

**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)**  
injection, 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 with squamous cell carcinoma of the head and neck treated with Erbitux and radiation therapy and in 3% of patients with squamous cell carcinoma of the head and neck treated with cetuximab in combination with platinum-based therapy with 5-fluorouracil (5-FU). Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after Erbitux administration. (5.2, 5.6)**

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

Boxed Warning	11/2011
Indications and Usage	
Squamous Cell Carcinoma of the Head and Neck (1.1)	11/2011
Dosage and Administration	
Squamous Cell Carcinoma of the Head and Neck (2.1)	11/2011
Warnings and Precautions	
Cardiopulmonary Arrest (5.2)	11/2011
Dermatologic Toxicity (5.4)	01/2012
Hypomagnesemia and Electrolyte Abnormalities (5.6)	11/2011

-----**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 locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with 5-FU. (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 H<sub>1</sub> antagonist. (2.3)
- Administer 400 mg/m<sup>2</sup> initial dose as a 120-minute intravenous infusion followed by 250 mg/m<sup>2</sup> weekly infused over 60 minutes. (2.1, 2.2)
- Initiate Erbitux one week prior to initiation of radiation therapy. Complete Erbitux administration 1 hour prior to platinum-based therapy with 5-FU. (2.1)
- Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 infusion reactions and non-serious NCI CTC Grade 3 infusion reaction. (2.4)
- Permanently discontinue for serious infusion reactions. (2.4)
- Withhold infusion for severe, persistent acneiform 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)
- **Hypomagnesemia:** Periodically monitor during and for at least 8 weeks following the completion of Erbitux. Replete electrolytes as necessary. (5.6)

-----**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](http://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: 01/2012

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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)*, *Adverse Reactions (6)*.]  
7 Immediately interrupt and permanently discontinue Erbitux infusion for serious infusion  
8 reactions. [See *Dosage and Administration (2.4)*, *Warnings and Precautions (5.1)*.]

9 **Cardiopulmonary Arrest:** Cardiopulmonary arrest and/or sudden death occurred in  
10 2% of patients with squamous cell carcinoma of the head and neck treated with Erbitux  
11 and radiation therapy in Study 1 and in 3% of patients with squamous cell carcinoma of  
12 the head and neck treated with European Union (EU)-approved cetuximab in  
13 combination with platinum-based therapy with 5-fluorouracil (5-FU) in Study 2. Closely  
14 monitor serum electrolytes, including serum magnesium, potassium, and calcium, during  
15 and after Erbitux administration. [See *Warnings and Precautions (5.2, 5.6)*, *Clinical*  
16 *Studies (14.1)*.]

17 **1 INDICATIONS AND USAGE**

18 **1.1 Squamous Cell Carcinoma of the Head and Neck**  
19 **(SCCHN)**

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

23 Erbitux is indicated in combination with platinum-based therapy with 5-FU for the first-  
24 line treatment of patients with recurrent locoregional disease or metastatic squamous cell  
25 carcinoma of the head and neck. [See *Clinical Studies (14.1)*.]

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

## 29 **1.2 Colorectal Cancer**

30 Erbitux, as a single agent, is indicated for the treatment of epidermal growth factor  
31 receptor (EGFR)-expressing metastatic colorectal cancer after failure of both irinotecan-  
32 and oxaliplatin-based regimens. Erbitux, as a single agent, is also indicated for the  
33 treatment of EGFR-expressing metastatic colorectal cancer in patients who are intolerant  
34 to irinotecan-based regimens. [See *Warnings and Precautions (5.7), Clinical Studies*  
35 *(14.2).*]

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

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

## 47 **2 DOSAGE AND ADMINISTRATION**

### 48 **2.1 Squamous Cell Carcinoma of the Head and Neck**

49 Erbitux in combination with radiation therapy or in combination with platinum-based  
50 therapy with 5-FU:

- 51 • The recommended initial dose is 400 mg/m<sup>2</sup> administered one week prior to  
52 initiation of a course of radiation therapy or on the day of initiation of platinum-  
53 based therapy with 5-FU as a 120-minute intravenous infusion (maximum  
54 infusion rate 10 mg/min). Complete Erbitux administration 1 hour prior to  
55 platinum-based therapy with 5-FU.
- 56 • The recommended subsequent weekly dose (all other infusions) is 250 mg/m<sup>2</sup>  
57 infused over 60 minutes (maximum infusion rate 10 mg/min) for the duration of  
58 radiation therapy (6–7 weeks) or until disease progression or unacceptable  
59 toxicity when administered in combination with platinum-based therapy with

60 5-FU. Complete Erbitux administration 1 hour prior to radiation therapy or  
61 platinum-based therapy with 5-FU.

62 Erbitux monotherapy:

- 63 • The recommended initial dose is 400 mg/m<sup>2</sup> administered as a 120-minute  
64 intravenous infusion (maximum infusion rate 10 mg/min).
- 65 • The recommended subsequent weekly dose (all other infusions) is 250 mg/m<sup>2</sup>  
66 infused over 60 minutes (maximum infusion rate 10 mg/min) until disease  
67 progression or unacceptable toxicity.

## 68 **2.2 Colorectal Cancer**

- 69 • The recommended initial dose, either as monotherapy or in combination with  
70 irinotecan, is 400 mg/m<sup>2</sup> administered as a 120-minute intravenous infusion  
71 (maximum infusion rate 10 mg/min).
- 72 • The recommended subsequent weekly dose, either as monotherapy or in  
73 combination with irinotecan, is 250 mg/m<sup>2</sup> infused over 60 minutes (maximum  
74 infusion rate 10 mg/min) until disease progression or unacceptable toxicity.

## 75 **2.3 Recommended Premedication**

76 Premedicate with an H<sub>1</sub> antagonist (eg, 50 mg of diphenhydramine) intravenously  
77 30–60 minutes prior to the first dose; premedication should be administered for  
78 subsequent Erbitux doses based upon clinical judgment and presence/severity of prior  
79 infusion reactions.

## 80 **2.4 Dose Modifications**

### 81 **Infusion Reactions**

82 Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 and non-serious NCI CTC  
83 Grade 3 infusion reaction.

84 Immediately and permanently discontinue Erbitux for serious infusion reactions,  
85 requiring medical intervention and/or hospitalization. [See *Warnings and Precautions*  
86 (5.1).]

