidence of positive EGFR expression. Primary tumor or tumor from a metastatic site
140 was tested with the DakoCytomation EGFR pharmDx™ test kit. Specimens were scored
141 based on the percentage of cells expressing EGFR and intensity (barely/faint, weak to
142 moderate, and strong). Response rate did not correlate with either the percentage of
143 positive cells or the intensity of EGFR expression.

144 **INDICATIONS AND USAGE**

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

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

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

154 **CONTRAINDICATIONS**

155 None.

156 **WARNINGS**

157 **Infusion Reactions (See **BOXED WARNING: Infusion Reactions,****
158 ****ADVERSE REACTIONS: Infusion Reactions, and DOSAGE AND****
159 ****ADMINISTRATION: Dose Modifications.****)

160 Severe infusion reactions occurred with the administration of ERBITUX in
161 approximately 3% (20/774) of patients, rarely with fatal outcome (<1 in 1000).
162 Approximately 90% of severe infusion reactions were associated with the first infusion of
163 ERBITUX despite the use of prophylactic antihistamines. These reactions were
164 characterized by the rapid onset of airway obstruction (bronchospasm, stridor,
165 hoarseness), urticaria, and/or hypotension. Caution must be exercised with every
166 ERBITUX infusion, as there were patients who experienced their first severe infusion

167 reaction during later infusions. A 1-hour observation period is recommended following
168 the ERBITUX infusion. Longer observation periods may be required in patients who
169 experience infusion reactions.

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

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

179 **Pulmonary Toxicity**

180 Interstitial lung disease (ILD) was reported in 3 of 774 (<0.5%) patients with advanced
181 colorectal cancer receiving ERBITUX. Interstitial pneumonitis with non-cardiogenic
182 pulmonary edema resulting in death was reported in one case. Two patients had pre-
183 existing fibrotic lung disease and experienced an acute exacerbation of their disease while
184 receiving ERBITUX in combination with irinotecan. In the clinical investigational
185 program, an additional case of interstitial pneumonitis was reported in a patient with head
186 and neck cancer treated with ERBITUX and cisplatin. The onset of symptoms occurred
187 between the fourth and eleventh doses of treatment in all reported cases.

188 In the event of acute onset or worsening pulmonary symptoms, ERBITUX therapy should
189 be interrupted and a prompt investigation of these symptoms should occur. If ILD is
190 confirmed, ERBITUX should be discontinued and the patient should be treated
191 appropriately.

192 **Dermatologic Toxicity (See **ADVERSE REACTIONS:****

193 **Dermatologic Toxicity and **DOSAGE AND ADMINISTRATION:****

194 **Dose Modifications**.)

195 In cynomolgus monkeys, ERBITUX, when administered at doses of approximately 0.4 to
196 4 times the weekly human exposure (based on total body surface area), resulted in
197 dermatologic findings, including inflammation at the injection site and desquamation of
198 the external integument. At the highest dose level, the epithelial mucosa of the nasal

199 passage, esophagus, and tongue were similarly affected, and degenerative changes in the
200 renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of
201 the animals at the highest dose level beginning after approximately 13 weeks of
202 treatment.

203 In clinical studies of ERBITUX, dermatologic toxicities, including acneform rash, skin
204 drying and fissuring, and inflammatory and infectious sequelae (eg, blepharitis, cheilitis,
205 cellulitis, cyst) were reported. In patients with advanced colorectal cancer, acneform rash
206 was reported in 89% (686/774) of all treated patients, and was severe (Grade 3 or 4) in
207 11% (84/774) of these patients. Subsequent to the development of severe dermatologic
208 toxicities, complications including *S. aureus* sepsis and abscesses requiring incision and
209 drainage were reported.

