

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ERBITUX safely and effectively. See full prescribing information for ERBITUX.

ERBITUX® (cetuximab)
Solution for intravenous infusion
Initial U.S. Approval: 2004

**WARNING: SERIOUS INFUSION REACTIONS and
CARDIOPULMONARY ARREST**

See full prescribing information for complete boxed warning.

- Serious infusion reactions, some fatal, occurred in approximately 3% of patients. (5.1)
- Cardiopulmonary arrest and/or sudden death occurred in 2% of patients receiving Erbitux in combination with radiation therapy. (5.2, 5.6)

-----**RECENT MAJOR CHANGES**-----

Indications and Usage	
Colorectal Cancer (1.2)	07/2009
Warnings and Precautions	
Infusion Reactions (5.1)	09/2008
Dermatologic Toxicity (5.4)	09/2008

-----**INDICATIONS AND USAGE**-----

Erbitux® is an epidermal growth factor receptor (EGFR) antagonist indicated for treatment of:

Head and Neck Cancer

- Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy. (1.1, 14.1)
- Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy. (1.1, 14.1)

Colorectal Cancer

- As a single agent, EGFR-expressing metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens or in patients who are intolerant to irinotecan-based regimens. (1.2, 14.2)
- In combination with irinotecan, EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. Approval is based on objective response rate; no data are available demonstrating an improvement in increased survival. (1.2, 14.2)
- Retrospective subset analyses of metastatic or advanced colorectal cancer trials have not shown a treatment benefit for Erbitux in patients whose tumors had *KRAS* mutations in codon 12 or 13. Use of Erbitux is not recommended for the treatment of colorectal cancer with these mutations. (1.2, 12.1, 14.2)

-----**DOSAGE AND ADMINISTRATION**-----

- Premedicate with an H₁ antagonist. (2.3)
- Administer 400 mg/m² initial dose as a 120-minute intravenous infusion followed by 250 mg/m² weekly infused over 60 minutes. (2.1, 2.2)
- Initiate Erbitux one week prior to initiation of radiation therapy. (2.1)
- Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 infusion reactions and non-serious NCI CTC Grades 3–4 infusion reactions. (2.4)
- Permanently discontinue for serious infusion reactions. (2.4)
- Withhold infusion for severe, persistent acneform rash. Reduce dose for recurrent, severe rash. (2.4)

-----**DOSAGE FORMS AND STRENGTHS**-----

- 100 mg/50 mL, single-use vial (3)
- 200 mg/100 mL, single-use vial (3)

-----**CONTRAINDICATIONS**-----

None (4)

-----**WARNINGS AND PRECAUTIONS**-----

- **Infusion Reactions:** Immediately stop and permanently discontinue Erbitux for serious infusion reactions. Monitor patients following infusion. (5.1)
- **Cardiopulmonary Arrest:** Closely monitor serum electrolytes during and after Erbitux. (5.2, 5.6)
- **Pulmonary Toxicity:** Interrupt therapy for acute onset or worsening of pulmonary symptoms. (5.3)
- **Dermatologic Toxicity:** Limit sun exposure. Monitor for inflammatory or infectious sequelae. (2.4, 5.4)

-----**ADVERSE REACTIONS**-----

The most common adverse reactions (incidence ≥25%) are: cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

-----**USE IN SPECIFIC POPULATIONS**-----

- **Pregnancy:** Administer Erbitux to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. (8.1)
- **Nursing Mothers:** Discontinue nursing during and for 60 days following treatment with Erbitux. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2009

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1 **FULL PRESCRIBING INFORMATION**

2 **WARNING: SERIOUS INFUSION REACTIONS and**
3 **CARDIOPULMONARY ARREST**

4 **Infusion Reactions:** Serious infusion reactions occurred with the administration of
5 Erbitux in approximately 3% of patients in clinical trials, with fatal outcome reported in
6 less than 1 in 1000. [See *Warnings and Precautions (5.1)* and *Adverse Reactions (6)*.]
7 Immediately interrupt and permanently discontinue Erbitux infusion for serious infusion
8 reactions. [See *Warnings and Precautions (5.1)* and *Dosage and Administration (2.4)*.]

9 **Cardiopulmonary Arrest:** Cardiopulmonary arrest and/or sudden death occurred in 2%
10 of 208 patients with squamous cell carcinoma of the head and neck treated with radiation
11 therapy and Erbitux. Closely monitor serum electrolytes, including serum magnesium,
12 potassium, and calcium, during and after Erbitux. [See *Warnings and Precautions (5.2,*
13 *5.6)*.]

14 **1 INDICATIONS AND USAGE**

15 **1.1 Squamous Cell Carcinoma of the Head and Neck**
16 **(SCCHN)**

17 Erbitux[®] is indicated in combination with radiation therapy for the initial treatment of
18 locally or regionally advanced squamous cell carcinoma of the head and neck. [See
19 *Clinical Studies (14.1)*.]

20 Erbitux, as a single agent, is indicated for the treatment of patients with recurrent or
21 metastatic squamous cell carcinoma of the head and neck for whom prior platinum-based
22 therapy has failed. [See *Clinical Studies (14.1)*.]

23 **1.2 Colorectal Cancer**

24 Erbitux, as a single agent, is indicated for the treatment of epidermal growth factor
25 receptor (EGFR)-expressing metastatic colorectal cancer after failure of both irinotecan-
26 and oxaliplatin-based regimens. Erbitux, as a single agent, is also indicated for the
27 treatment of EGFR-expressing metastatic colorectal cancer in patients who are intolerant
28 to irinotecan-based regimens. [See *Clinical Studies (14.2)* and *Warnings and Precautions*
29 *(5.7)*.]

