

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

Indications and Usage	
Colorectal Cancer (1.2)	07/2012
Dosage and Administration	
Colorectal Cancer (2.2)	07/2012
Warnings and Precautions	
Use of Erbitux in Combination With Radiation and Cisplatin (5.5)	03/2013
K-Ras Testing in Metastatic or Advanced Colorectal Cancer Patients (5.7)	07/2012

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

K-Ras mutation-negative (wild-type), EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved tests

- in combination with FOLFIRI for first-line treatment,
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan. (1.2, 5.7, 12.1, 14.2)

Limitation of Use: Erbitux is not indicated for treatment of K-Ras mutation-positive colorectal cancer. (5.7, 14.2)

DOSAGE AND ADMINISTRATION

- Premedicate with an H₁ antagonist. (2.3)
- Administer 400 mg/m² initial dose as a 120-minute intravenous infusion followed by 250 mg/m² weekly infused over 60 minutes. (2.1, 2.2)
- Initiate Erbitux one week prior to initiation of radiation therapy. Complete Erbitux administration 1 hour prior to platinum-based therapy with 5-FU (2.1) and FOLFIRI (2.2).
- 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

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: 03/2013

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 K-Ras Mutation-negative, EGFR-expressing 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 K-Ras Testing in Metastatic or Advanced Colorectal Cancer Patients
- 5.8 Epidermal Growth Factor Receptor (EGFR) Expression and Response

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Immunogenicity
- 6.3 Postmarketing Experience

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
- 12.2 Pharmacodynamics
- 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

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

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

18 **1 INDICATIONS AND USAGE**

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

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

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

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

30 **1.2 K-Ras Mutation-negative, EGFR-expressing Colorectal**
31 **Cancer**

32 Erbitux is indicated for the treatment of *K-Ras* mutation-negative (wild-type), epidermal
33 growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC) as
34 determined by FDA-approved tests for this use [see *Dosage and Administration (2.2)*,
35 *Warnings and Precautions (5.7)*, *Clinical Studies (14.2)*]

- 36 • in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-
37 line treatment,
- 38 • in combination with irinotecan in patients who are refractory to irinotecan-
39 based chemotherapy,
- 40 • as a single agent in patients who have failed oxaliplatin- and irinotecan-based
41 chemotherapy or who are intolerant to irinotecan. [See *Warnings and*
42 *Precautions (5.7)*, *Clinical Pharmacology (12.1)*, *Clinical Studies (14.2)*.]

43 Limitation of Use: Erbitux is not indicated for treatment of *K-Ras* mutation-positive
44 colorectal cancer [see *Warnings and Precautions (5.7)*, *Clinical Studies (14.2)*].

45 **2 DOSAGE AND ADMINISTRATION**

46 **2.1 Squamous Cell Carcinoma of the Head and Neck**

47 Erbitux in combination with radiation therapy or in combination with platinum-based
48 therapy with 5-FU:

- 49 • The recommended initial dose is 400 mg/m² administered one week prior to
50 initiation of a course of radiation therapy or on the day of initiation of platinum-
51 based therapy with 5-FU as a 120-minute intravenous infusion (maximum
52 infusion rate 10 mg/min). Complete Erbitux administration 1 hour prior to
53 platinum-based therapy with 5-FU.
- 54 • The recommended subsequent weekly dose (all other infusions) is 250 mg/m²
55 infused over 60 minutes (maximum infusion rate 10 mg/min) for the duration of
56 radiation therapy (6–7 weeks) or until disease progression or unacceptable
57 toxicity when administered in combination with platinum-based therapy with
58 5-FU. Complete Erbitux administration 1 hour prior to radiation therapy or
59 platinum-based therapy with 5-FU.

60 Erbitux monotherapy:

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

66 **2.2 Colorectal Cancer**

- 67 • Determine *K-Ras* mutation and EGFR-expression status using FDA-approved
68 tests prior to initiating treatment. Only patients whose tumors are *K-Ras* mutation-
69 negative (wild-type) should receive Erbitux.
- 70 • The recommended initial dose, either as monotherapy or in combination with
71 irinotecan or FOLFIRI (irinotecan, 5-fluorouracil, leucovorin), is 400 mg/m²
72 administered as a 120-minute intravenous infusion (maximum infusion rate
73 10 mg/min). Complete Erbitux administration 1 hour prior to FOLFIRI.
- 74 • The recommended subsequent weekly dose, either as monotherapy or in
75 combination with irinotecan or FOLFIRI, is 250 mg/m² infused over 60 minutes
76 (maximum infusion rate 10 mg/min) until disease progression or unacceptable
77 toxicity. Complete Erbitux administration 1 hour prior to FOLFIRI.

