

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 use
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)

10/2007

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)

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)

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SERIOUS INFUSION REACTIONS AND CARDIOPULMONARY ARREST

1 INDICATIONS AND USAGE

- 1.1 Squamous Cell Carcinoma of the Head and Neck (SCCHN)

- 1.2 Colorectal Cancer

2 DOSAGE AND ADMINISTRATION

- 2.1 Squamous Cell Carcinoma of the Head and Neck
- 2.2 Colorectal Cancer
- 2.3 Recommended Premedication
- 2.4 Dose Modifications
- 2.5 Preparation for Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Infusion Reactions
- 5.2 Cardiopulmonary Arrest
- 5.3 Pulmonary Toxicity
- 5.4 Dermatologic Toxicity
- 5.5 Use of Erbitux® in Combination With Radiation and Cisplatin
- 5.6 Hypomagnesemia and Electrolyte Abnormalities
- 5.7 Epidermal Growth Factor Receptor (EGFR) Expression and Response

6 ADVERSE REACTIONS

- 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 Grade 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: 10/2007

- 6.1 Clinical Trials Experience
- 6.2 Immunogenicity

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Pharmacology and/or Toxicology

14 CLINICAL STUDIES

- 14.1 Squamous Cell Carcinoma of the Head and Neck (SCCHN)
- 14.2 Colorectal Cancer

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFUSION REACTIONS and CARDIOPULMONARY ARREST

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

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

1 INDICATIONS AND USAGE

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

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

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

1.2 Colorectal Cancer

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

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

2 DOSAGE AND ADMINISTRATION

2.1 Squamous Cell Carcinoma of the Head and Neck

Erbitux[®] in combination with radiation therapy:

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

Erbitux[®] monotherapy:

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

2.2 Colorectal Cancer

- The recommended initial dose, either as monotherapy or in combination with irinotecan, is 400 mg/m² administered as a 120-minute intravenous infusion (maximum infusion rate 10 mg/min).

- The recommended subsequent weekly dose, either as monotherapy or in combination with irinotecan, is 250 mg/m² infused over 60 minutes (maximum infusion rate 10 mg/min) until disease progression or unacceptable toxicity.

2.3 Recommended Premedication

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

2.4 Dose Modifications

Infusion Reactions

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

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

Dermatologic Toxicity

Recommended dose modifications for severe (NCI-CTC Grade 3 or 4) acneform rash are 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 [®]		

74 **2.5 Preparation for Administration**

75 **Do not administer Erbitux[®] as an intravenous push or bolus.**

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

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

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

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

83 **3 DOSAGE FORMS AND STRENGTHS**

84 100 mg/50 mL, single-use vial

85 200 mg/100 mL, single-use vial

86 **4 CONTRAINDICATIONS**

87 None.

88 **5 WARNINGS AND PRECAUTIONS**

89 **5.1 Infusion Reactions**

90 Serious infusion reactions, requiring medical intervention and immediate, permanent
91 discontinuation of Erbitux[®] included rapid onset of airway obstruction (bronchospasm,
92 stridor, hoarseness), hypotension, and/or cardiac arrest. Severe (NCI CTC Grade 3 and 4)
93 infusion reactions occurred in 2–5% of 1373 patients in clinical trials, with fatal outcome
94 in 1 patient.

95 Approximately 90% of severe infusion reactions occurred with the first infusion despite
96 premedication with antihistamines.

97 Monitor patients for 1 hour following Erbitux[®] infusions in a setting with resuscitation
98 equipment and other agents necessary to treat anaphylaxis (eg, epinephrine,

99 corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Monitor longer
100 to confirm resolution of the event in patients requiring treatment for infusion reactions.

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

103 **5.2 Cardiopulmonary Arrest**

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

116 **5.3 Pulmonary Toxicity**

117 Interstitial lung disease (ILD), including 1 fatality, occurred in 4 of 1570 (<0.5%) patients
118 receiving Erbitux[®] in clinical trials. Interrupt Erbitux[®] for acute onset or worsening of
119 pulmonary symptoms. Permanently discontinue Erbitux[®] for confirmed ILD.