30 Erbitux, in combination with irinotecan, is indicated for the treatment of
31 EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to
32 irinotecan-based chemotherapy. The effectiveness of Erbitux in combination with
33 irinotecan is based on objective response rates. Currently, no data are available that
34 demonstrate an improvement in disease-related symptoms or increased survival with
35 Erbitux in combination with irinotecan for the treatment of EGFR-expressing, metastatic
36 colorectal carcinoma. [See *Clinical Studies (14.2)* and *Warnings and Precautions (5.7)*.]

37 Retrospective subset analyses of metastatic or advanced colorectal cancer trials have not
38 shown a treatment benefit for Erbitux in patients whose tumors had *KRAS* mutations in
39 codon 12 or 13. Use of Erbitux is not recommended for the treatment of colorectal cancer
40 with these mutations [see *Clinical Studies (14.2)* and *Clinical Pharmacology (12.1)*].

41 **2 DOSAGE AND ADMINISTRATION**

42 **2.1 Squamous Cell Carcinoma of the Head and Neck**

43 Erbitux in combination with radiation therapy:

- 44 • The recommended initial dose is 400 mg/m² administered one week prior to
45 initiation of a course of radiation therapy as a 120-minute intravenous infusion
46 (maximum infusion rate 10 mg/min).
- 47 • The recommended subsequent weekly dose (all other infusions) is 250 mg/m²
48 infused over 60 minutes (maximum infusion rate 10 mg/min) for the duration of
49 radiation therapy (6–7 weeks). Complete Erbitux administration 1 hour prior to
50 radiation therapy.

51 Erbitux monotherapy:

- 52 • The recommended initial dose is 400 mg/m² administered as a 120-minute
53 intravenous infusion (maximum infusion rate 10 mg/min).
- 54 • The recommended subsequent weekly dose (all other infusions) is 250 mg/m²
55 infused over 60 minutes (maximum infusion rate 10 mg/min) until disease
56 progression or unacceptable toxicity.

57 **2.2 Colorectal Cancer**

- 58 • The recommended initial dose, either as monotherapy or in combination with
59 irinotecan, is 400 mg/m² administered as a 120-minute intravenous infusion
60 (maximum infusion rate 10 mg/min).
- 61 • The recommended subsequent weekly dose, either as monotherapy or in
62 combination with irinotecan, is 250 mg/m² infused over 60 minutes (maximum
63 infusion rate 10 mg/min) until disease progression or unacceptable toxicity.

64 **2.3 Recommended Premedication**

65 Premedicate with an H₁ antagonist (eg, 50 mg of diphenhydramine) intravenously 30–60
66 minutes prior to the first dose; premedication should be administered for subsequent
67 Erbitux doses based upon clinical judgment and presence/severity of prior infusion
68 reactions.

69 **2.4 Dose Modifications**

70 **Infusion Reactions**

71 Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 and non-serious NCI CTC
72 Grades 3–4 infusion reactions.

73 Immediately and permanently discontinue Erbitux for serious infusion reactions,
74 requiring medical intervention and/or hospitalization. [See *Warnings and Precautions*
75 (5.1).]

76 **Dermatologic Toxicity**

77 Recommended dose modifications for severe (NCI CTC Grade 3 or 4) acneform rash are
78 specified in Table 1. [See *Warnings and Precautions* (5.4).]

Table 1: Erbitux Dose Modification Guidelines for Rash

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		

79 **2.5 Preparation for Administration**

80 **Do not administer Erbitux as an intravenous push or bolus.**

81 Administer via infusion pump or syringe pump. Do not exceed an infusion rate of
82 10 mg/min.

83 **Administer through a low protein binding 0.22-micrometer in-line filter.**

84 Parenteral drug products should be inspected visually for particulate matter and
85 discoloration prior to administration, whenever solution and container permit.

86 The solution should be clear and colorless and may contain a small amount of easily
87 visible, white, amorphous, cetuximab particulates. **Do not shake or dilute.**

88 **3 DOSAGE FORMS AND STRENGTHS**

89 100 mg/50 mL, single-use vial

90 200 mg/100 mL, single-use vial

91 **4 CONTRAINDICATIONS**

92 None.

93 **5 WARNINGS AND PRECAUTIONS**

94 **5.1 Infusion Reactions**

95 Serious infusion reactions, requiring medical intervention and immediate, permanent
96 discontinuation of Erbitux included rapid onset of airway obstruction (bronchospasm,
97 stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction,
98 and/or cardiac arrest. Severe (NCI CTC Grades 3 and 4) infusion reactions occurred in
99 2–5% of 1373 patients in clinical trials, with fatal outcome in 1 patient.

100 Approximately 90% of severe infusion reactions occurred with the first infusion despite
101 premedication with antihistamines.

102 Monitor patients for 1 hour following Erbitux infusions in a setting with resuscitation
103 equipment and other agents necessary to treat anaphylaxis (eg, epinephrine,
104 corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Monitor longer
105 to confirm resolution of the event in patients requiring treatment for infusion reactions.

106 Immediately and permanently discontinue Erbitux in patients with serious infusion
107 reactions. [See *Boxed Warning* and *Dosage and Administration (2.4)*.]