78 **2.3 Recommended Premedication**

79 Premedicate with an H₁ antagonist (eg, 50 mg of diphenhydramine) intravenously
80 30–60 minutes prior to the first dose; premedication should be administered for
81 subsequent Erbitux doses based upon clinical judgment and presence/severity of prior
82 infusion reactions.

83 **2.4 Dose Modifications**

84 **Infusion Reactions**

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

87 Immediately and permanently discontinue Erbitux for serious infusion reactions,
88 requiring medical intervention and/or hospitalization. [See *Warnings and Precautions*
89 (5.1).]

90 **Dermatologic Toxicity**

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

Table 1: Erbitux Dose Modification Guidelines for Rash

Severe Acneiform 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		

93 **2.5 Preparation for Administration**

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

95 Administer via infusion pump or syringe pump. Do not exceed an infusion rate of
96 10 mg/min.

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

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

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

102 **3 DOSAGE FORMS AND STRENGTHS**

103 100 mg/50 mL, single-use vial

104 200 mg/100 mL, single-use vial

105 **4 CONTRAINDICATIONS**

106 None.

107 **5 WARNINGS AND PRECAUTIONS**

108 **5.1 Infusion Reactions**

109 Serious infusion reactions, requiring medical intervention and immediate, permanent
110 discontinuation of Erbitux included rapid onset of airway obstruction (bronchospasm,
111 stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction,
112 and/or cardiac arrest. Severe (NCI CTC Grades 3 and 4) infusion reactions occurred in
113 2–5% of 1373 patients in Studies 1, 3, 5, and 6 receiving Erbitux, with fatal outcome in
114 1 patient. [See *Clinical Studies (14.1, 14.2).*]

115 Approximately 90% of severe infusion reactions occurred with the first infusion despite
116 premedication with antihistamines.

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

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

123 **5.2 Cardiopulmonary Arrest**

124 Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients treated
125 with radiation therapy and Erbitux as compared to none of 212 patients treated with
126 radiation therapy alone in Study 1. Three patients with prior history of coronary artery
127 disease died at home, with myocardial infarction as the presumed cause of death. One of
128 these patients had arrhythmia and one had congestive heart failure. Death occurred 27,
129 32, and 43 days after the last dose of Erbitux. One patient with no prior history of

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

141 **5.3 Pulmonary Toxicity**

142 Interstitial lung disease (ILD), including 1 fatality, occurred in 4 of 1570 (<0.5%) patients
143 receiving Erbitux in Studies 1, 3, and 6, as well as other studies, in colorectal cancer and
144 head and neck cancer. Interrupt Erbitux for acute onset or worsening of pulmonary
145 symptoms. Permanently discontinue Erbitux for confirmed ILD.

146 **5.4 Dermatologic Toxicity**

147 Dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychia
148 inflammation, infectious sequelae (for example, *S. aureus* sepsis, abscess formation,
149 cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual
150 acuity, cheilitis), and hypertrichosis occurred in patients receiving Erbitux therapy.
151 Acneiform rash occurred in 76–88% of 1373 patients receiving Erbitux in Studies 1, 3, 5,
152 and 6. Severe acneiform rash occurred in 1–17% of patients.

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

158 **5.5 Use of Erbitux in Combination With Radiation and**
159 **Cisplatin**

160 In a controlled study, 940 patients with locally advanced SCCHN were randomized 1:1 to
161 receive either Erbitux in combination with radiation therapy and cisplatin or radiation
162 therapy and cisplatin alone. The addition of Erbitux resulted in an increase in the
163 incidence of Grade 3–4 mucositis, radiation recall syndrome, acneiform rash, cardiac
164 events, and electrolyte disturbances compared to radiation and cisplatin alone. Adverse
165 reactions with fatal outcome were reported in 20 patients (4.4%) in the Erbitux
166 combination arm and 14 patients (3.0%) in the control arm. Nine patients in the Erbitux
167 arm (2.0%) experienced myocardial ischemia compared to 4 patients (0.9%) in the
168 control arm. The main efficacy outcome of the study was progression-free survival (PFS).
169 The addition of Erbitux to radiation and cisplatin did not improve PFS.

170 **5.6 Hypomagnesemia and Electrolyte Abnormalities**

171 In patients evaluated during clinical trials, hypomagnesemia occurred in 55% of
172 365 patients receiving Erbitux in Study 5 and two other clinical trials in colorectal
173 cancer and head and neck cancer, respectively, and was severe (NCI CTC Grades 3 and
174 4) in 6–17%.