120 **5.4 Dermatologic Toxicity**

121 Dermatologic toxicities, including acneform rash, skin drying and fissuring, paronychia
122 inflammation, and infectious sequelae (for example *S. aureus* sepsis, abscess formation,
123 cellulitis, blepharitis, cheilitis) occurred in patients receiving Erbitux[®] therapy. Acneform
124 rash occurred in 76–88% of 1373 patients receiving Erbitux[®] in clinical trials. Severe
125 acneform rash occurred in 1–17 % of patients.

126 Acneform rash usually developed within the first two weeks of therapy and resolved in a
127 majority of the patients after cessation of treatment, although in nearly half, the event

128 continued beyond 28 days. Monitor patients receiving Erbitux[®] for dermatologic
129 toxicities and infectious sequelae. Instruct patients to limit sun exposure during Erbitux[®].
130 [See *Dose Modifications* (2.4).]

131 **5.5 Use of Erbitux[®] in Combination With Radiation and** 132 **Cisplatin**

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

139 **5.6 Hypomagnesemia and Electrolyte Abnormalities**

140 In patients evaluated during clinical trials, hypomagnesemia occurred in 55% of patients
141 (199/365) receiving Erbitux[®] and was severe (NCI-CTC Grade 3 and 4) in 6–17%. The
142 onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to
143 months after initiation of Erbitux[®]. Periodically monitor patients for hypomagnesemia,
144 hypocalcemia, and hypokalemia, during and for at least 8 weeks following the
145 completion of Erbitux[®]. Replete electrolytes as necessary.

146 **5.7 Epidermal Growth Factor Receptor (EGFR) Expression** 147 **and Response**

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

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

157 6 ADVERSE REACTIONS

158 The following adverse reactions are discussed in greater detail in other sections of the
159 label:

- 160 • Infusion reactions [See *Boxed Warning and Warnings and Precautions (5.1).*]
- 161 • Cardiopulmonary arrest [See *Boxed Warning and Warnings and Precautions (5.2).*]
- 162 • Pulmonary toxicity [See *Warnings and Precautions (5.3).*]
- 163 • Dermatologic toxicity [See *Warnings and Precautions (5.4).*]
- 164 • Hypomagnesemia and Electrolyte Abnormalities [See *Warnings and Precautions*
165 *(5.6).*]

166
167 The most common adverse reactions with Erbitux[®] (incidence $\geq$ 25%) are cutaneous
168 adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and
169 infection.

170 The most serious adverse reactions with Erbitux[®] are infusion reactions,
171 cardiopulmonary arrest, dermatologic toxicity and radiation dermatitis, sepsis, renal
172 failure, interstitial lung disease, and pulmonary embolus.

173 Across all studies, Erbitux[®] was discontinued in 3–10% of patients because of adverse
174 reactions.

175 6.1 Clinical Trials Experience

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

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

183 **Infusion reactions:** Infusion reactions, which included pyrexia, chills, rigors, dyspnea,
184 bronchospasm, angioedema, urticaria, hypertension, and hypotension occurred in 15–
185 21% of patients across studies. Grades 3 and 4 infusion reactions occurred in 2–5% of
186 patients; infusion reactions were fatal in 1 patient.

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

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

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

191 Table 2 contains selected adverse events in 420 patients receiving radiation therapy either
 192 alone or with Erbitux[®] for locally or regionally advanced SCCHN in Study 1. Erbitux[®]
 193 was administered at the recommended dose and schedule (400 mg/m² initial dose,
 194 followed 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	Erbitux [®] plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
	Grades 1–4	Grades 3 and 4	Grades 1–4	Grades 3 and 4
% of Patients				
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

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

Body System Preferred Term	Eributux [®] 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			
Respiratory				
Pharyngitis	26	3	19	4
Skin/Appendages				
Acneform Rash ³	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 Acneform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.