108 **5.2 Cardiopulmonary Arrest**

109 Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients treated
110 with radiation therapy and Erbitux as compared to none of 212 patients treated with
111 radiation therapy alone in a randomized, controlled trial in patients with SCCHN. Three
112 patients with prior history of coronary artery disease died at home, with myocardial
113 infarction as the presumed cause of death. One of these patients had arrhythmia and one
114 had congestive heart failure. Death occurred 27, 32, and 43 days after the last dose of
115 Erbitux. One patient with no prior history of coronary artery disease died one day after
116 the last dose of Erbitux. Carefully consider use of Erbitux in combination with radiation
117 therapy in head and neck cancer patients with a history of coronary artery disease,
118 congestive heart failure, or arrhythmias in light of these risks. Closely monitor serum
119 electrolytes, including serum magnesium, potassium, and calcium, during and after
120 Erbitux. [See *Boxed Warning* and *Warnings and Precautions (5.6)*.]

121 **5.3 Pulmonary Toxicity**

122 Interstitial lung disease (ILD), including 1 fatality, occurred in 4 of 1570 (<0.5%) patients
123 receiving Erbitux in clinical trials. Interrupt Erbitux for acute onset or worsening of
124 pulmonary symptoms. Permanently discontinue Erbitux for confirmed ILD.

125 **5.4 Dermatologic Toxicity**

126 Dermatologic toxicities, including acneform rash, skin drying and fissuring, paronychia
127 inflammation, infectious sequelae (for example *S. aureus* sepsis, abscess formation,
128 cellulitis, blepharitis, conjunctivitis, keratitis, cheilitis), and hypertrichosis occurred in
129 patients receiving Erbitux therapy. Acneform rash occurred in 76–88% of 1373 patients
130 receiving Erbitux in clinical trials. Severe acneform rash occurred in 1–17% of patients.

131 Acneform rash usually developed within the first two weeks of therapy and resolved in a
132 majority of the patients after cessation of treatment, although in nearly half, the event
133 continued beyond 28 days. Monitor patients receiving Erbitux for dermatologic toxicities
134 and infectious sequelae. Instruct patients to limit sun exposure during Erbitux therapy.
135 [See *Dose Modifications (2.4)*.]

136 **5.5 Use of Erbitux in Combination With Radiation and**
137 **Cisplatin**

138 The safety of Erbitux in combination with radiation therapy and cisplatin has not been
139 established. Death and serious cardiotoxicity were observed in a single-arm trial with
140 Erbitux, radiation therapy, and cisplatin (100 mg/m²) in patients with locally advanced
141 SCCHN. Two of 21 patients died, one as a result of pneumonia and one of an unknown
142 cause. Four patients discontinued treatment due to adverse events. Two of these
143 discontinuations were due to cardiac events.

144 **5.6 Hypomagnesemia and Electrolyte Abnormalities**

145 In patients evaluated during clinical trials, hypomagnesemia occurred in 55% of patients
146 (199/365) receiving Erbitux and was severe (NCI CTC Grades 3 and 4) in 6–17%. The
147 onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to
148 months after initiation of Erbitux. Periodically monitor patients for hypomagnesemia,
149 hypocalcemia, and hypokalemia, during and for at least 8 weeks following the
150 completion of Erbitux. Replete electrolytes as necessary.

151 **5.7 Epidermal Growth Factor Receptor (EGFR) Expression**
152 **and Response**

153 Because expression of EGFR has been detected in nearly all SCCHN tumor specimens,
154 patients enrolled in the head and neck cancer clinical studies were not required to have
155 immunohistochemical evidence of EGFR tumor expression prior to study entry.

156 Patients enrolled in the colorectal cancer clinical studies were required to have
157 immunohistochemical evidence of EGFR tumor expression. Primary tumor or tumor
158 from a metastatic site was tested with the DakoCytomation EGFR pharmDx™ test kit.
159 Specimens were scored based on the percentage of cells expressing EGFR and intensity
160 (barely/faint, weak-to-moderate, and strong). Response rate did not correlate with either
161 the percentage of positive cells or the intensity of EGFR expression.

162 **6 ADVERSE REACTIONS**

163 The following adverse reactions are discussed in greater detail in other sections of the
164 label:

- 165 • Infusion reactions [See *Boxed Warning* and *Warnings and Precautions (5.1)*.]
- 166 • Cardiopulmonary arrest [See *Boxed Warning* and *Warnings and Precautions (5.2)*.]
- 167 • Pulmonary toxicity [See *Warnings and Precautions (5.3)*.]
- 168 • Dermatologic toxicity [See *Warnings and Precautions (5.4)*.]
- 169 • Hypomagnesemia and Electrolyte Abnormalities [See *Warnings and Precautions*
170 *(5.6)*.]

171 The most common adverse reactions with Erbitux (incidence $\geq 25\%$) are cutaneous
172 adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and
173 infection.

174 The most serious adverse reactions with Erbitux are infusion reactions, cardiopulmonary
175 arrest, dermatologic toxicity and radiation dermatitis, sepsis, renal failure, interstitial lung
176 disease, and pulmonary embolus.

177 Across all studies, Erbitux was discontinued in 3–10% of patients because of adverse
178 reactions.

179 **6.1 Clinical Trials Experience**

180 Because clinical trials are conducted under widely varying conditions, adverse reaction
181 rates observed in the clinical trials of a drug cannot be directly compared to rates in the
182 clinical trials of another drug and may not reflect the rates observed in practice.

183 The data below reflect exposure to Erbitux in 1373 patients with colorectal cancer or
184 SCCHN in randomized Phase 3 (Studies 1 and 3) or Phase 2 (Studies 2 and 4) trials
185 treated at the recommended dose and schedule for a median of 7 to 14 weeks. [See
186 *Clinical Studies (14).*]

187 **Infusion reactions:** Infusion reactions, which included pyrexia, chills, rigors, dyspnea,
188 bronchospasm, angioedema, urticaria, hypertension, and hypotension occurred in
189 15–21% of patients across studies. Grades 3 and 4 infusion reactions occurred in 2–5% of
190 patients; infusion reactions were fatal in 1 patient.