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

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

186 **5.7 K-Ras Testing in Metastatic or Advanced Colorectal**
187 **Cancer Patients**

188 Determination of *K-Ras* mutational status in colorectal tumors using an FDA-approved
189 test indicated for this use is necessary for selection of patients for treatment with Erbitux.
190 Erbitux is indicated only for patients with EGFR-expressing *K-Ras* mutation-negative
191 (wild-type) mCRC. Erbitux is not an effective treatment for patients with colorectal
192 cancer that harbor somatic mutations in codons 12 and 13 (exon 2). Studies 4 and 5,
193 conducted in patients with colorectal cancer, demonstrated a benefit with Erbitux
194 treatment only in the subset of patients whose tumors were *K-Ras* mutation-negative
195 (wild-type). Erbitux is not effective for the treatment of *K-Ras* mutation-positive
196 colorectal cancer as determined by an FDA-approved test for this use. [See *Indications*
197 *and Usage (1.2)*, *Clinical Pharmacology (12.1)*, *Clinical Studies (14.2)*.]

198 Perform the assessment for *K-Ras* mutation status in colorectal cancer in laboratories
199 with demonstrated proficiency in the specific technology being utilized. Improper assay
200 performance can lead to unreliable test results.

201 Refer to an FDA-approved test's package insert for instructions on the identification of
202 patients eligible for the treatment of Erbitux.

203 **5.8 Epidermal Growth Factor Receptor (EGFR) Expression**
204 **and Response**

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

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

214 **6 ADVERSE REACTIONS**

215 The following adverse reactions are discussed in greater detail in other sections of the
216 label:

- 217 • Infusion reactions [See *Boxed Warning, Warnings and Precautions (5.1).*]
- 218 • Cardiopulmonary arrest [See *Boxed Warning, Warnings and Precautions (5.2).*]
- 219 • Pulmonary toxicity [See *Warnings and Precautions (5.3).*]
- 220 • Dermatologic toxicity [See *Warnings and Precautions (5.4).*]
- 221 • Hypomagnesemia and Electrolyte Abnormalities [See *Warnings and Precautions*
222 *(5.6).*]

223 The most common adverse reactions in Erbitux clinical trials (incidence $\geq 25\%$) include
224 cutaneous adverse reactions (including rash, pruritus, and nail changes), headache,
225 diarrhea, and infection.

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

229 Across Studies 1, 3, 5, and 6, Erbitux was discontinued in 3–10% of patients because of
230 adverse reactions.

231 **6.1 Clinical Trials Experience**

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

235 The data below reflect exposure to Erbitux in 1373 patients with SCCHN or colorectal
236 cancer in randomized Phase 3 (Studies 1 and 5) or Phase 2 (Studies 3 and 6) trials treated
237 at the recommended dose and schedule for medians of 7 to 14 weeks. [See *Clinical*
238 *Studies (14).*]

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

243 **Infections:** The incidence of infection was variable across studies, ranging from
 244 13–35%. Sepsis occurred in 1–4% of patients.

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

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

247 ***Erbix in Combination with Radiation Therapy***

248 Table 2 contains selected adverse reactions in 420 patients receiving radiation therapy
 249 either alone or with Erbix for locally or regionally advanced SCCHN in Study 1.
 250 Erbix was administered at the recommended dose and schedule (400 mg/m² initial
 251 dose, followed by 250 mg/m² weekly). Patients received a median of 8 infusions (range
 252 1–11).

Table 2: Incidence of Selected Adverse Reactions (≥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				
Body as a Whole				
Asthenia	56	4	49	5
Fever ^a	29	1	13	1
Headache	19	<1	8	<1
Infusion Reaction ^b	15	3	2	0
Infection	13	1	9	1
Chills ^a	16	0	5	0
Digestive				
Nausea	49	2	37	2
Emesis	29	2	23	4
Diarrhea	19	2	13	1
Dyspepsia	14	0	9	1
Metabolic/Nutritional				
Weight Loss	84	11	72	7
Dehydration	25	6	19	8
Alanine Transaminase, high ^c	43	2	21	1
Aspartate Transaminase, high ^c	38	1	24	1

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

Body System Preferred Term	Eribitux plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
	Grades 1-4	Grades 3 and 4	Grades 1-4	Grades 3 and 4
% of Patients				
Alkaline Phosphatase, high ^c	33	<1	24	0
Respiratory				
Pharyngitis	26	3	19	4
Skin/Appendages				
Acneiform Rash ^d	87	17	10	1
Radiation Dermatitis	86	23	90	18
Application Site Reaction	18	0	12	1
Pruritus	16	0	4	0

^a Includes cases also reported as infusion reaction.

^b 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”.