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

216 **PRECAUTIONS**

217 **General**

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

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

222 **EGF Receptor Testing**

223 Patients enrolled in the clinical studies were required to have immunohistochemical
224 evidence of positive EGFR expression using the DakoCytomation EGFR pharmDx™ test
225 kit. Assessment for EGFR expression should be performed by laboratories with
226 demonstrated proficiency in the specific technology being utilized. Improper assay
227 performance, including use of suboptimally fixed tissue, failure to utilize specified
228 reagents, deviation from specific assay instructions, and failure to include appropriate
229 controls for assay validation, can lead to unreliable results. Refer to the DakoCytomation

230 test kit package insert for full instructions on assay performance. (See **CLINICAL**
231 **STUDIES: EGFR Expression and Response.**)

232 **Laboratory Tests: Electrolyte Monitoring**

233 Patients should be periodically monitored for hypomagnesemia, and accompanying
234 hypocalcemia and hypokalemia, during and following the completion of ERBITUX
235 therapy. Monitoring should continue for a period of time commensurate with the half-life
236 and persistence of the product; i.e., 8 weeks. (See **ADVERSE REACTIONS:**
237 **Electrolyte Depletion.**)

238 **Drug Interactions**

239 A drug interaction study was performed in which ERBITUX was administered in
240 combination with irinotecan. There was no evidence of any pharmacokinetic interactions
241 between ERBITUX and irinotecan.

242 **Immunogenicity**

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

256 The observed incidence of anti-ERBITUX antibody responses may be influenced by the
257 low sensitivity of available assays, inadequate to reliably detect lower antibody titers.
258 Other factors which might influence the incidence of anti-ERBITUX antibody response
259 include sample handling, timing of sample collection, concomitant medications, and

260 underlying disease. For these reasons, comparison of the incidence of antibodies to
261 ERBITUX with the incidence of antibodies to other products may be misleading.

262 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

274 **Pregnancy Category C**

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

289 **Nursing Mothers**

290 It is not known whether ERBITUX is secreted in human milk. Because human IgG is
291 secreted in human milk, the potential for absorption and harm to the infant after ingestion

292 exists. Based on the mean half-life of ERBITUX after multiple dosing of 114 hours
293 [range 75-188 hours] (see **CLINICAL PHARMACOLOGY: Human**
294 **Pharmacokinetics**), women should be advised to discontinue nursing during treatment
295 with ERBITUX and for 60 days following the last dose of ERBITUX.

296 **Pediatric Use**

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

298 **Geriatric Use**

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

303 **ADVERSE REACTIONS**

304 Except where indicated, the data described below reflect exposure to ERBITUX in 774
305 patients with advanced metastatic colorectal cancer. ERBITUX was studied in
306 combination with irinotecan (n=354) or as monotherapy (n=420). Patients receiving
307 ERBITUX plus irinotecan received a median of 12 doses [with 88/354 (25%) treated for
308 over 6 months], and patients receiving ERBITUX monotherapy received a median of 7
309 doses [with 36/420 (9%) treated for over 6 months]. The population had a median age of
310 59 and was 59% male and 91% Caucasian. The range of dosing for patients receiving
311 ERBITUX plus irinotecan was 1-84 infusions, and the range of dosing for patients
312 receiving ERBITUX monotherapy was 1-63 infusions.

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

- 314 • Infusion reaction (3%) (see **BOXED WARNING, WARNINGS, and DOSAGE**
315 **AND ADMINISTRATION: Dose Modifications**);
- 316 • Dermatologic toxicity (1%) (see **WARNINGS and DOSAGE AND**
317 **ADMINISTRATION: Dose Modifications**);
- 318 • Interstitial lung disease (0.4%) (see **WARNINGS**);
- 319 • Fever (5%);
- 320 • Sepsis (3%);
- 321 • Kidney failure (2%);

322 • Pulmonary embolus (1%);
323 • Dehydration (5%) in patients receiving ERBITUX plus irinotecan, 2% in patients
324 receiving ERBITUX monotherapy;
325 • Diarrhea (6%) in patients receiving ERBITUX plus irinotecan, 0.2% in patients
326 receiving ERBITUX monotherapy.

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

330 The most common adverse events seen in 354 patients receiving ERBITUX plus
331 irinotecan were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), nausea
332 (55%), abdominal pain (45%), and vomiting (41%).

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

336 Because clinical trials are conducted under widely varying conditions, adverse reaction
337 rates observed in the clinical trials of a drug cannot be directly compared to rates in the
338 clinical trials of another drug and may not reflect the rates observed in practice. The
339 adverse reaction information from clinical trials does, however, provide a basis for
340 identifying the adverse events that appear to be related to drug use and for approximating
341 rates.

342 Data in patients with advanced colorectal carcinoma in Table 3 are based on the
343 experience of 354 patients treated with ERBITUX plus irinotecan and 420 patients
344 treated with ERBITUX monotherapy.