87 **Dermatologic Toxicity**

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

**Table 1: Erbitux Dose Modification Guidelines for Rash**

<b>Severe Acneiform Rash</b>	<b>Erbitux</b>	<b>Outcome</b>	<b>Erbitux Dose Modification</b>
1st occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 250 mg/m <sup>2</sup>
		No Improvement	Discontinue Erbitux
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 200 mg/m <sup>2</sup>
		No Improvement	Discontinue Erbitux
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 150 mg/m <sup>2</sup>
		No Improvement	Discontinue Erbitux
4th occurrence	Discontinue Erbitux		

90 **2.5 Preparation for Administration**

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

92 Administer via infusion pump or syringe pump. Do not exceed an infusion rate of  
93 10 mg/min.

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

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

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

99 **3 DOSAGE FORMS AND STRENGTHS**

100 100 mg/50 mL, single-use vial

101 200 mg/100 mL, single-use vial

102 **4 CONTRAINDICATIONS**

103 None

104 **5 WARNINGS AND PRECAUTIONS**

105 **5.1 Infusion Reactions**

106 Serious infusion reactions, requiring medical intervention and immediate, permanent  
107 discontinuation of Erbitux included rapid onset of airway obstruction (bronchospasm,  
108 stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction,  
109 and/or cardiac arrest. Severe (NCI CTC Grades 3 and 4) infusion reactions occurred in  
110 2–5% of 1373 patients in Studies 1, 3, 4, and 5 receiving Erbitux, with fatal outcome in  
111 1 patient. [See *Clinical Studies (14.1, 14.2).*]

112 Approximately 90% of severe infusion reactions occurred with the first infusion despite  
113 premedication with antihistamines.

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

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

120 **5.2 Cardiopulmonary Arrest**

121 Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients treated  
122 with radiation therapy and Erbitux as compared to none of 212 patients treated with  
123 radiation therapy alone in Study 1. Three patients with prior history of coronary artery  
124 disease died at home, with myocardial infarction as the presumed cause of death. One of  
125 these patients had arrhythmia and one had congestive heart failure. Death occurred 27,  
126 32, and 43 days after the last dose of Erbitux. One patient with no prior history of

127 coronary artery disease died one day after the last dose of Erbitux. In Study 2, fatal  
128 cardiac disorders and/or sudden death occurred in 7 (3%) of 219 patients treated with  
129 EU-approved cetuximab and platinum-based therapy with 5-FU as compared to 4 (2%) of  
130 215 patients treated with chemotherapy alone. Five of these 7 patients in the  
131 chemotherapy plus cetuximab arm received concomitant cisplatin and 2 patients received  
132 concomitant carboplatin. All 4 patients in the chemotherapy-alone arm received cisplatin.  
133 Carefully consider use of Erbitux in combination with radiation therapy or platinum-  
134 based therapy with 5-FU in head and neck cancer patients with a history of coronary  
135 artery disease, congestive heart failure, or arrhythmias in light of these risks. Closely  
136 monitor serum electrolytes, including serum magnesium, potassium, and calcium, during  
137 and after Erbitux. [See *Boxed Warning, Warnings and Precautions (5.6).*]

### 138 **5.3 Pulmonary Toxicity**

139 Interstitial lung disease (ILD), including 1 fatality, occurred in 4 of 1570 (<0.5%) patients  
140 receiving Erbitux in Studies 1, 3, and 5, as well as other studies, in colorectal cancer and  
141 head and neck cancer. Interrupt Erbitux for acute onset or worsening of pulmonary  
142 symptoms. Permanently discontinue Erbitux for confirmed ILD.

### 143 **5.4 Dermatologic Toxicity**

144 Dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychia  
145 inflammation, infectious sequelae (for example *S. aureus* sepsis, abscess formation,  
146 cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual  
147 acuity, cheilitis), and hypertrichosis occurred in patients receiving Erbitux therapy.  
148 Acneiform rash occurred in 76–88% of 1373 patients receiving Erbitux in Studies 1, 3, 4,  
149 and 5. Severe acneiform rash occurred in 1–17% of patients.

150 Acneiform rash usually developed within the first two weeks of therapy and resolved in a  
151 majority of the patients after cessation of treatment, although in nearly half, the event  
152 continued beyond 28 days. Monitor patients receiving Erbitux for dermatologic toxicities  
153 and infectious sequelae. Instruct patients to limit sun exposure during Erbitux therapy.  
154 [See *Dosage and Administration (2.4).*]

### 155 **5.5 Use of Erbitux in Combination With Radiation and** 156 **Cisplatin**

157 The safety of Erbitux in combination with radiation therapy and cisplatin has not been  
158 established. Death and serious cardiotoxicity were observed in a single-arm trial with

159 Erbitux, radiation therapy, and cisplatin (100 mg/m<sup>2</sup>) in patients with locally advanced  
160 SCCHN. Two of 21 patients died, one as a result of pneumonia and one of an unknown  
161 cause. Four patients discontinued treatment due to adverse events. Two of these  
162 discontinuations were due to cardiac events.

## 163 **5.6 Hypomagnesemia and Electrolyte Abnormalities**

164 In patients evaluated during clinical trials, hypomagnesemia occurred in 55% of  
165 365 patients receiving Erbitux in Study 4 and two other clinical trials in colorectal  
166 cancer and head and neck cancer, respectively, and was severe (NCI CTC Grades 3 and  
167 4) in 6–17%.

168 In Study 2, where EU-approved cetuximab was administered in combination with  
169 platinum-based therapy, the addition of cetuximab to cisplatin and 5-FU resulted in an  
170 increased incidence of hypomagnesemia (14% vs. 6%) and of Grade 3–4  
171 hypomagnesemia (7% vs. 2%) compared to cisplatin and 5-FU alone. In contrast, the  
172 incidences of hypomagnesemia were similar for those who received cetuximab,  
173 carboplatin, and 5-FU compared to carboplatin and 5-FU (4% vs. 4%). No patient  
174 experienced Grade 3–4 hypomagnesemia in either arm in the carboplatin subgroup.

175 The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred  
176 days to months after initiation of Erbitux. Periodically monitor patients for  
177 hypomagnesemia, hypocalcemia, and hypokalemia, during and for at least 8 weeks  
178 following the completion of Erbitux. Replete electrolytes as necessary.