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

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

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

255 **Late Radiation Toxicity**

256 The overall incidence of late radiation toxicities (any grade) was higher in Eribitux in
257 combination with radiation therapy compared with radiation therapy alone. The following
258 sites were affected: salivary glands (65% versus 56%), larynx (52% versus 36%),
259 subcutaneous tissue (49% versus 45%), mucous membrane (48% versus 39%), esophagus
260 (44% versus 35%), skin (42% versus 33%). The incidence of Grade 3 or 4 late radiation
261 toxicities was similar between the radiation therapy alone and the Eribitux plus radiation
262 treatment groups.

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

265 Study 2 used EU-approved cetuximab. Since U.S.-licensed Erbitux provides
 266 approximately 22% higher exposure relative to the EU-approved cetuximab, the data
 267 provided below may underestimate the incidence and severity of adverse reactions
 268 anticipated with Erbitux for this indication. However, the tolerability of the
 269 recommended dose is supported by safety data from additional studies of Erbitux [see
 270 *Clinical Pharmacology (12.3)*].

271 Table 3 contains selected adverse reactions in 434 patients with recurrent locoregional
 272 disease or metastatic SCCHN receiving EU-approved cetuximab in combination with
 273 platinum-based therapy with 5-FU or platinum-based therapy with 5-FU alone in Study 2.
 274 Cetuximab was administered at 400 mg/m² for the initial dose, followed by 250 mg/m²
 275 weekly. Patients received a median of 17 infusions (range 1–89).

Table 3: Incidence of Selected Adverse Reactions (≥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			
Eye Disorders				
Conjunctivitis	10	0	0	0
Gastrointestinal Disorders				
Nausea	54	4	47	4
Diarrhea	26	5	16	1
General Disorders and Administration Site Conditions				
Pyrexia	22	0	13	1
Infusion Reaction ^a	10	2	<1	0
Infections and Infestations				
Infection ^b	44	11	27	8
Metabolism and Nutrition Disorders				
Anorexia	25	5	14	1
Hypocalcemia	12	4	5	1
Hypokalemia	12	7	7	5

Table 3: Incidence of Selected Adverse Reactions (≥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			
Hypomagnesemia	11	5	5	1
Skin and Subcutaneous Tissue Disorders				
Acneiform Rash ^c	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

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

^b Infection – this term excludes sepsis-related events which are presented separately.

^c 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

276 For cardiac disorders, approximately 9% of subjects in both the EU-approved cetuximab
 277 plus chemotherapy and chemotherapy-only treatment arms in Study 2 experienced a
 278 cardiac event. The majority of these events occurred in patients who received
 279 cisplatin/5-FU, with or without cetuximab as follows: 11% and 12% in patients who
 280 received cisplatin/5-FU with or without cetuximab, respectively, and 6% or 4% in
 281 patients who received carboplatin/5-FU with or without cetuximab, respectively. In both
 282 arms, the incidence of cardiovascular events was higher in the cisplatin with 5-FU
 283 containing subgroup. Death attributed to cardiovascular event or sudden death was
 284 reported in 3% of the patients in the cetuximab plus platinum-based therapy with 5-FU
 285 arm and 2% in the platinum-based chemotherapy with 5-FU alone arm.

286 **Colorectal Cancer**

287 **Study 4: EU-Approved Cetuximab in Combination with FOLFIRI**

288 Study 4 used EU-approved cetuximab. U.S.-licensed Erbitux provides approximately
 289 22% higher exposure to cetuximab relative to the EU-approved cetuximab. The data
 290 provided below for Study 4 is consistent in incidence and severity of adverse reactions
 291 with those seen for Erbitux in this indication. The tolerability of the recommended dose is
 292 supported by safety data from additional studies of Erbitux [see *Clinical Pharmacology*
 293 (12.3)].

294 Table 4 contains selected adverse reactions in 667 patients with *K-Ras* mutation-negative
 295 (wild-type), EGFR-expressing, metastatic colorectal cancer receiving EU-approved
 296 cetuximab plus FOLFIRI or FOLFIRI alone in Study 4 [see *Warnings and Precautions*
 297 (5.8)]. Cetuximab was administered at the recommended dose and schedule (400 mg/m²
 298 initial dose, followed by 250 mg/m² weekly). Patients received a median of 26 infusions
 299 (range 1–224).