191 **Infections:** The incidence of infection was variable across studies, ranging from 13–35%.
192 Sepsis occurred in 1–4% of patients.

193 **Renal:** Renal failure occurred in 1% of patients with colorectal cancer.

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

195 Table 2 contains selected adverse events in 420 patients receiving radiation therapy either
196 alone or with Erbitux for locally or regionally advanced SCCHN in Study 1. Erbitux was
197 administered at the recommended dose and schedule (400 mg/m² initial dose, followed
198 by 250 mg/m² weekly). Patients received a median of 8 infusions (range 1–11).

Table 2: Incidence of Selected Adverse Events (≥10%) in Patients with Locoregionally Advanced SCCHN

Body System Preferred Term	Eribitux plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
	Grades 1-4	Grades 3 and 4	Grades 1-4	Grades 3 and 4
% of Patients				
Body as a Whole				
Asthenia	56	4	49	5
Fever ¹	29	1	13	1
Headache	19	<1	8	<1
Infusion Reaction ²	15	3	2	0
Infection	13	1	9	1
Chills ¹	16	0	5	0
Digestive				
Nausea	49	2	37	2
Emesis	29	2	23	4
Diarrhea	19	2	13	1
Dyspepsia	14	0	9	1
Metabolic/Nutritional				
Weight Loss	84	11	72	7
Dehydration	25	6	19	8
Alanine Transaminase, high ³	43	2	21	1
Aspartate Transaminase, high ³	38	1	24	1
Alkaline Phosphatase, high ³	33	<1	24	0
Respiratory				
Pharyngitis	26	3	19	4
Skin/Appendages				
Acneform Rash ⁴	87	17	10	1
Radiation Dermatitis	86	23	90	18
Application Site Reaction	18	0	12	1
Pruritus	16	0	4	0

¹ Includes cases also reported as infusion reaction.

² 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”.

³ Based on laboratory measurements, not on reported adverse events, the number of subjects with tested samples varied from 205–206 for Eribitux plus Radiation arm; 209–210 for Radiation alone.

Table 2: Incidence of Selected Adverse Events (≥10%) in Patients with Locoregionally Advanced SCCHN

Body System Preferred Term	Eribitux plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
	Grades 1-4	Grades 3 and 4	Grades 1-4	Grades 3 and 4
	% of Patients			

⁴ Acneform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.

199 The incidence and severity of mucositis, stomatitis, and xerostomia were similar in both
200 arms of the study.

201 ***Late Radiation Toxicity***

202 The overall incidence of late radiation toxicities (any grade) was higher in Eribitux in
203 combination with radiation therapy compared with radiation therapy alone. The following
204 sites were affected: salivary glands (65% versus 56%), larynx (52% versus 36%),
205 subcutaneous tissue (49% versus 45%), mucous membrane (48% versus 39%), esophagus
206 (44% versus 35%), skin (42% versus 33%). The incidence of Grade 3 or 4 late radiation
207 toxicities was similar between the radiation therapy alone and the Eribitux plus radiation
208 treatment groups.

209 **Colorectal Cancer**

210 Table 3 contains selected adverse events in 562 patients receiving best supportive care
211 (BSC) alone or with Eribitux monotherapy for metastatic colorectal cancer in Study 3.
212 Eribitux was administered at the recommended dose and schedule (400 mg/m² initial
213 dose, followed by 250 mg/m² weekly).

Table 3: Incidence of Selected Adverse Events Occurring in ≥10% of Patients with Advanced Colorectal Carcinoma¹ Treated with Erbitux Monotherapy

Body System Preferred Term	Erbitux plus BSC (n=288)		BSC alone (n=274)	
	Any Grades ²	Grades 3 and 4	Any Grades	Grades 3 and 4
% of Patients				
Dermatology				
Rash/Desquamation	89	12	16	<1
Dry Skin	49	0	11	0
Pruritus	40	2	8	0
Other-Dermatology	27	1	6	1
Nail Changes	21	0	4	0
Body as a Whole				
Fatigue	89	33	76	26
Fever	30	1	18	<1
Infusion Reactions ³	20	5		
Rigors, Chills	13	<1	4	0
Pain				
Abdominal Pain	59	14	52	16
Pain-Other	51	16	34	7
Headache	33	4	11	0
Bone Pain	15	3	7	2
Pulmonary				
Dyspnea	48	16	43	12
Cough	29	2	19	1
Gastrointestinal				
Constipation	46	4	38	5
Diarrhea	39	2	20	2
Vomiting	37	6	29	6
Stomatitis	25	1	10	<1
Other-Gastrointestinal	23	10	18	8
Mouth Dryness	11	0	4	0
Infection				
Infection without neutropenia	35	13	17	6
Neurology				
Insomnia	30	1	15	1
Confusion	15	6	9	2
Anxiety	14	2	8	1
Depression	13	1	6	<1

Table 3: Incidence of Selected Adverse Events Occurring in ≥10% of Patients with Advanced Colorectal Carcinoma¹ Treated with Erbitux Monotherapy

Body System Preferred Term	Erbitux plus BSC (n=288)		BSC alone (n=274)	
	Any Grades ²	Grades 3 and 4	Any Grades	Grades 3 and 4
% of Patients				

¹ Adverse reactions occurring more frequently in Erbitux-treated patients compared with controls.