## 179 **5.7 Epidermal Growth Factor Receptor (EGFR) Expression** 180 **and Response**

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

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

## 190 **6 ADVERSE REACTIONS**

191 The following adverse reactions are discussed in greater detail in other sections of the  
192 label:

- 193 • Infusion reactions [See *Boxed Warning, Warnings and Precautions (5.1).*]
- 194 • Cardiopulmonary arrest [See *Boxed Warning, Warnings and Precautions (5.2).*]
- 195 • Pulmonary toxicity [See *Warnings and Precautions (5.3).*]
- 196 • Dermatologic toxicity [See *Warnings and Precautions (5.4).*]
- 197 • Hypomagnesemia and Electrolyte Abnormalities [See *Warnings and Precautions*  
198 *(5.6).*]

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

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

205 Across Studies 1, 3, 4, and 5, Erbitux was discontinued in 3–10% of patients because of  
206 adverse reactions.

### 207 **6.1 Clinical Trials Experience**

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

211 The data below reflect exposure to Erbitux in 1373 patients with colorectal cancer or  
212 SCCHN in randomized Phase 3 (Studies 1 and 4) or Phase 2 (Studies 3 and 5) trials  
213 treated at the recommended dose and schedule for medians of 7 to 14 weeks. [See  
214 *Clinical Studies (14).*]

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

219 **Infections:** The incidence of infection was variable across studies, ranging from  
220 13–35%. Sepsis occurred in 1–4% of patients.

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

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

223 ***Erbixut in Combination with Radiation Therapy***

224 Table 2 contains selected adverse events in 420 patients receiving radiation therapy either  
225 alone or with Erbixut for locally or regionally advanced SCCHN in Study 1. Erbixut was  
226 administered at the recommended dose and schedule (400 mg/m<sup>2</sup> initial dose, followed  
227 by 250 mg/m<sup>2</sup> 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	Erbixut 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				
<b>Body as a Whole</b>				
Asthenia	56	4	49	5
Fever <sup>a</sup>	29	1	13	1
Headache	19	<1	8	<1
Infusion Reaction <sup>b</sup>	15	3	2	0
Infection	13	1	9	1
Chills <sup>a</sup>	16	0	5	0
<b>Digestive</b>				
Nausea	49	2	37	2
Emesis	29	2	23	4
Diarrhea	19	2	13	1
Dyspepsia	14	0	9	1
<b>Metabolic/Nutritional</b>				
Weight Loss	84	11	72	7
Dehydration	25	6	19	8
Alanine Transaminase, high <sup>c</sup>	43	2	21	1
Aspartate Transaminase, high <sup>c</sup>	38	1	24	1
Alkaline Phosphatase, high <sup>c</sup>	33	<1	24	0

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

Body System Preferred Term	Erbix 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			
<b>Respiratory</b>				
Pharyngitis	26	3	19	4
<b>Skin/Appendages</b>				
Acneiform Rash <sup>d</sup>	87	17	10	1
Radiation Dermatitis	86	23	90	18
Application Site Reaction	18	0	12	1
Pruritus	16	0	4	0

<sup>a</sup> Includes cases also reported as infusion reaction.

<sup>b</sup> Infusion reaction is defined as any event described at any time during the clinical study as “allergic reaction” or “anaphylactoid reaction”, or any event occurring on the first day of dosing described as “allergic reaction”, “anaphylactoid reaction”, “fever”, “chills”, “chills and fever”, or “dyspnea”.

<sup>c</sup> Based on laboratory measurements, not on reported adverse events, the number of subjects with tested samples varied from 205–206 for Erbitux plus Radiation arm; 209–210 for Radiation alone.

<sup>d</sup> Acneiform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.

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

230 ***Late Radiation Toxicity***

231 The overall incidence of late radiation toxicities (any grade) was higher in Erbitux in  
232 combination with radiation therapy compared with radiation therapy alone. The following  
233 sites were affected: salivary glands (65% versus 56%), larynx (52% versus 36%),  
234 subcutaneous tissue (49% versus 45%), mucous membrane (48% versus 39%), esophagus  
235 (44% versus 35%), skin (42% versus 33%). The incidence of Grade 3 or 4 late radiation  
236 toxicities was similar between the radiation therapy alone and the Erbitux plus radiation  
237 treatment groups.

238 ***Study 2: EU-Approved Cetuximab in Combination with Platinum-based***  
239 ***Therapy with 5-Fluorouracil***

240 Study 2 used EU-approved cetuximab. Since U.S.-licensed Erbitux provides  
241 approximately 22% higher exposure relative to the EU-approved cetuximab, the data

242 provided below may underestimate the incidence and severity of adverse reactions  
243 anticipated with Erbitux for this indication. However, the tolerability of the  
244 recommended dose is supported by safety data from additional studies of Erbitux [see  
245 *Clinical Pharmacology (12.3)*].

246 Table 3 contains selected adverse events in 434 patients with recurrent locoregional  
247 disease or metastatic SCCHN receiving EU-approved cetuximab in combination with  
248 platinum-based therapy with 5-FU or platinum-based therapy with 5-FU alone in Study 2.  
249 Cetuximab was administered at 400 mg/m<sup>2</sup> for the initial dose, followed by 250 mg/m<sup>2</sup>  
250 weekly. Patients received a median of 17 infusions (range 1–89).

**Table 3: Incidence of Selected Adverse Events (≥10%) in Patients with Recurrent Locoregional Disease or Metastatic SCCHN**

System Organ Class Preferred Term	EU-Approved Cetuximab plus Platinum-based Therapy with 5-FU (n=219)		Platinum-based Therapy with 5-FU Alone (n=215)	
	Grades 1–4	Grades 3 and 4	Grades 1–4	Grades 3 and 4
% of Patients				
<b>Eye Disorders</b>				
Conjunctivitis	10	0	0	0
<b>Gastrointestinal Disorders</b>				
Nausea	54	4	47	4
Diarrhea	26	5	16	1
<b>General Disorders and Administration Site Conditions</b>				
Pyrexia	22	0	13	1
Infusion Reaction <sup>a</sup>	10	2	<1	0
<b>Infections and Infestations</b>				
Infection <sup>b</sup>	44	11	27	8
<b>Metabolism and Nutrition Disorders</b>				
Anorexia	25	5	14	1
Hypocalcemia	12	4	5	1
Hypokalemia	12	7	7	5
Hypomagnesemia	11	5	5	1