Table 4: Incidence of Selected Adverse Reactions Occurring in ≥10% of Patients with *K-Ras* Mutation-negative (Wild-type) and EGFR-expressing, Metastatic Colorectal Cancer^a

Body System Preferred Term	EU-Approved Cetuximab plus FOLFIRI (n=317)		FOLFIRI Alone (n=350)	
	Grades 1–4 ^b	Grades 3 and 4	Grades 1–4	Grades 3 and 4
% of Patients				
Blood and Lymphatic System Disorders				
Neutropenia	49	31	42	24
Eye Disorders				
Conjunctivitis	18	<1	3	0
Gastrointestinal Disorders				
Diarrhea	66	16	60	10
Stomatitis	31	3	19	1
Dyspepsia	16	0	9	0
General Disorders and Administration Site Conditions				
Infusion-related Reaction ^c	14	2	<1	0
Pyrexia	26	1	14	1

Table 4: Incidence of Selected Adverse Reactions Occurring in ≥10% of Patients with *K-Ras* Mutation-negative (Wild-type) and EGFR-expressing, Metastatic Colorectal Cancer^a

Body System Preferred Term	EU-Approved Cetuximab plus FOLFIRI (n=317)		FOLFIRI Alone (n=350)	
	Grades 1-4 ^b	Grades 3 and 4	Grades 1-4	Grades 3 and 4
% of Patients				
Infections and Infestations				
Paronychia	20	4	<1	0
Investigations				
Weight Decreased	15	1	9	1
Metabolism and Nutrition Disorders				
Anorexia	30	3	23	2
Skin and Subcutaneous Tissue Disorders				
Acne-like Rash ^d	86	18	13	<1
Rash	44	9	4	0
Dermatitis Acneiform	26	5	<1	0
Dry Skin	22	0	4	0
Acne	14	2	0	0
Pruritus	14	0	3	0
Palmar-plantar Erythrodysesthesia Syndrome	19	4	4	<1
Skin Fissures	19	2	1	0

^a Adverse reactions occurring in at least 10% of Erbitux combination arm with a frequency at least 5% greater than that seen in the FOLFIRI arm.

^b Adverse reactions were graded using the NCI CTC, V 2.0.

^c Infusion related reaction is defined as any event meeting the medical concepts of allergy/anaphylaxis at any time during the clinical study or any event occurring on the first day of dosing and meeting the medical concepts of dyspnea and fever or by the following events using MedDRA preferred terms: “acute myocardial infarction”, “angina pectoris”, “angioedema”, “autonomic seizure”, “blood pressure abnormal”, “blood pressure decreased”, “blood pressure increased”, “cardiac failure”, “cardiopulmonary failure”, “cardiovascular insufficiency”, “clonus”, “convulsion”, “coronary no-reflow phenomenon”, “epilepsy”, “hypertension”, “hypertensive crisis”, “hypertensive emergency”, “hypotension”, “infusion related reaction”, “loss of consciousness”, “myocardial infarction”, “myocardial ischaemia”, “prinzmetal angina”, “shock”, “sudden death”, “syncope”, or “systolic hypertension”.

^d Acne-like rash is defined by the events using MedDRA preferred terms and included “acne”, “acne pustular”, “butterfly rash”, “dermatitis acneiform”, “drug rash with eosinophilia and systemic symptoms”, “dry skin”, “erythema”, “exfoliative rash”, “folliculitis”, “genital rash”, “mucocutaneous rash”, “pruritus”, “rash”, “rash erythematous”, “rash follicular”, “rash generalized”, “rash macular”, “rash maculopapular”, “rash maculovesicular”, “rash morbilliform”, “rash papular”, “rash papulosquamous”, “rash pruritic”, “rash pustular”, “rash rubelliform”, “rash scarlatiniform”, “rash vesicular”, “skin exfoliation”, “skin hyperpigmentation”, “skin plaque”, “telangiectasia”, or “xerosis”.

300 **Erbix Monotherapy**

301 Table 5 contains selected adverse reactions in 242 patients with *K-Ras* mutation-negative
 302 (wild-type), EGFR-expressing, metastatic colorectal cancer who received best supportive
 303 care (BSC) alone or with Erbix in Study 5 [see *Warnings and Precautions* (5.8)].
 304 Erbix was administered at the recommended dose and schedule (400 mg/m² initial
 305 dose, followed by 250 mg/m² weekly). Patients received a median of 17 infusions (range
 306 1–51).

Table 5: Incidence of Selected Adverse Reactions Occurring in ≥10% of Patients with *K-Ras* Mutation-negative (Wild-type), EGFR-expressing, Metastatic Colorectal Cancer Treated with Erbix Monotherapy^a

Body System Preferred Term	Erbix plus BSC (n=118)		BSC alone (n=124)	
	Grades 1–4 ^b	Grades 3 and 4	Grades 1–4	Grades 3 and 4
% of Patients				
Dermatology/Skin				
Rash/Desquamation	95	16	21	1
Dry Skin	57	0	15	0
Pruritus	47	2	11	0
Other-Dermatology	35	0	7	2
Nail Changes	31	0	4	0
Constitutional Symptoms				
Fatigue	91	31	79	29
Fever	25	3	16	0
Infusion Reactions ^c	18	3	0	0
Rigors, Chills	16	1	3	0
Pain				
Pain-Other	59	18	37	10
Headache	38	2	11	0
Bone Pain	15	4	8	2
Pulmonary				
Dyspnea	49	16	44	13
Cough	30	2	19	2