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

197 **Late Radiation Toxicity**

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

205 **Colorectal Cancer**

206 Table 3 contains selected adverse events in 562 patients receiving best supportive care
207 (BSC) alone or with Eributux[®] monotherapy for metastatic colorectal cancer in Study 3.

208 Erbitux[®] was administered at the recommended dose and schedule (400 mg/m² initial
209 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

Table 3: Incidence of Selected Adverse Events Occurring in $\geq 10\%$ 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				
Neurology				
Insomnia	30	1	15	1
Confusion	15	6	9	2
Anxiety	14	2	8	1
Depression	13	1	6	<1

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

210 The most frequently reported adverse events in 354 patients treated with Erbitux[®] plus
211 irinotecan in clinical trials were acneform rash (88%), asthenia/malaise (73%), diarrhea
212 (72%), and nausea (55%). The most common Grade 3/4 adverse events included diarrhea
213 (22%), leukopenia (17%), asthenia/malaise (16%), and acneform rash (14%).

214 **6.2 Immunogenicity**

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

222 The incidence of antibody formation is highly dependent on the sensitivity and specificity
223 of the assay. Additionally, the observed incidence of antibody (including neutralizing
224 antibody) positivity in an assay may be influenced by several factors including assay

225 methodology, sample handling, timing of sample collection, concomitant medications,
226 and underlying disease. For these reasons, comparison of the incidence of antibodies to
227 Erbitux[®] with the incidence of antibodies to other products may be misleading.

228 **7 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 **8 USE IN SPECIFIC POPULATIONS**

233 **8.1 Pregnancy**

234 **Pregnancy Category C**

235 Animal reproduction studies have not been conducted with cetuximab. However, the
236 EGFR has been implicated in the control of prenatal development and may be essential
237 for normal organogenesis, proliferation, and differentiation in the developing embryo. In
238 addition, human IgG1 is known to cross the placental barrier; therefore, cetuximab has
239 the potential to be transmitted from the mother to the developing fetus. It is not known
240 whether Erbitux[®] can cause fetal harm when administered to a pregnant woman or
241 whether Erbitux[®] can affect reproductive capacity. There are no adequate and well-
242 controlled studies of Erbitux[®] in pregnant women. Erbitux[®] should only be given to a
243 pregnant woman, or any woman not employing adequate contraception if the potential
244 benefit justifies the potential risk to the fetus. All patients should be counseled regarding
245 the potential risk of Erbitux[®] treatment to the developing fetus prior to initiation of
246 therapy. If the patient becomes pregnant while receiving this drug, she should be apprised
247 of the potential hazard to the fetus and/or the potential risk for loss of the pregnancy.

248 **8.3 Nursing Mothers**

249 It is not known whether Erbitux[®] is secreted in human milk. IgG antibodies, such as
250 Erbitux[®], can be excreted in human milk. Because many drugs are excreted in human
251 milk and because of the potential for serious adverse reactions in nursing infants from
252 Erbitux[®], a decision should be made whether to discontinue nursing or to discontinue the
253 drug, taking into account the importance of the drug to the mother. If nursing is

254 interrupted, based on the mean half-life of cetuximab [see *Clinical Pharmacology* (12.3)],
255 nursing should not be resumed earlier than 60 days following the last dose of Erbitux®.

256 **8.4 Pediatric Use**

257 The safety and effectiveness of Erbitux® in pediatric patients have not been established.
258 The pharmacokinetics of cetuximab have not been studied in pediatric populations.

259 **8.5 Geriatric Use**

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

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

268 **10 OVERDOSAGE**

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

271 **11 DESCRIPTION**

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

278 Erbitux® is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small
279 amount of easily visible, white, amorphous cetuximab particulates. Erbitux® is supplied
280 at a concentration of 2 mg/mL in either 100 mg (50 mL) or 200 mg (100 mL), single-use
281 vials. Cetuximab is formulated in a preservative-free solution containing 8.48 mg/mL

282 sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.41 mg/mL
283 sodium phosphate monobasic monohydrate, and Water for Injection, USP.

