CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

STN/BLA 125084

APPROVED LABELING

ERBITUX™

Rx only

(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, 0.42 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP.

CLINICAL PHARMACOLOGY

General

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

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

Human Pharmacokinetics

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

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

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

Special Populations

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

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

ERBITUX has not been studied in pediatric populations.

CLINICAL STUDIES

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

Randomized, Controlled Trial

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

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

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

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

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

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

[a]95% confidence interval for the difference in objective response rates.
[b]Cochran-Mantel-Haenszel test.

The median duration of response in the overall population was 5.7 months in the combination arm and 4.2 months in the monotherapy arm. Compared with patients randomized to ERBITUX alone, patients randomized to ERBITUX and irinotecan 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

[a]Hazard ratio of ERBITUX + irinotecan: ERBITUX monotherapy with 95% confidence interval.

Single-Arm Trials

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

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

EGFR Expression and Response

Patients enrolled in the clinical studies were required to have immunohistochemical evidence of positive EGFR expression. Primary tumor or tumor from a metastatic site was tested with the DakoCytomation EGFR pharmDx™ 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 ADMINSTRATION:**
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[1]	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			
Body as a Whole				
Asthenia/Malaise[2]	73	16	49	10
Abdominal Pain	45	8	25	7
Fever[3]	34	4	33	0
Pain	23	6	19	5
Infusion Reaction[4]	19	3	25	2
Infection	16	1	11	1
Back Pain	16	3	11	3
Headache	14	2	25	3
Digestive				
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[1]	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
Hematic/Lymphatic				
Leukopenia	25	17	1	0
Anemia	16	5	10	4
Metabolic/Nutritional				
Weight Loss	21	0	9	1
Peripheral Edema	16	1	10	<1
Dehydration	15	6	9	2
Nervous				
Insomnia	12	0	10	<1
Depression	10	0	9	0
Respiratory				
Dyspnea[3]	23	2	20	7
Cough Increased	20	0	10	1
Skin/Appendages				
Acneform Rash[5]	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

[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".

335

Infusion Reactions (see BOXED WARNING: Infusion Reactions)

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

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

Dermatologic Toxicity and Related Disorders

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

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

Use with Radiation Therapy

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

The recommended dose of ERBITUX, in combination with irinotecan or as monotherapy, is 400 mg/m^2 as an initial loading dose (first infusion) administered as a 120-minute IV infusion (maximum infusion rate 5 mL/min). The recommended weekly maintenance dose (all other infusions) is 250 mg/m^2 infused over 60 minutes (maximum infusion rate 5 mL/min). Premedication with an H_1 antagonist (eg, 50 mg of diphenhydramine IV) is recommended. Appropriate medical resources for the treatment of severe infusion reactions should be available during ERBITUX infusions. (See **WARNINGS: Infusion Reactions**.)

Dose Modifications

Infusion Reactions

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

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

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		

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).

Stability and Storage

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

US Patent No. 6,217,866

ERBITUX? is a trademark of ImClone Systems Incorporated.

Manufactured by ImClone Systems Incorporated, Branchburg, NJ 08876
Distributed and Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543

ImClone Systems Incorporated Bristol-Myers Squibb Company

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