Table 5: Incidence of Selected Adverse Reactions Occurring in $\geq 10\%$ of Patients with *K-Ras* Mutation-negative (Wild-type), EGFR-expressing, Metastatic Colorectal Cancer Treated with Erbitux Monotherapy^a

Body System Preferred Term	Erbitux plus BSC (n=118)		BSC alone (n=124)	
	Grades 1-4 ^b	Grades 3 and 4	Grades 1-4	Grades 3 and 4
% of Patients				
Gastrointestinal				
Nausea	64	6	50	6
Constipation	53	3	38	3
Diarrhea	42	2	23	2
Vomiting	40	5	26	5
Stomatitis	32	1	10	0
Other-Gastrointestinal	22	12	16	5
Dehydration	13	5	3	0
Mouth Dryness	12	0	6	0
Taste Disturbance	10	0	5	0
Infection				
Infection without neutropenia	38	11	19	5
Musculoskeletal				
Arthralgia	14	3	6	0
Neurology				
Neuropathy-sensory	45	1	38	2
Insomnia	27	0	13	0
Confusion	18	6	10	2
Anxiety	14	1	5	1
Depression	14	0	5	0

^a Adverse reactions occurring in at least 10% of Erbitux plus BSC arm with a frequency at least 5% greater than that seen in the BSC alone arm.

^b Adverse reactions were graded using the NCI CTC, V 2.0.

^c Infusion reaction is defined as any event (chills, rigors, dyspnea, tachycardia, bronchospasm, chest tightness, swelling, urticaria, hypotension, flushing, rash, hypertension, nausea, angioedema, pain, sweating, tremors, shaking, drug fever, or other hypersensitivity reaction) recorded by the investigator as infusion-related.

307 ***Erbix in Combination with Irinotecan***

308 The most frequently reported adverse reactions in 354 patients treated with Erbitux plus
309 irinotecan in clinical trials were acneiform rash (88%), asthenia/malaise (73%), diarrhea
310 (72%), and nausea (55%). The most common Grades 3–4 adverse reactions included
311 diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneiform rash (14%).

312 **6.2 Immunogenicity**

313 As with all therapeutic proteins, there is potential for immunogenicity. Immunogenic
314 responses to cetuximab were assessed using either a double antigen radiometric assay or
315 an ELISA assay. Due to limitations in assay performance and sampling timing, the
316 incidence of antibody development in patients receiving Erbitux has not been adequately
317 determined. Non-neutralizing anti-cetuximab antibodies were detected in 5% (49 of
318 1001) of evaluable patients without apparent effect on the safety or antitumor activity of
319 Erbitux.

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

326 **6.3 Postmarketing Experience**

327 The following adverse reactions have been identified during post-approval use of Erbitux.
328 Because these reactions are reported from a population of uncertain size, it is not always
329 possible to reliably estimate their frequency or establish a causal relationship to drug
330 exposure.

- 331 • Aseptic meningitis
- 332 • Mucosal inflammation

333 **7 DRUG INTERACTIONS**

334 A drug interaction study was performed in which Erbitux was administered in
335 combination with irinotecan. There was no evidence of any pharmacokinetic interactions
336 between Erbitux and irinotecan.

337 **8 USE IN SPECIFIC POPULATIONS**

338 **8.1 Pregnancy**

339 **Pregnancy Category C**

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

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

354 **8.3 Nursing Mothers**

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

362 **8.4 Pediatric Use**

363 The safety and effectiveness of Erbitux in pediatric patients have not been established.
364 The pharmacokinetics of cetuximab, in combination with irinotecan, were evaluated in
365 pediatric patients with refractory solid tumors in an open-label, single-arm, dose-finding
366 study. Erbitux was administered once-weekly, at doses up to 250 mg/m², to 27 patients

367 ranging from 1 to 12 years old; and in 19 patients ranging from 13 to 18 years old. No
368 new safety signals were identified in pediatric patients. The pharmacokinetic profiles of
369 cetuximab between the two age groups were similar at the 75 and 150 mg/m² single dose
370 levels. The volume of the distribution appeared to be independent of dose and
371 approximated the vascular space of 2–3 L/m². Following a single dose of 250 mg/m², the
372 geometric mean AUC_{0-inf} (CV%) value was 17.7 mg•h/mL (34%) in the younger age
373 group (1–12 years, n=9) and 13.4 mg•h/mL (38%) in the adolescent group (13–18 years,
374 n=6). The mean half-life of cetuximab was 110 hours (range 69 to 188 hours) for the
375 younger age group, and 82 hours (range 55 to 117 hours) for the adolescent age group.