² Adverse events were graded using the NCI CTC, V 2.0.

³ Infusion reaction is defined as any event (chills, rigors, dyspnea, tachycardia, bronchospasm, chest tightness, swelling, urticaria, hypotension, flushing, rash, hypertension, nausea, angioedema, pain, pruritus, sweating, tremors, shaking, cough, visual disturbances, or other) recorded by the investigator as infusion-related.

BSC = best supportive care

214 The most frequently reported adverse events in 354 patients treated with Erbitux plus
215 irinotecan in clinical trials were acneform rash (88%), asthenia/malaise (73%), diarrhea
216 (72%), and nausea (55%). The most common Grades 3–4 adverse events included
217 diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneform rash (14%).

218 **6.2 Immunogenicity**

219 As with all therapeutic proteins, there is potential for immunogenicity. Immunogenic
220 responses to cetuximab were assessed using either a double antigen radiometric assay or
221 an ELISA assay. Due to limitations in assay performance and sampling timing, the
222 incidence of antibody development in patients receiving Erbitux has not been adequately
223 determined. Non-neutralizing anti-cetuximab antibodies were detected in 5% (49 of
224 1001) of evaluable patients without apparent effect on the safety or antitumor activity of
225 Erbitux.

226 The incidence of antibody formation is highly dependent on the sensitivity and specificity
227 of the assay. Additionally, the observed incidence of antibody (including neutralizing
228 antibody) positivity in an assay may be influenced by several factors including assay
229 methodology, sample handling, timing of sample collection, concomitant medications,
230 and underlying disease. For these reasons, comparison of the incidence of antibodies to
231 Erbitux with the incidence of antibodies to other products may be misleading.

232 **7 DRUG INTERACTIONS**

233 A drug interaction study was performed in which Erbitux was administered in
234 combination with irinotecan. There was no evidence of any pharmacokinetic interactions
235 between Erbitux and irinotecan.

236 **8 USE IN SPECIFIC POPULATIONS**

237 **8.1 Pregnancy**

238 **Pregnancy Category C**

239 There are no adequate and well-controlled studies of Erbitux in pregnant women. Based
240 on animal models, EGFR has been implicated in the control of prenatal development and
241 may be essential for normal organogenesis, proliferation, and differentiation in the
242 developing embryo. Human IgG is known to cross the placental barrier; therefore,
243 Erbitux may be transmitted from the mother to the developing fetus, and has the potential
244 to cause fetal harm when administered to pregnant women. Erbitux should be used during
245 pregnancy only if the potential benefit justifies the potential risk to the fetus.

246 Pregnant cynomolgus monkeys were treated weekly with 0.4 to 4 times the recommended
247 human dose of cetuximab (based on body surface area) during the period of
248 organogenesis (gestation day [GD] 20–48). Cetuximab was detected in the amniotic fluid
249 and in the serum of embryos from treated dams at GD 49. No fetal malformations or
250 other teratogenic effects occurred in offspring. However, significant increases in
251 embryoletality and abortions occurred at doses of approximately 1.6 to 4 times the
252 recommended human dose of cetuximab (based on total body surface area).

253 **8.3 Nursing Mothers**

254 It is not known whether Erbitux is secreted in human milk. IgG antibodies, such as
255 Erbitux, can be excreted in human milk. Because many drugs are excreted in human milk
256 and because of the potential for serious adverse reactions in nursing infants from Erbitux,
257 a decision should be made whether to discontinue nursing or to discontinue the drug,
258 taking into account the importance of the drug to the mother. If nursing is interrupted,
259 based on the mean half-life of cetuximab [see *Clinical Pharmacology (12.3)*], nursing
260 should not be resumed earlier than 60 days following the last dose of Erbitux.

261 **8.4 Pediatric Use**

262 The safety and effectiveness of Erbitux in pediatric patients have not been established.

263 The pharmacokinetics of cetuximab have not been studied in pediatric populations.

264 **8.5 Geriatric Use**

265 Of the 1062 patients who received Erbitux with irinotecan or Erbitux monotherapy in five
266 studies of advanced colorectal cancer, 363 patients were 65 years of age or older. No
267 overall differences in safety or efficacy were observed between these patients and
268 younger patients.

269 Clinical studies of Erbitux conducted in patients with head and neck cancer did not
270 include sufficient number of subjects aged 65 and over to determine whether they
271 respond differently from younger subjects. Of the 208 patients with head and neck cancer
272 who received Erbitux with radiation therapy, 45 patients were 65 years of age or older.

273 **10 OVERDOSAGE**

274 The maximum single dose of Erbitux administered is 1000 mg/m² in one patient. No
275 adverse events were reported for this patient.

276 **11 DESCRIPTION**

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

283 Erbitux is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small
284 amount of easily visible, white, amorphous cetuximab particulates. Erbitux is supplied at
285 a concentration of 2 mg/mL in either 100 mg (50 mL) or 200 mg (100 mL), single-use
286 vials. Cetuximab is formulated in a preservative-free solution containing 8.48 mg/mL
287 sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.41 mg/mL
288 sodium phosphate monobasic monohydrate, and Water for Injection, USP.

289 **12 CLINICAL PHARMACOLOGY**

290 **12.1 Mechanism of Action**

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

296 Cetuximab binds specifically to the EGFR on both normal and tumor cells, and
297 competitively inhibits the binding of epidermal growth factor (EGF) and other ligands,
298 such as transforming growth factor- α . *In vitro* assays and *in vivo* animal studies have
299 shown that binding of cetuximab to the EGFR blocks phosphorylation and activation of
300 receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis,
301 and decreased matrix metalloproteinase and vascular endothelial growth factor
302 production. Signal transduction through the EGFR results in activation of wild-type
303 KRAS protein. However, in cells with activating *KRAS* somatic mutations, the mutant
304 KRAS protein is continuously active and appears independent of EGFR regulation.