**Table 3: Incidence of Selected Adverse Events (≥10%) in Patients with Recurrent Locoregional Disease or Metastatic SCCHN**

System Organ Class Preferred Term	EU-Approved Cetuximab plus Platinum-based Therapy with 5-FU (n=219)		Platinum-based Therapy with 5-FU Alone (n=215)	
	Grades 1-4	Grades 3 and 4	Grades 1-4	Grades 3 and 4
<b>% of Patients</b>				
<b>Skin and Subcutaneous Tissue Disorders</b>				
Acneiform Rash <sup>c</sup>	70	9	2	0
Rash	28	5	2	0
Acne	22	2	0	0
Dermatitis Acneiform	15	2	0	0
Dry Skin	14	0	<1	0
Alopecia	12	0	7	0

<sup>a</sup> Infusion reaction defined as any event of “anaphylactic reaction”, “hypersensitivity”, “fever and/or chills”, “dyspnea”, or “pyrexia” on the first day of dosing.

<sup>b</sup> Infection – this term excludes sepsis-related events which are presented separately.

<sup>c</sup> Acneiform rash defined as any event described as “acne”, “dermatitis acneiform”, “dry skin”, “exfoliative rash”, “rash”, “rash erythematous”, “rash macular”, “rash papular”, or “rash pustular”.

Chemotherapy = cisplatin + 5-fluorouracil or carboplatin + 5-fluorouracil

251 For cardiac disorders, approximately 9% of subjects in both the EU-approved cetuximab  
252 plus chemotherapy and chemotherapy-only treatment arms in Study 2 experienced a  
253 cardiac event. The majority of these events occurred in patients who received  
254 cisplatin/5-FU, with or without cetuximab as follows: 11% and 12% in patients who  
255 received cisplatin/5-FU with or without cetuximab, respectively, and 6% or 4% in  
256 patients who received carboplatin/5-FU with or without cetuximab, respectively. In both  
257 arms, the incidence of cardiovascular events was higher in the cisplatin with 5-FU  
258 containing subgroup. Death attributed to cardiovascular event or sudden death was  
259 reported in 3% of the patients in the cetuximab plus platinum-based therapy with 5-FU  
260 arm and 2% in the platinum-based chemotherapy with 5-FU alone arm.

261 **Colorectal Cancer**

262 ***Erbix Monotherapy***

263 Table 4 contains selected adverse events in 562 patients receiving best supportive care  
264 (BSC) alone or with Erbitux monotherapy for metastatic colorectal cancer in Study 4.  
265 Erbitux was administered at the recommended dose and schedule (400 mg/m<sup>2</sup> initial  
266 dose, followed by 250 mg/m<sup>2</sup> weekly).

**Table 4: Incidence of Selected Adverse Events Occurring in ≥10% of Patients with Advanced Colorectal Carcinoma<sup>a</sup> Treated with Erbitux Monotherapy**

Body System Preferred Term	Erbitux plus BSC (n=288)		BSC alone (n=274)	
	Any Grades <sup>b</sup>	Grades 3 and 4	Any Grades	Grades 3 and 4
% of Patients				
<b>Dermatology</b>				
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
<b>Body as a Whole</b>				
Fatigue	89	33	76	26
Fever	30	1	18	<1
Infusion Reactions <sup>c</sup>	20	5		
Rigors, Chills	13	<1	4	0
<b>Pain</b>				
Abdominal Pain	59	14	52	16
Pain-Other	51	16	34	7
Headache	33	4	11	0
Bone Pain	15	3	7	2
<b>Pulmonary</b>				
Dyspnea	48	16	43	12
Cough	29	2	19	1

**Table 4: Incidence of Selected Adverse Events Occurring in ≥10% of Patients with Advanced Colorectal Carcinoma<sup>a</sup> Treated with Erbitux Monotherapy**

Body System Preferred Term	Erbitux plus BSC (n=288)		BSC alone (n=274)	
	Any Grades <sup>b</sup>	Grades 3 and 4	Any Grades	Grades 3 and 4
% of Patients				
<b>Gastrointestinal</b>				
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
<b>Infection</b>				
Infection without neutropenia	35	13	17	6
<b>Neurology</b>				
Insomnia	30	1	15	1
Confusion	15	6	9	2
Anxiety	14	2	8	1
Depression	13	1	6	<1

<sup>a</sup> Adverse reactions occurring more frequently in Erbitux-treated patients compared with controls.

<sup>b</sup> Adverse events were graded using the NCI CTC, V 2.0.

<sup>c</sup> 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

## 267 **Erbitux in Combination with Irinotecan**

268 The most frequently reported adverse events in 354 patients treated with Erbitux plus  
269 irinotecan in clinical trials were acneiform rash (88%), asthenia/malaise (73%), diarrhea  
270 (72%), and nausea (55%). The most common Grades 3–4 adverse events included  
271 diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneiform rash (14%).

## 272 **6.2 Immunogenicity**

273 As with all therapeutic proteins, there is potential for immunogenicity. Immunogenic  
274 responses to cetuximab were assessed using either a double antigen radiometric assay or

275 an ELISA assay. Due to limitations in assay performance and sampling timing, the  
276 incidence of antibody development in patients receiving Erbitux has not been adequately  
277 determined. Non-neutralizing anti-cetuximab antibodies were detected in 5% (49 of  
278 1001) of evaluable patients without apparent effect on the safety or antitumor activity of  
279 Erbitux.

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

### 286 **6.3 Postmarketing Experience**

287 The following adverse reaction has been identified during post-approval use of Erbitux.  
288 Because this reaction was reported from a population of uncertain size, it was not always  
289 possible to reliably estimate its frequency or establish a causal relationship to drug  
290 exposure.

- 291 • Aseptic meningitis

## 292 **7 DRUG INTERACTIONS**

293 A drug interaction study was performed in which Erbitux was administered in  
294 combination with irinotecan. There was no evidence of any pharmacokinetic interactions  
295 between Erbitux and irinotecan.