376 **8.5 Geriatric Use**

377 Of the 1662 patients who received Erbitux with irinotecan, FOLFIRI or Erbitux
378 monotherapy in six studies of advanced colorectal cancer, 588 patients were 65 years of
379 age or older. No overall differences in safety or efficacy were observed between these
380 patients and younger patients.

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

384 **10 OVERDOSAGE**

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

387 **11 DESCRIPTION**

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

394 Erbitux is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small
395 amount of easily visible, white, amorphous cetuximab particulates. Erbitux is supplied at
396 a concentration of 2 mg/mL in either 100 mg (50 mL) or 200 mg (100 mL), single-use

397 vials. Cetuximab is formulated in a solution with no preservatives, which contains
398 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate,
399 0.41 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP.

400 **12 CLINICAL PHARMACOLOGY**

401 **12.1 Mechanism of Action**

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

407 Cetuximab binds specifically to the EGFR on both normal and tumor cells, and
408 competitively inhibits the binding of epidermal growth factor (EGF) and other ligands,
409 such as transforming growth factor- α . *In vitro* assays and *in vivo* animal studies have
410 shown that binding of cetuximab to the EGFR blocks phosphorylation and activation of
411 receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis,
412 and decreased matrix metalloproteinase and vascular endothelial growth factor
413 production. Signal transduction through the EGFR results in activation of wild-type
414 *K-Ras* protein. However, in cells with activating *K-Ras* somatic mutations, the mutant
415 *K-Ras* protein is continuously active and appears independent of EGFR regulation.

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

423 **12.2 Pharmacodynamics**

424 **Effects on Electrocardiogram (ECG)**

425 The effect of cetuximab on QT interval was evaluated in an open-label, single-arm,
426 monotherapy trial in 37 subjects with advanced malignancies who received an initial dose
427 of 400 mg/m², followed by weekly infusions of 250 mg/m² for a total of 5 weeks. No

428 large changes in the mean QT interval of >20 ms from baseline were detected in the trial
429 based on the Fridericia correction method. A small increase in the mean QTc interval of
430 <10 ms cannot be excluded because of the limitations in the trial design.

431 **12.3 Pharmacokinetics**

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

439 Following the recommended dose regimen (400 mg/m² initial dose; 250 mg/m² weekly
440 dose), concentrations of cetuximab reached steady-state levels by the third weekly
441 infusion with mean peak and trough concentrations across studies ranging from 168 to
442 235 and 41 to 85 µg/mL, respectively. The mean half-life of cetuximab was
443 approximately 112 hours (range 63–230 hours). The pharmacokinetics of cetuximab were
444 similar in patients with SCCHN and those with colorectal cancer.

445 Erbitux had an approximately 22% (90% confidence interval; 6%, 38%) higher systemic
446 exposure relative to the EU-approved cetuximab used in Studies 2 and 4 based on a
447 population pharmacokinetic analysis. [See *Clinical Studies (14.1)*.]

448 **13 NONCLINICAL TOXICOLOGY**

449 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

450 Long-term animal studies have not been performed to test cetuximab for carcinogenic
451 potential, and no mutagenic or clastogenic potential of cetuximab was observed in the
452 *Salmonella-Escherichia coli* (Ames) assay or in the *in vivo* rat micronucleus test.
453 Menstrual cyclicity was impaired in female cynomolgus monkeys receiving weekly doses
454 of 0.4 to 4 times the human dose of cetuximab (based on total body surface area).
455 Cetuximab-treated animals exhibited increased incidences of irregular or absent cycles,
456 as compared to control animals. These effects were initially noted beginning week 25 of
457 cetuximab treatment and continued through the 6-week recovery period. In this same
458 study, there were no effects of cetuximab treatment on measured male fertility parameters

459 (ie, serum testosterone levels and analysis of sperm counts, viability, and motility) as
460 compared to control male monkeys. It is not known if cetuximab can impair fertility in
461 humans.

462 **13.2 Animal Pharmacology and/or Toxicology**

463 In cynomolgus monkeys, cetuximab, when administered at doses of approximately 0.4 to
464 4 times the weekly human exposure (based on total body surface area), resulted in
465 dermatologic findings, including inflammation at the injection site and desquamation of
466 the external integument. At the highest dose level, the epithelial mucosa of the nasal
467 passage, esophagus, and tongue were similarly affected, and degenerative changes in the
468 renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of
469 the animals at the highest dose level beginning after approximately 13 weeks of
470 treatment.