305 *In vitro*, cetuximab can mediate antibody-dependent cellular cytotoxicity (ADCC) against
306 certain human tumor types. *In vitro* assays and *in vivo* animal studies have shown that
307 cetuximab inhibits the growth and survival of tumor cells that express the EGFR. No
308 anti-tumor effects of cetuximab were observed in human tumor xenografts lacking EGFR
309 expression. The addition of cetuximab to radiation therapy or irinotecan in human tumor
310 xenograft models in mice resulted in an increase in anti-tumor effects compared to
311 radiation therapy or chemotherapy alone.

312 **12.3 Pharmacokinetics**

313 Erbitux administered as monotherapy or in combination with concomitant chemotherapy
314 or radiation therapy exhibits nonlinear pharmacokinetics. The area under the
315 concentration time curve (AUC) increased in a greater than dose proportional manner
316 while clearance of cetuximab decreased from 0.08 to 0.02 L/h/m² as the dose increased
317 from 20 to 200 mg/m², and at doses >200 mg/m², it appeared to plateau. The volume of
318 the distribution for cetuximab appeared to be independent of dose and approximated the
319 vascular space of 2–3 L/m².

320 Following the recommended dose regimen (400 mg/m² initial dose; 250 mg/m² weekly
321 dose), concentrations of cetuximab reached steady-state levels by the third weekly
322 infusion with mean peak and trough concentrations across studies ranging from 168 to
323 235 and 41 to 85 µg/mL, respectively. The mean half-life of cetuximab was
324 approximately 112 hours (range 63–230 hours). The pharmacokinetics of cetuximab were
325 similar in patients with SCCHN and those with colorectal cancer.

326 Based on a population pharmacokinetic analysis, female patients with colorectal cancer
327 had a 25% lower intrinsic clearance of cetuximab than male patients. Qualitatively
328 similar, but smaller gender differences in cetuximab clearance were observed in patients
329 with SCCHN. The gender differences in clearance do not necessitate any alteration of
330 dosing because of a similar safety profile.

331 **13 NONCLINICAL TOXICOLOGY**

332 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

333 Long-term animal studies have not been performed to test cetuximab for carcinogenic
334 potential, and no mutagenic or clastogenic potential of cetuximab was observed in the
335 *Salmonella-Escherichia coli* (Ames) assay or in the *in vivo* rat micronucleus test.
336 Menstrual cyclicity was impaired in female cynomolgus monkeys receiving weekly doses
337 of 0.4 to 4 times the human dose of cetuximab (based on total body surface area).
338 Cetuximab-treated animals exhibited increased incidences of irregular or absent cycles,
339 as compared to control animals. These effects were initially noted beginning week 25 of
340 cetuximab treatment and continued through the 6-week recovery period. In this same
341 study, there were no effects of cetuximab treatment on measured male fertility parameters
342 (ie, serum testosterone levels and analysis of sperm counts, viability, and motility) as
343 compared to control male monkeys. It is not known if cetuximab can impair fertility in
344 humans.

345 **13.2 Animal Pharmacology and/or Toxicology**

346 In cynomolgus monkeys, cetuximab, when administered at doses of approximately 0.4 to
347 4 times the weekly human exposure (based on total body surface area), resulted in
348 dermatologic findings, including inflammation at the injection site and desquamation of
349 the external integument. At the highest dose level, the epithelial mucosa of the nasal
350 passage, esophagus, and tongue were similarly affected, and degenerative changes in the
351 renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of

352 the animals at the highest dose level beginning after approximately 13 weeks of
353 treatment.

354 **14 CLINICAL STUDIES**

355 **14.1 Squamous Cell Carcinoma of the Head and Neck** 356 **(SCCHN)**

357 Study 1 was a randomized, multicenter, controlled trial of 424 patients with locally or
358 regionally advanced SCCHN. Patients with Stage III/IV SCCHN of the oropharynx,
359 hypopharynx, or larynx with no prior therapy were randomized (1:1) to receive either
360 Erbitux plus radiation therapy or radiation therapy alone. Stratification factors were
361 Karnofsky Performance Status (60–80 versus 90–100), nodal stage (N0 versus N+),
362 tumor stage (T1–3 versus T4 using American Joint Committee on Cancer 1998 staging
363 criteria), and radiation therapy fractionation (concomitant boost versus once-daily versus
364 twice-daily). Radiation therapy was administered for 6–7 weeks as once daily, twice
365 daily, or concomitant boost. Erbitux was administered as a 400 mg/m² initial dose
366 beginning one week prior to initiation of radiation therapy, followed by 250 mg/m²
367 weekly administered 1 hour prior to radiation therapy for the duration of radiation
368 therapy (6–7 weeks).

369 Of the 424 randomized patients, the median age was 57 years, 80% were male, 83% were
370 Caucasian, and 90% had baseline Karnofsky Performance Status ≥80. There were
371 258 patients enrolled in US sites (61%). Sixty percent of patients had oropharyngeal,
372 25% laryngeal, and 15% hypopharyngeal primary tumors; 28% had AJCC T4 tumor
373 stage. Fifty-six percent of the patients received radiation therapy with concomitant boost,
374 26% received once-daily regimen, and 18% twice-daily regimen.