## 296 **8 USE IN SPECIFIC POPULATIONS**

### 297 **8.1 Pregnancy**

#### 298 **Pregnancy Category C**

299 There are no adequate and well-controlled studies of Erbitux in pregnant women. Based  
300 on animal models, EGFR has been implicated in the control of prenatal development and  
301 may be essential for normal organogenesis, proliferation, and differentiation in the  
302 developing embryo. Human IgG is known to cross the placental barrier; therefore,  
303 Erbitux may be transmitted from the mother to the developing fetus, and has the potential

304 to cause fetal harm when administered to pregnant women. Erbitux should be used during  
305 pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

### 313 **8.3 Nursing Mothers**

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

### 321 **8.4 Pediatric Use**

322 The safety and effectiveness of Erbitux in pediatric patients have not been established.  
323 The pharmacokinetics of cetuximab, in combination with irinotecan, were evaluated in  
324 pediatric patients with refractory solid tumors in an open-label, single-arm, dose-finding  
325 study. Erbitux was administered once weekly, at doses up to  $250 \text{ mg/m}^2$ , to 27 patients  
326 ranging from 1 to 12 years old; and in 19 patients ranging from 13 to 18 years old. No  
327 new safety signals were identified in pediatric patients. The pharmacokinetic profiles of  
328 cetuximab between the two age groups were similar at the 75 and  $150 \text{ mg/m}^2$  single dose  
329 levels. The volume of the distribution appeared to be independent of dose and  
330 approximated the vascular space of  $2\text{--}3 \text{ L/m}^2$ . Following a single dose of  $250 \text{ mg/m}^2$ , the  
331 geometric mean  $\text{AUC}_{0\text{-inf}}$  (CV%) value was  $17.7 \text{ mg}\cdot\text{h/mL}$  (34%) in the younger age  
332 group (1–12 years,  $n=9$ ) and  $13.4 \text{ mg}\cdot\text{h/mL}$  (38%) in the adolescent group (13–18 years,  
333  $n=6$ ). The mean half-life of cetuximab was 110 hours (range 69 to 188 hours) for the  
334 younger age group, and 82 hours (range 55 to 117 hours) for the adolescent age group.

## 335 **8.5 Geriatric Use**

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

340 Clinical studies of Erbitux conducted in patients with head and neck cancer did not  
341 include sufficient number of subjects aged 65 and over to determine whether they  
342 respond differently from younger subjects.

## 343 **10 OVERDOSAGE**

344 The maximum single dose of Erbitux administered is 1000 mg/m<sup>2</sup> in one patient. No  
345 adverse events were reported for this patient.

## 346 **11 DESCRIPTION**

347 Erbitux<sup>®</sup> (cetuximab) is a recombinant, human/mouse chimeric monoclonal antibody that  
348 binds specifically to the extracellular domain of the human epidermal growth factor  
349 receptor (EGFR). Cetuximab is composed of the Fv regions of a murine anti-EGFR  
350 antibody with human IgG1 heavy and kappa light chain constant regions and has an  
351 approximate molecular weight of 152 kDa. Cetuximab is produced in mammalian  
352 (murine myeloma) cell culture.

353 Erbitux is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small  
354 amount of easily visible, white, amorphous cetuximab particulates. Erbitux is supplied at  
355 a concentration of 2 mg/mL in either 100 mg (50 mL) or 200 mg (100 mL), single-use  
356 vials. Cetuximab is formulated in a solution with no preservatives, which contains  
357 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate,  
358 0.41 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP.

## 359 **12 CLINICAL PHARMACOLOGY**

### 360 **12.1 Mechanism of Action**

361 The epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) is a transmembrane  
362 glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including  
363 EGFR, HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal

364 epithelial tissues, including the skin and hair follicle. Expression of EGFR is also  
365 detected in many human cancers including those of the head and neck, colon, and rectum.

366 Cetuximab binds specifically to the EGFR on both normal and tumor cells, and  
367 competitively inhibits the binding of epidermal growth factor (EGF) and other ligands,  
368 such as transforming growth factor- $\alpha$ . *In vitro* assays and *in vivo* animal studies have  
369 shown that binding of cetuximab to the EGFR blocks phosphorylation and activation of  
370 receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis,  
371 and decreased matrix metalloproteinase and vascular endothelial growth factor  
372 production. Signal transduction through the EGFR results in activation of wild-type  
373 KRAS protein. However, in cells with activating *KRAS* somatic mutations, the mutant  
374 KRAS protein is continuously active and appears independent of EGFR regulation.

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

### 382 **12.3 Pharmacokinetics**

383 Erbitux administered as monotherapy or in combination with concomitant chemotherapy  
384 or radiation therapy exhibits nonlinear pharmacokinetics. The area under the  
385 concentration time curve (AUC) increased in a greater than dose proportional manner  
386 while clearance of cetuximab decreased from 0.08 to 0.02 L/h/m<sup>2</sup> as the dose increased  
387 from 20 to 200 mg/m<sup>2</sup>, and at doses >200 mg/m<sup>2</sup>, it appeared to plateau. The volume of  
388 the distribution for cetuximab appeared to be independent of dose and approximated the  
389 vascular space of 2–3 L/m<sup>2</sup>.

390 Following the recommended dose regimen (400 mg/m<sup>2</sup> initial dose; 250 mg/m<sup>2</sup> weekly  
391 dose), concentrations of cetuximab reached steady-state levels by the third weekly  
392 infusion with mean peak and trough concentrations across studies ranging from 168 to  
393 235 and 41 to 85  $\mu$ g/mL, respectively. The mean half-life of cetuximab was  
394 approximately 112 hours (range 63–230 hours). The pharmacokinetics of cetuximab were  
395 similar in patients with SCCHN and those with colorectal cancer.

396 Erbitux had an approximately 22% (90% confidence interval; 6%, 38%) higher systemic  
397 exposure relative to the EU-approved cetuximab used in Study 2 based on a population  
398 pharmacokinetic analysis. [See *Clinical Studies (14.1)*.]

## 399 **13 NONCLINICAL TOXICOLOGY**

### 400 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

### 413 **13.2 Animal Pharmacology and/or Toxicology**

414 In cynomolgus monkeys, cetuximab, when administered at doses of approximately 0.4 to  
415 4 times the weekly human exposure (based on total body surface area), resulted in  
416 dermatologic findings, including inflammation at the injection site and desquamation of  
417 the external integument. At the highest dose level, the epithelial mucosa of the nasal  
418 passage, esophagus, and tongue were similarly affected, and degenerative changes in the  
419 renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of  
420 the animals at the highest dose level beginning after approximately 13 weeks of  
421 treatment.