Table 3: Incidence of Adverse Events (≥10%) in Patients with Advanced Colorectal Carcinoma

Body System Preferred Term ¹	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			
Body as a Whole				
Asthenia/Malaise ²	73	16	48	10
Abdominal Pain	45	8	26	9
Fever ³	34	4	27	<1
Pain	23	6	17	5
Infusion Reaction ⁴	19	3	21	2
Infection	16	1	14	1
Back Pain	16	3	10	2
Headache	14	2	26	2
Digestive				
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
Hematic/Lymphatic				
Leukopenia	25	17	<1	0
Anemia	16	5	9	3
Metabolic/Nutritional				
Weight Loss	21	0	7	1
Peripheral Edema	16	1	10	1
Dehydration	15	6	10	3
Nervous				
Insomnia	12	0	10	<1
Depression	10	0	7	0
Respiratory				
Dyspnea ³	23	2	17	7
Cough Increased	20	0	11	1

Table 3: Incidence of Adverse Events (≥10%) in Patients with Advanced Colorectal Carcinoma

Body System Preferred Term ¹	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			
Skin/Appendages				
Acneform Rash ⁵	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

¹ 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.

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

³ Includes cases reported as infusion reaction.

⁴ 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”.

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

345 **Infusion Reactions (see [BOXED WARNING: Infusion Reactions](#))**

346 In clinical trials, severe, potentially fatal infusion reactions were reported. These events
 347 include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness),
 348 urticaria, and/or hypotension. In studies in advanced colorectal cancer, severe infusion
 349 reactions were observed in 3% of patients receiving ERBITUX plus irinotecan and 2% of
 350 patients receiving ERBITUX monotherapy. Grade 1 and 2 infusion reactions, including
 351 chills, fever, and dyspnea usually occurring on the first day of initial dosing, were
 352 observed in 16% of patients receiving ERBITUX plus irinotecan and 19% of patients
 353 receiving ERBITUX monotherapy. (See [WARNINGS: Infusion Reactions](#) and
 354 [DOSAGE AND ADMINISTRATION: Dose Modifications](#).)

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

358 **Dermatologic Toxicity and Related Disorders**

359 Non-suppurative acneform rash described as “acne”, “rash”, “maculopapular rash”,
360 “pustular rash”, “dry skin”, or “exfoliative dermatitis” was observed in patients receiving
361 ERBITUX plus irinotecan or ERBITUX monotherapy. One or more of the
362 dermatological adverse events were reported in 88% (14% Grade 3) of patients receiving
363 ERBITUX plus irinotecan and in 90% (8% Grade 3) of patients receiving ERBITUX
364 monotherapy. Acneform rash most commonly occurred on the face, upper chest, and
365 back, but could extend to the extremities and was characterized by multiple follicular- or
366 pustular-appearing lesions. Skin drying and fissuring were common in some instances,
367 and were associated with inflammatory and infectious sequelae (eg, blepharitis, cellulitis,
368 cyst). Two cases of *S. aureus* sepsis were reported. The onset of acneform rash was
369 generally within the first two weeks of therapy. Although in a majority of the patients the
370 event resolved following cessation of treatment, in nearly half of the cases, the event
371 continued beyond 28 days. (See **WARNINGS: Dermatologic Toxicity** and **DOSAGE
372 AND ADMINISTRATION: Dose Modifications.**)

373 A related nail disorder, occurring in 14% of patients (0.4% Grade 3), was characterized
374 as a paronychia inflammation with associated swelling of the lateral nail folds of the toes
375 and fingers, with the great toes and thumbs as the most commonly affected digits.

376 **Use with Radiation Therapy**

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

383 **Electrolyte Depletion**

384 In 244 patients evaluated in ongoing, controlled clinical trials, the incidence of
385 hypomagnesemia, both overall and severe (NCI-CTC Grades 3 and 4), was increased in

386 patients receiving ERBITUX alone or in combination with chemotherapy as compared to
387 those receiving best supportive care or chemotherapy alone. Approximately one-half of
388 these patients receiving ERBITUX experienced hypomagnesemia and 10-15%
389 experienced severe hypomagnesemia. The onset of electrolyte abnormalities has been
390 reported to occur from days to months after initiation of ERBITUX. Electrolyte repletion
391 was necessary in some patients and in severe cases, intravenous replacement was
392 required. The time to resolution of electrolyte abnormalities is not well known, hence
393 monitoring after ERBITUX treatment is recommended. (See **PRECAUTIONS:**
394 **Laboratory Tests.**)

395 **OVERDOSAGE**

396 Single doses of ERBITUX higher than 500 mg/m² have not been tested. There is no
397 experience with overdosage in human clinical trials.