284 **12 CLINICAL PHARMACOLOGY**

285 **12.1 Mechanism of Action**

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

291 Cetuximab binds specifically to the EGFR on both normal and tumor cells, and
292 competitively inhibits the binding of epidermal growth factor (EGF) and other ligands,
293 such as transforming growth factor- α . *In vitro* assays and *in vivo* animal studies have
294 shown that binding of cetuximab to the EGFR blocks phosphorylation and activation of
295 receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis,
296 and decreased matrix metalloproteinase and vascular endothelial growth factor
297 production. *In vitro*, cetuximab can mediate antibody-dependent cellular cytotoxicity
298 (ADCC) against certain human tumor types. *In vitro* assays and *in vivo* animal studies
299 have shown that cetuximab inhibits the growth and survival of tumor cells that express
300 the EGFR. No anti-tumor effects of cetuximab were observed in human tumor xenografts
301 lacking EGFR expression. The addition of cetuximab to radiation therapy or irinotecan in
302 human tumor xenograft models in mice resulted in an increase in anti-tumor effects
303 compared to radiation therapy or chemotherapy alone.

304 **12.3 Pharmacokinetics**

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

312 Following the recommended dose regimen (400 mg/m² initial dose; 250 mg/m² weekly
313 dose), concentrations of cetuximab reached steady-state levels by the third weekly
314 infusion with mean peak and trough concentrations across studies ranging from 168 to
315 235 and 41 to 85 µg/mL, respectively. The mean half-life of cetuximab was
316 approximately 112 hours (range 63–230 hours). The pharmacokinetics of cetuximab were
317 similar in patients with SCCHN and those with colorectal cancer.

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

323 **13 NONCLINICAL TOXICOLOGY**

324 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

337 **13.2 Animal Pharmacology and/or Toxicology**

338 In cynomolgus monkeys, cetuximab, when administered at doses of approximately 0.4 to
339 4 times the weekly human exposure (based on total body surface area), resulted in
340 dermatologic findings, including inflammation at the injection site and desquamation of
341 the external integument. At the highest dose level, the epithelial mucosa of the nasal
342 passage, esophagus, and tongue were similarly affected, and degenerative changes in the
343 renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of

344 the animals at the highest dose level beginning after approximately 13 weeks of
345 treatment.

346 **14 CLINICAL STUDIES**

347 **14.1 Squamous Cell Carcinoma of the Head and Neck** 348 **(SCCHN)**

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

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

367 The main outcome measure of this trial was duration of locoregional control. Overall
368 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