422 **14 CLINICAL STUDIES**

423 **14.1 Squamous Cell Carcinoma of the Head and Neck**  
 424 **(SCCHN)**

425 Study 1 was a randomized, multicenter, controlled trial of 424 patients with locally or  
 426 regionally advanced SCCHN. Patients with Stage III/IV SCCHN of the oropharynx,  
 427 hypopharynx, or larynx with no prior therapy were randomized (1:1) to receive either  
 428 Erbitux plus radiation therapy or radiation therapy alone. Stratification factors were  
 429 Karnofsky Performance Status (60–80 versus 90–100), nodal stage (N0 versus N+),  
 430 tumor stage (T1–3 versus T4 using American Joint Committee on Cancer 1998 staging  
 431 criteria), and radiation therapy fractionation (concomitant boost versus once-daily versus  
 432 twice-daily). Radiation therapy was administered for 6–7 weeks as once daily, twice  
 433 daily, or concomitant boost. Erbitux was administered as a 400 mg/m<sup>2</sup> initial dose  
 434 beginning one week prior to initiation of radiation therapy, followed by 250 mg/m<sup>2</sup>  
 435 weekly administered 1 hour prior to radiation therapy for the duration of radiation  
 436 therapy (6–7 weeks).

437 Of the 424 randomized patients, the median age was 57 years, 80% were male, 83% were  
 438 Caucasian, and 90% had baseline Karnofsky Performance Status ≥80. There were  
 439 258 patients enrolled in U.S. sites (61%). Sixty percent of patients had oropharyngeal,  
 440 25% laryngeal, and 15% hypopharyngeal primary tumors; 28% had AJCC T4 tumor  
 441 stage. Fifty-six percent of the patients received radiation therapy with concomitant boost,  
 442 26% received once-daily regimen, and 18% twice-daily regimen.

443 The main outcome measure of this trial was duration of locoregional control. Overall  
 444 survival was also assessed. Results are presented in Table 5.

**Table 5: Study 1: Clinical Efficacy in Locoregionally Advanced SCCHN**

	<b>Erbitux + Radiation (n=211)</b>	<b>Radiation Alone (n=213)</b>	<b>Hazard Ratio (95% CI<sup>a</sup>)</b>	<b>Stratified Log-rank p-value</b>
<b>Locoregional Control</b>				
Median duration (months)	24.4	14.9	0.68 (0.52–0.89)	0.005
<b>Overall Survival</b>				
Median duration (months)	49.0	29.3	0.74 (0.57–0.97)	0.03

<sup>a</sup> CI = confidence interval

445 Study 2 was an open-label, randomized, multicenter, controlled trial of 442 patients with  
446 recurrent locoregional disease or metastatic SCCHN conducted outside the U.S. using an  
447 EU-approved cetuximab as the clinical trial material. Erbitux provides approximately  
448 22% higher exposure relative to the EU-approved cetuximab used in Study 2; these  
449 pharmacokinetic data, together with the results of Study 2 and other clinical trial data  
450 establish the efficacy of Erbitux at the recommended dose [see *Clinical Pharmacology*  
451 (12.3)].

452 Patients with no prior therapy for recurrent locoregional disease or metastatic SCCHN  
453 were randomized (1:1) to receive EU-approved cetuximab plus cisplatin or carboplatin  
454 and 5-FU, or cisplatin or carboplatin and 5-FU alone. Choice of cisplatin or carboplatin  
455 was at the discretion of the treating physician. Stratification factors were  
456 Karnofsky Performance Status (<80 versus ≥80) and previous chemotherapy. Cisplatin  
457 (100 mg/m<sup>2</sup>, Day 1) or carboplatin (AUC 5, Day 1) plus intravenous 5-FU  
458 (1000 mg/m<sup>2</sup>/day, Days 1–4) were administered every 3 weeks (1 cycle) for a maximum  
459 of 6 cycles in the absence of disease progression or unacceptable toxicity. Cetuximab was  
460 administered at a 400 mg/m<sup>2</sup> initial dose, followed by a 250 mg/m<sup>2</sup> weekly dose in  
461 combination with chemotherapy. Patients demonstrating at least stable disease on  
462 cetuximab in combination with chemotherapy were to continue cetuximab monotherapy  
463 at 250 mg/m<sup>2</sup> weekly, in the absence of disease progression or unacceptable toxicity after  
464 completion of 6 planned courses of platinum-based therapy. For patients where treatment  
465 was delayed because of the toxic effects of chemotherapy, weekly cetuximab was  
466 continued. If chemotherapy was discontinued for toxicity, cetuximab could be continued  
467 as monotherapy until disease progression or unacceptable toxicity.

468 Of the 442 randomized patients, the median age was 57 years, 90% were male, 98% were  
469 Caucasian, and 88% had baseline Karnofsky Performance Status ≥80. Thirty-four percent  
470 of patients had oropharyngeal, 25% laryngeal, 20% oral cavity, and 14% hypopharyngeal  
471 primary tumors. Fifty-three percent of patients had recurrent locoregional disease only  
472 and 47% had metastatic disease. Fifty-eight percent had AJCC Stage IV disease and  
473 21% had Stage III disease. Sixty-four percent of patients received cisplatin therapy and  
474 34% received carboplatin as initial therapy. Approximately fifteen percent of the patients  
475 in the cisplatin alone arm switched to carboplatin during the treatment period.