375 The main outcome measure of this trial was duration of locoregional control. Overall
376 survival was also assessed. Results are presented in Table 4.

Table 4: Study 1: Clinical Efficacy in Locoregionally Advanced SCCHN

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

377 ^a CI = confidence interval

378 Study 2 was a single-arm, multicenter clinical trial in 103 patients with recurrent or
379 metastatic SCCHN. All patients had documented disease progression within 30 days of a
380 platinum-based chemotherapy regimen. Patients received a 20-mg test dose of Erbitux on
381 Day 1, followed by a 400-mg/m² initial dose, and 250 mg/m² weekly until disease
382 progression or unacceptable toxicity.

383 The median age was 57 years, 82% were male, 100% Caucasian, and 62% had a
384 Karnofsky Performance Status of ≥80.

385 The objective response rate was 13% (95% confidence interval 7%–21%). Median
386 duration of response was 5.8 months (range 1.2–5.8 months).

387 **14.2 Colorectal Cancer**

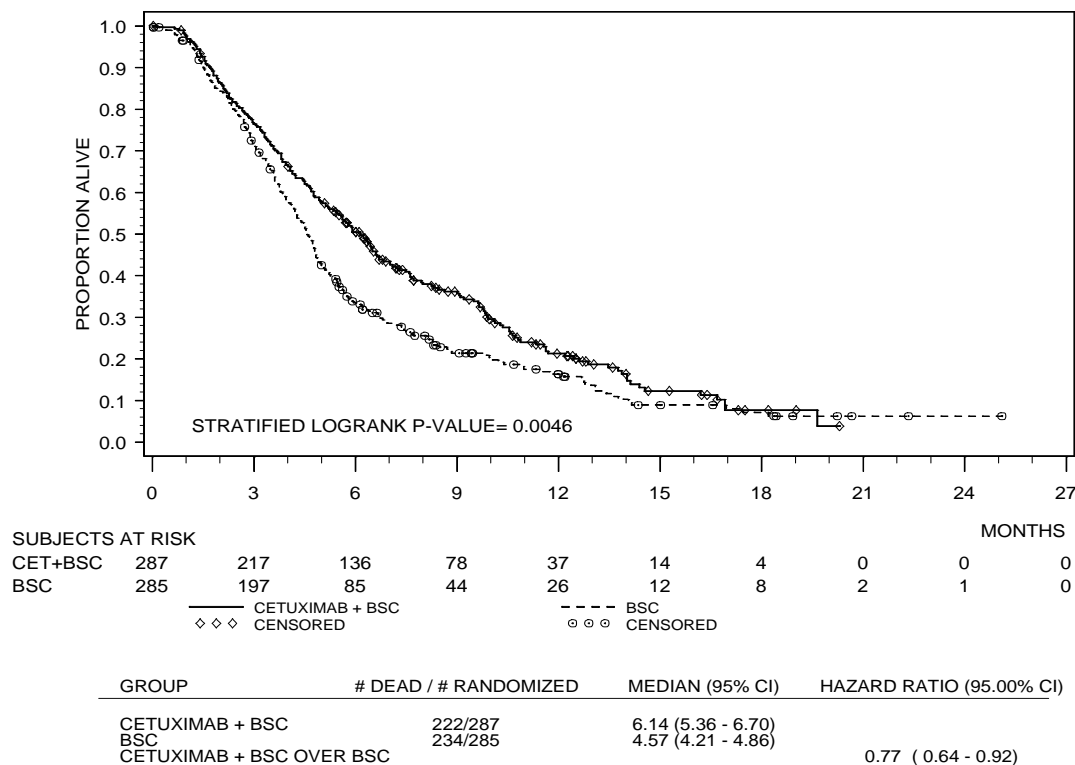
388 **Erbix Clinical Trials in EGFR-Expressing, Recurrent, Metastatic** 389 **Colorectal Cancer**

390 Study 3 was a multicenter, open-label, randomized, clinical trial conducted in
391 572 patients with EGFR-expressing, previously treated, recurrent, metastatic colorectal
392 cancer (mCRC). Patients were randomized (1:1) to receive either Erbitux plus best
393 supportive care (BSC) or BSC alone. Erbitux was administered as a 400-mg/m² initial
394 dose, followed by 250 mg/m² weekly until disease progression or unacceptable toxicity.

395 Of the 572 randomized patients, the median age was 63 years, 64% were male, 89% were
396 Caucasian, and 77% had baseline ECOG Performance Status of 0–1. All patients were to
397 have received and progressed on prior therapy including an irinotecan-containing
398 regimen and an oxaliplatin-containing regimen.

399 The main outcome measure of the study was overall survival. The results are presented in
 400 Figure 1.

401 **Figure 1: Kaplan Meier Curve for Overall Survival in Patients with**
 402 **Metastatic Colorectal Cancer**



403

404 Study 4 was a multicenter, clinical trial conducted in 329 patients with EGFR-expressing
 405 recurrent mCRC. Patients were randomized (2:1) to receive either Erbitux plus irinotecan
 406 (218 patients) or Erbitux monotherapy (111 patients). Erbitux was administered as a 400-
 407 mg/m² initial dose, followed by 250 mg/m² weekly until disease progression or
 408 unacceptable toxicity. In the Erbitux plus irinotecan arm, irinotecan was added to Erbitux
 409 using the same dose and schedule for irinotecan as the patient had previously failed.
 410 Acceptable irinotecan schedules were 350 mg/m² every 3 weeks, 180 mg/m² every 2
 411 weeks, or 125 mg/m² weekly times four doses every 6 weeks. Of the 329 patients, the
 412 median age was 59 years, 63% were male, 98% were Caucasian, and 88% had baseline
 413 Karnofsky Performance Status ≥80. Approximately two-thirds had previously failed
 414 oxaliplatin treatment.