398 **DOSAGE AND ADMINISTRATION**

399 The recommended dose of ERBITUX, in combination with irinotecan or as monotherapy,
400 is 400 mg/m² as an initial loading dose (first infusion) administered as a 120-minute IV
401 infusion (maximum infusion rate 5 mL/min). The recommended weekly maintenance
402 dose (all other infusions) is 250 mg/m² infused over 60 minutes (maximum infusion rate
403 5 mL/min). Premedication with an H₁ antagonist (eg, 50 mg of diphenhydramine IV) is
404 recommended. Appropriate medical resources for the treatment of severe infusion
405 reactions should be available during ERBITUX infusions. (See **WARNINGS: Infusion**
406 **Reactions.**)

407 **Dose Modifications**

408 **Infusion Reactions**

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

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

414 **Dermatologic Toxicity and Related Disorders**

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

Table 4: 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 ²
		No Improvement	Discontinue ERBITUX
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 200 mg/m ²
		No Improvement	Discontinue ERBITUX
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 150 mg/m ²
		No Improvement	Discontinue ERBITUX
4th occurrence	Discontinue ERBITUX		

419 **Preparation for Administration**

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

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

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

427 USING APPROPRIATE ASEPTIC TECHNIQUE, ERBITUX SHOULD BE
428 ADMINISTERED VIA INFUSION PUMP OR SYRINGE PUMP.

429 **Infusion Pump:**

- 430
- Draw up the volume of a vial using a sterile syringe attached to an appropriate
431 needle (a vented spike or other appropriate transfer device may be used).

- 432 • Fill ERBITUX into a sterile evacuated container or bag such as glass containers,
433 polyolefin bags (eg, Baxter Intravia), ethylene vinyl acetate bags (eg, Baxter
434 Clintec), DEHP plasticized PVC bags (eg, Abbott Lifecare), or PVC bags.
- 435 • Repeat procedure until the calculated volume has been put into the container. Use
436 a new needle for each vial.
- 437 • Administer through a low protein binding 0.22-micrometer in-line filter (placed as
438 proximal to the patient as practical).
- 439 • Affix the infusion line and prime it with ERBITUX before starting the infusion.
- 440 • Maximum infusion rate should not exceed 5 mL/min.
- 441 • Use 0.9% saline solution to flush line at the end of infusion.

442 **Syringe Pump:**

- 443 • Draw up the volume of a vial using a sterile syringe attached to an appropriate
444 needle (a vented spike may be used).
- 445 • Place the syringe into the syringe driver of a syringe pump and set the rate.
- 446 • Administer through a low protein binding 0.22-micrometer in-line filter rated for
447 syringe pump use (placed as proximal to the patient as practical).
- 448 • Connect up the infusion line and start the infusion after priming the line with
449 ERBITUX.
- 450 • Repeat procedure until the calculated volume has been infused.
- 451 • Use a new needle and filter for each vial.
- 452 • Maximum infusion rate should not exceed 5 mL/min.
- 453 • Use 0.9% saline solution to flush line at the end of infusion.

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

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

458 **HOW SUPPLIED**

459 ERBITUX[®] (Cetuximab) is supplied as a single-use, 50-mL vial containing 100 mg of
460 Cetuximab as a sterile, preservative-free, injectable liquid. Each carton contains one
461 ERBITUX vial (NDC 66733-948-23).

462 **Stability and Storage**

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

470

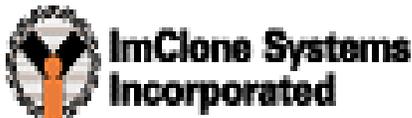
471 US Patent No. 6,217,866

472 ERBITUX[®] is a registered trademark of ImClone Systems Incorporated.

473 Manufactured by ImClone Systems Incorporated, Branchburg, NJ 08876

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

475



477

478 Copyright ©2005 by ImClone Systems Incorporated and Bristol-Myers Squibb Company. All rights
479 reserved.

480

481

Revised August 2005

482