476 The main outcome measure of this trial was overall survival. Results are presented in  
477 Table 6 and Figure 1.

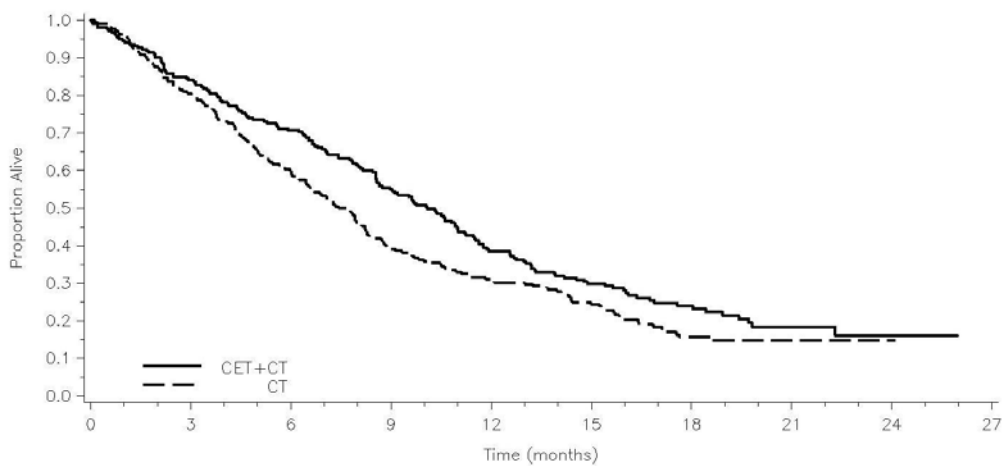
**Table 6: Study 2: Clinical Efficacy in Recurrent Locoregional Disease or Metastatic SCCHN**

	<b>EU-Approved Cetuximab + Platinum-based Therapy + 5-FU (n=222)</b>	<b>Platinum-based Therapy + 5-FU (n=220)</b>	<b>Hazard Ratio (95% CI<sup>a</sup>)</b>	<b>Stratified Log-rank p-value</b>
<b>Overall Survival</b>				
Median duration (months)	10.1	7.4	0.80 (0.64, 0.98)	0.034
<b>Progression-free Survival</b>				
Median duration (months)	5.5	3.3	0.57 (0.46, 0.72)	<0.0001
	<b>EU-Approved Cetuximab + Platinum-based Therapy + 5-FU</b>	<b>Platinum-based Therapy + 5-FU</b>	<b>Odds Ratio (95% CI<sup>a</sup>)</b>	<b>CMH<sup>b</sup> test p-value</b>
<b>Objective Response Rate</b>	35.6%	19.5%	2.33 (1.50, 3.60)	0.0001

<sup>a</sup> CI = confidence interval

<sup>b</sup> CMH = Cochran-Mantel-Haenszel

478 **Figure 1: Kaplan-Meier Curve for Overall Survival in Patients with**  
 479 **Recurrent Locoregional Disease or Metastatic Squamous Cell**  
 480 **Carcinoma of the Head and Neck**



Patients at Risk	0	3	6	9	12	15	18	21	24	27
CET+CT	222	184	153	118	82	57	30	15	3	0
CT	220	173	127	83	65	47	19	8	1	0

481  
 482 CT = Platinum-based therapy with 5-FU  
 483 CET = EU-approved cetuximab

484 In exploratory subgroup analyses of Study 2 by initial platinum therapy (cisplatin or  
485 carboplatin), for patients (N=284) receiving the EU-approved cetuximab plus cisplatin  
486 with 5-FU compared to cisplatin with 5-FU alone, the difference in median overall  
487 survival was 3.3 months (10.6 versus 7.3 months respectively; HR 0.71; 95% CI 0.54,  
488 0.93). The difference in median progression-free survival was 2.1 months (5.6 versus  
489 3.5 months respectively; HR 0.55; 95% CI 0.41, 0.73). The objective response rate was  
490 39% and 23% respectively (OR 2.18; 95% CI 1.29, 3.69). For patients (N=149) receiving  
491 cetuximab plus carboplatin with 5-FU compared to carboplatin with 5-FU alone, the  
492 difference in median overall survival was 1.4 months (9.7 versus 8.3 months; HR 0.99;  
493 95% CI 0.69, 1.43). The difference in median progression-free survival was 1.7 months  
494 (4.8 versus 3.1 months respectively; HR 0.61; 95% CI 0.42, 0.89). The objective response  
495 rate was 30% and 15% respectively (OR 2.45; 95% CI 1.10, 5.46).

496 Study 3 was a single-arm, multicenter clinical trial in 103 patients with recurrent or  
497 metastatic SCCHN. All patients had documented disease progression within 30 days of a  
498 platinum-based chemotherapy regimen. Patients received a 20-mg test dose of Erbitux on  
499 Day 1, followed by a 400 mg/m<sup>2</sup> initial dose, and 250 mg/m<sup>2</sup> weekly until disease  
500 progression or unacceptable toxicity.

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

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

## 505 **14.2 Colorectal Cancer**

### 506 **Erbitux Clinical Trials in EGFR-Expressing, Recurrent, Metastatic** 507 **Colorectal Cancer**

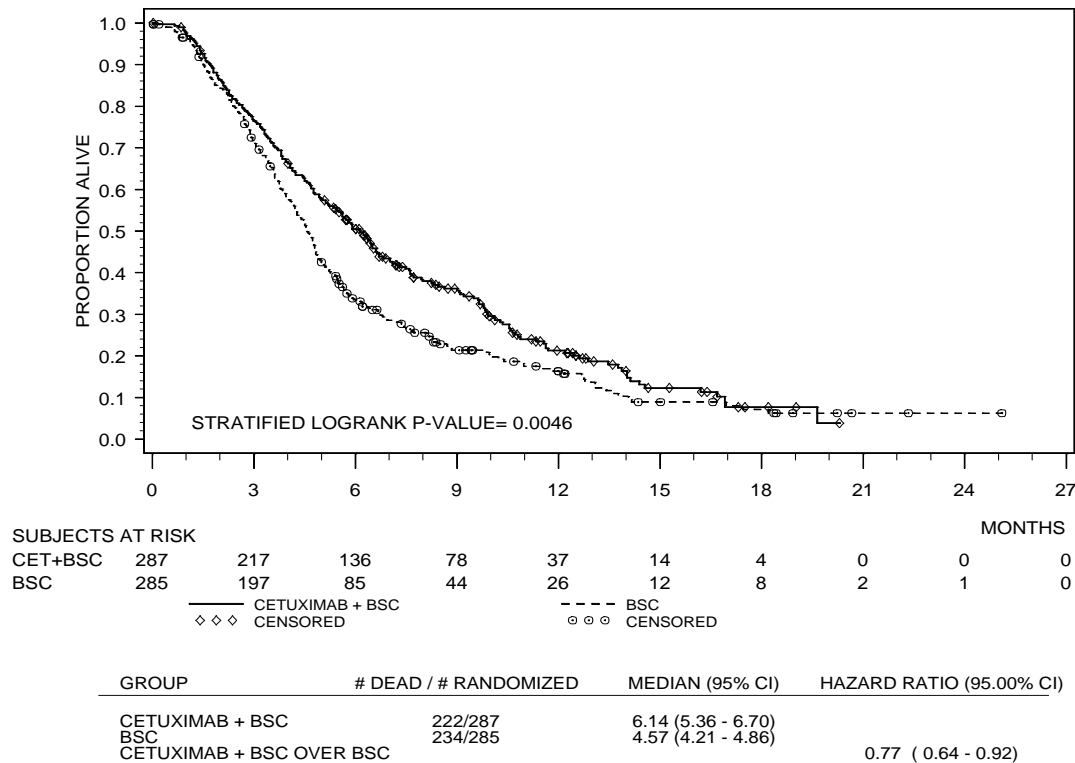
508 Study 4 was a multicenter, open-label, randomized, clinical trial conducted in  
509 572 patients with EGFR-expressing, previously treated, recurrent, metastatic colorectal  
510 cancer (mCRC). Patients were randomized (1:1) to receive either Erbitux plus best  
511 supportive care (BSC) or BSC alone. Erbitux was administered as a 400 mg/m<sup>2</sup> initial  
512 dose, followed by 250 mg/m<sup>2</sup> weekly until disease progression or unacceptable toxicity.