^a CI = confidence interval

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

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

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

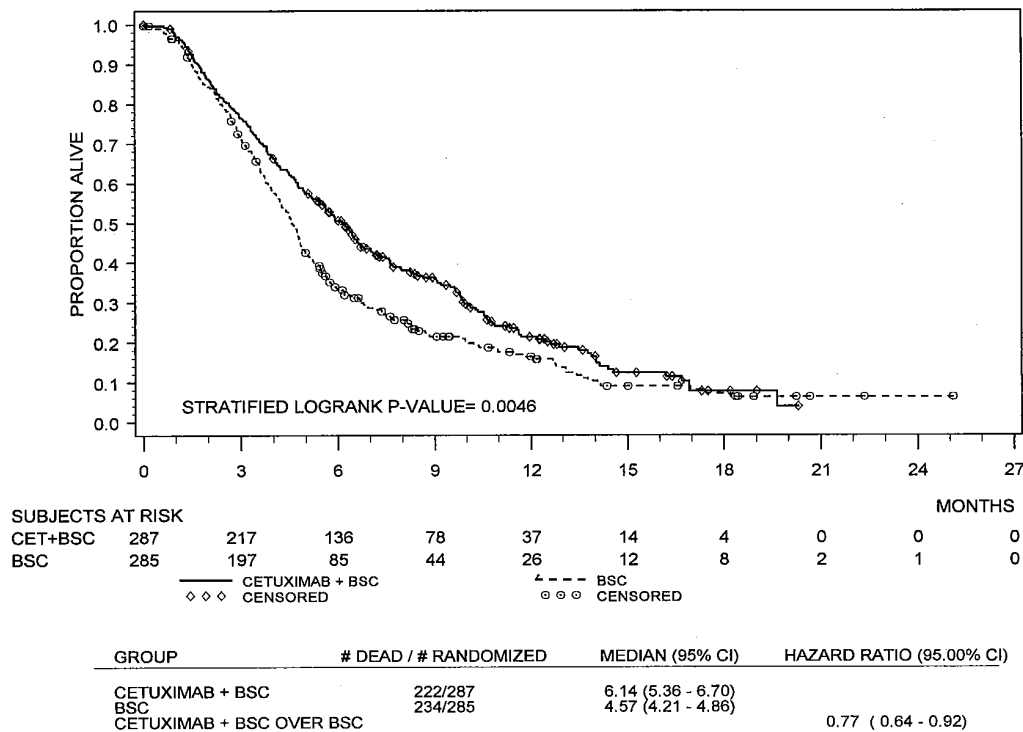
14.2 Colorectal Cancer

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

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

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

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



393

394 Study 4 was a multicenter, clinical trial conducted in 329 patients with EGFR-expressing
395 recurrent metastatic colorectal cancer. Patients were randomized (2:1) to receive either
396 Erbitux[®] plus irinotecan (218 patients) or Erbitux[®] monotherapy (111 patients). Erbitux[®]
397 was administered as a 400-mg/m² initial dose, followed by 250 mg/m² weekly until
398 disease progression or unacceptable toxicity. In the Erbitux[®] plus irinotecan arm,
399 irinotecan was added to Erbitux[®] using the same dose and schedule for irinotecan as the
400 patient had previously failed. Acceptable irinotecan schedules were 350 mg/m² every
401 3 weeks, 180 mg/m² every 2 weeks, or 125 mg/m² weekly times four doses every 6
402 weeks. Of the 329 patients, the median age was 59 years, 63% were male, 98% were
403 Caucasian, and 88% had baseline Karnofsky Performance Status ≥80. Approximately
404 two-thirds had previously failed oxaliplatin treatment.

405 The efficacy of Erbitux[®] plus irinotecan or Erbitux[®] monotherapy, based on durable
406 objective responses, was evaluated in all randomized patients and in two pre-specified
407 subpopulations: irinotecan refractory patients, and irinotecan and oxaliplatin failures. In
408 patients receiving Erbitux[®] plus irinotecan, the objective response rate was 23% (95%
409 confidence interval 18%–29%), median duration of response was 5.7 months, and median
410 time to progression was 4.1 months. In patients receiving Erbitux[®] monotherapy, the
411 objective response rate was 11% (95% confidence interval 6%–18%), median duration of
412 response was 4.2 months, and median time to progression was 1.5 months. Similar
413 response rates were observed in the pre-defined subsets in both the combination arm and
414 monotherapy arm of the study.

415 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

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

421 Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). **Do not freeze.** Increased
422 particulate formation may occur at temperatures at or below 0° C. This product contains
423 no preservatives. Preparations of Erbitux[®] in infusion containers are chemically and
424 physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at
425 controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining
426 solution in the infusion container after 8 hours at controlled room temperature or after
427 12 hours at 2° C to 8° C. Discard any unused portion of the vial.

428 **17 PATIENT COUNSELING INFORMATION**

429 Advise patients:

- 430 • To report signs and symptoms of infusion reactions such as fever, chills, or breathing
431 problems.

- 432 • Of the potential risks of using Erbitux[®] during pregnancy or nursing and of the need
433 to use adequate contraception in both males and females during and for 6 months
434 following the last dose of Erbitux[®] therapy.
- 435 • That nursing is not recommended during, and for 2 months following the last dose of
436 Erbitux[®] therapy.
- 437 • To limit sun exposure (use sunscreen, wear hats) while receiving and for 2 months
438 following the last dose of Erbitux[®].
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439

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

441 Manufactured by ImClone Systems Incorporated, Branchburg, NJ 08876

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

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