415 The efficacy of Erbitux plus irinotecan or Erbitux monotherapy, based on durable
 416 objective responses, was evaluated in all randomized patients and in two pre-specified

417 subpopulations: irinotecan refractory patients, and irinotecan and oxaliplatin failures. In
418 patients receiving Erbitux plus irinotecan, the objective response rate was 23% (95%
419 confidence interval 18%–29%), median duration of response was 5.7 months, and median
420 time to progression was 4.1 months. In patients receiving Erbitux monotherapy, the
421 objective response rate was 11% (95% confidence interval 6%–18%), median duration of
422 response was 4.2 months, and median time to progression was 1.5 months. Similar
423 response rates were observed in the pre-defined subsets in both the combination arm and
424 monotherapy arm of the study.

425 **Lack of Efficacy of Anti-EGFR Monoclonal Antibodies in Patients With**
426 **mCRC Containing *KRAS* Mutations**

427 Retrospective analyses as presented in Table 5 across seven randomized clinical trials
428 suggest that anti-EGFR monoclonal antibodies are not effective for the treatment of
429 patients with mCRC containing *KRAS* mutations. In these trials, patients received
430 standard of care (ie, BSC or chemotherapy) and were randomized to receive either an
431 anti-EGFR antibody (cetuximab or panitumumab) or no additional therapy. In all studies,
432 investigational tests were used to detect *KRAS* mutations in codon 12 or 13. The
433 percentage of study populations for which *KRAS* status was assessed ranged from 23% to
434 92%. [See *Clinical Pharmacology (12.1)*.]

435

Table 5: Retrospective Analyses of Treatment Effect in the Subset of Patients with mCRC Containing *KRAS* Mutations Enrolled in Randomized Clinical Trials

Population (n: ITT ¹)	Treatment	Number of Patients with <i>KRAS</i> Results (% ITT)	Number of Patients with <i>KRAS</i> mutant (mAb ² /control)	Effect of mAb on Endpoints: <i>KRAS</i> Mutant ³
1 st line treatment mCRC (1198)	FOLFIRI ± Erbitux	540 (45%)	105/87	PFS²: no difference OS ² : no difference ORR ² : decreased
1 st line treatment mCRC (337)	FOLFOX-4 ± Erbitux	233 (69%)	52/47	ORR: decreased PFS: decreased OS: no difference
1 st line treatment mCRC (1053)	oxaliplatin or irinotecan-based chemotherapy, bevacizumab ± panitumumab	oxaliplatin 664 (81%)	135/125	PFS: decreased OS: no difference ORR: increased
		irinotecan 201 (87%)	47/39	ORR: decreased PFS: decreased OS: decreased
1 st line treatment mCRC (736)	bevacizumab, capecitabine, oxaliplatin ± Erbitux	528 (72%)	98/108	PFS: decreased OS: decreased ORR: decreased
2 nd line treatment mCRC (1298)	irinotecan ± Erbitux	300 (23%)	49/59	OS: decreased PFS: no difference ORR: increased
Study 3 3 rd line treatment mCRC (572)	BSC ± Erbitux	394 (69%)	81/83	OS: no difference PFS: no difference ORR: increased
3 rd line treatment mCRC (463)	BSC ± panitumumab	427 (92%)	84/100	PFS: no difference OS: no difference ORR: no difference

¹ ITT: intent-to-treat.

² mAb: EGFR monoclonal antibody; PFS: progression-free survival; ORR: overall response rate; OS: overall survival.

³ Results from the primary efficacy endpoint are in bold. A given endpoint is designated as “decreased” if there was a numerically smaller result and as “increased” if there was a numerically higher result in the mAb group than in the control group.

436

437 **16 HOW SUPPLIED/STORAGE AND HANDLING**

438 Erbitux[®] (cetuximab) is supplied at a concentration of 2 mg/mL as a 100 mg/50 mL,
439 single-use vial or as a 200 mg/100 mL, single-use vial as a sterile, preservative-free,
440 injectable liquid.

441 NDC 66733-948-23 100 mg/50 mL, single-use vial, individually packaged in a carton

442 NDC 66733-958-23 200 mg/100 mL, single-use vial, individually packaged in a carton

443 Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). **Do not freeze.** Increased
444 particulate formation may occur at temperatures at or below 0° C. This product contains
445 no preservatives. Preparations of Erbitux in infusion containers are chemically and
446 physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at
447 controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining
448 solution in the infusion container after 8 hours at controlled room temperature or after
449 12 hours at 2° C to 8° C. Discard any unused portion of the vial.

450 **17 PATIENT COUNSELING INFORMATION**

451 Advise patients:

- 452 • To report signs and symptoms of infusion reactions such as fever, chills, or breathing
453 problems.
- 454 • Of the potential risks of using Erbitux during pregnancy or nursing and of the need to
455 use adequate contraception in both males and females during and for 6 months
456 following the last dose of Erbitux therapy.
- 457 • That nursing is not recommended during, and for 2 months following the last dose of
458 Erbitux therapy.
- 459 • To limit sun exposure (use sunscreen, wear hats) while receiving and for 2 months
460 following the last dose of Erbitux.

461 Erbitux[®] is a registered trademark of ImClone Systems Incorporated.

462

463 Manufactured by ImClone Systems Incorporated, Branchburg, NJ 08876

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

465



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