513 Of the 572 randomized patients, the median age was 63 years, 64% were male, 89% were  
514 Caucasian, and 77% had baseline ECOG Performance Status of 0–1. All patients were to

515 have received and progressed on prior therapy including an irinotecan-containing  
 516 regimen and an oxaliplatin-containing regimen.

517 The main outcome measure of the study was overall survival. The results are presented in  
 518 Figure 2.

519 **Figure 2: Kaplan-Meier Curve for Overall Survival in Patients with**  
 520 **Metastatic Colorectal Cancer**



521

522 Study 5 was a multicenter, clinical trial conducted in 329 patients with EGFR-expressing  
 523 recurrent mCRC. Patients were randomized (2:1) to receive either Erbitux plus irinotecan  
 524 (218 patients) or Erbitux monotherapy (111 patients). Erbitux was administered as a  
 525 400 mg/m<sup>2</sup> initial dose, followed by 250 mg/m<sup>2</sup> weekly until disease progression or  
 526 unacceptable toxicity. In the Erbitux plus irinotecan arm, irinotecan was added to Erbitux  
 527 using the same dose and schedule for irinotecan as the patient had previously failed.  
 528 Acceptable irinotecan schedules were 350 mg/m<sup>2</sup> every 3 weeks, 180 mg/m<sup>2</sup> every  
 529 2 weeks, or 125 mg/m<sup>2</sup> weekly times four doses every 6 weeks. Of the 329 patients, the  
 530 median age was 59 years, 63% were male, 98% were Caucasian, and 88% had baseline  
 531 Karnofsky Performance Status ≥80. Approximately two-thirds had previously failed  
 532 oxaliplatin treatment.

533 The efficacy of Erbitux plus irinotecan or Erbitux monotherapy, based on durable  
534 objective responses, was evaluated in all randomized patients and in two pre-specified  
535 subpopulations: irinotecan refractory patients, and irinotecan and oxaliplatin failures. In  
536 patients receiving Erbitux plus irinotecan, the objective response rate was  
537 23% (95% confidence interval 18%–29%), median duration of response was 5.7 months,  
538 and median time to progression was 4.1 months. In patients receiving Erbitux  
539 monotherapy, the objective response rate was 11% (95% confidence interval 6%–18%),  
540 median duration of response was 4.2 months, and median time to progression was  
541 1.5 months. Similar response rates were observed in the pre-defined subsets in both the  
542 combination arm and monotherapy arm of the study.

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

545 Retrospective analyses as presented in Table 7 across seven randomized clinical trials  
546 suggest that anti-EGFR monoclonal antibodies are not effective for the treatment of  
547 patients with mCRC containing *KRAS* mutations. In these trials, patients received  
548 standard of care (ie, BSC or chemotherapy) and were randomized to receive either an  
549 anti-EGFR antibody (cetuximab or panitumumab) or no additional therapy. In all studies,  
550 investigational tests were used to detect *KRAS* mutations in codon 12 or 13. The  
551 percentage of study populations for which *KRAS* status was assessed ranged from 23% to  
552 92%. [See *Clinical Pharmacology (12.1)*.]

**Table 7: Retrospective Analyses of Treatment Effect in the Subset of Patients with mCRC Containing *KRAS* Mutations Enrolled in Randomized Clinical Trials**

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

<sup>a</sup> ITT: intent-to-treat.

<sup>b</sup> mAb: EGFR monoclonal antibody; PFS: progression-free survival; ORR: overall response rate; OS: overall survival.

<sup>c</sup> 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.

553 **16 HOW SUPPLIED/STORAGE AND HANDLING**

554 Erbitux<sup>®</sup> (cetuximab) is supplied at a concentration of 2 mg/mL as a 100 mg/50 mL,  
555 single-use vial or as a 200 mg/100 mL, single-use vial as a sterile, injectable liquid  
556 containing no preservatives.

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

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

559 Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). **Do not freeze.** Increased  
560 particulate formation may occur at temperatures at or below 0° C. This product contains  
561 no preservatives. Preparations of Erbitux in infusion containers are chemically and  
562 physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at  
563 controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining  
564 solution in the infusion container after 8 hours at controlled room temperature or after  
565 12 hours at 2° C to 8° C. Discard any unused portion of the vial.

566 **17 PATIENT COUNSELING INFORMATION**

567 Advise patients:

- 568 • To report signs and symptoms of infusion reactions such as fever, chills, or breathing  
569 problems.
- 570 • Of the potential risks of using Erbitux during pregnancy or nursing and of the need  
571 to use adequate contraception in both males and females during and for 6 months  
572 following the last dose of Erbitux therapy.
- 573 • That nursing is not recommended during, and for 2 months following the last dose of  
574 Erbitux therapy.
- 575 • To limit sun exposure (use sunscreen, wear hats) while receiving and for 2 months  
576 following the last dose of Erbitux.

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578 Eli Lilly and Company.

579 Manufactured by ImClone LLC a wholly-owned subsidiary of Eli Lilly and Company,  
580 Branchburg, NJ 08876 USA  
581 Distributed and marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA  
582 Co-marketed by Eli Lilly and Company, Indianapolis, IN 46285 USA



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