471 **14 CLINICAL STUDIES**

472 Studies 2 and 4 were conducted outside the U.S. using an EU-approved cetuximab as the
473 clinical trial material. Erbitux provides approximately 22% higher exposure relative to
474 the EU-approved cetuximab used in Studies 2 and 4; these pharmacokinetic data, together
475 with the results of Studies 2, 4, and other clinical trial data establish the efficacy of
476 Erbitux at the recommended dose in SCCHN and mCRC [see *Clinical Pharmacology*
477 (12.3)].

478 **14.1 Squamous Cell Carcinoma of the Head and Neck** 479 **(SCCHN)**

480 Study 1 was a randomized, multicenter, controlled trial of 424 patients with locally or
481 regionally advanced SCCHN. Patients with Stage III/IV SCCHN of the oropharynx,
482 hypopharynx, or larynx with no prior therapy were randomized (1:1) to receive either
483 Erbitux plus radiation therapy or radiation therapy alone. Stratification factors were
484 Karnofsky performance status (60–80 versus 90–100), nodal stage (N0 versus N+), tumor
485 stage (T1–3 versus T4 using American Joint Committee on Cancer 1998 staging criteria),
486 and radiation therapy fractionation (concomitant boost versus once-daily versus twice-
487 daily). Radiation therapy was administered for 6–7 weeks as once-daily, twice-daily, or
488 concomitant boost. Erbitux was administered as a 400 mg/m² initial dose beginning one
489 week prior to initiation of radiation therapy, followed by 250 mg/m² weekly administered
490 1 hour prior to radiation therapy for the duration of radiation therapy (6–7 weeks).

491 Of the 424 randomized patients, the median age was 57 years, 80% were male, 83% were
 492 Caucasian, and 90% had baseline Karnofsky performance status ≥ 80 . There were
 493 258 patients enrolled in U.S. sites (61%). Sixty percent of patients had oropharyngeal,
 494 25% laryngeal, and 15% hypopharyngeal primary tumors; 28% had AJCC T4 tumor
 495 stage. Fifty-six percent of the patients received radiation therapy with concomitant boost,
 496 26% received once-daily regimen, and 18% twice-daily regimen.

497 The main outcome measure of this trial was duration of locoregional control. Overall
 498 survival was also assessed. Results are presented in Table 6.

Table 6: 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

499 Study 2 was an open-label, randomized, multicenter, controlled trial of 442 patients with
 500 recurrent locoregional disease or metastatic SCCHN.

501 Patients with no prior therapy for recurrent locoregional disease or metastatic SCCHN
 502 were randomized (1:1) to receive EU-approved cetuximab plus cisplatin or carboplatin
 503 and 5-FU, or cisplatin or carboplatin and 5-FU alone. Choice of cisplatin or carboplatin
 504 was at the discretion of the treating physician. Stratification factors were
 505 Karnofsky performance status (< 80 versus ≥ 80) and previous chemotherapy. Cisplatin
 506 (100 mg/m^2 , Day 1) or carboplatin (AUC 5, Day 1) plus intravenous 5-FU
 507 ($1000 \text{ mg/m}^2/\text{day}$, Days 1–4) were administered every 3 weeks (1 cycle) for a maximum
 508 of 6 cycles in the absence of disease progression or unacceptable toxicity. Cetuximab was
 509 administered at a 400 mg/m^2 initial dose, followed by a 250 mg/m^2 weekly dose in
 510 combination with chemotherapy. Patients demonstrating at least stable disease on
 511 cetuximab in combination with chemotherapy were to continue cetuximab monotherapy
 512 at 250 mg/m^2 weekly, in the absence of disease progression or unacceptable toxicity after
 513 completion of 6 planned courses of platinum-based therapy. For patients where treatment
 514 was delayed because of the toxic effects of chemotherapy, weekly cetuximab was
 515 continued. If chemotherapy was discontinued for toxicity, cetuximab could be continued
 516 as monotherapy until disease progression or unacceptable toxicity.

517 Of the 442 randomized patients, the median age was 57 years, 90% were male, 98% were
 518 Caucasian, and 88% had baseline Karnofsky performance status ≥ 80 . Thirty-four percent
 519 of patients had oropharyngeal, 25% laryngeal, 20% oral cavity, and 14% hypopharyngeal
 520 primary tumors. Fifty-three percent of patients had recurrent locoregional disease only
 521 and 47% had metastatic disease. Fifty-eight percent had AJCC Stage IV disease and
 522 21% had Stage III disease. Sixty-four percent of patients received cisplatin therapy and
 523 34% received carboplatin as initial therapy. Approximately fifteen percent of the patients
 524 in the cisplatin alone arm switched to carboplatin during the treatment period.

525 The main outcome measure of this trial was overall survival. Results are presented in
 526 Table 7 and Figure 1.

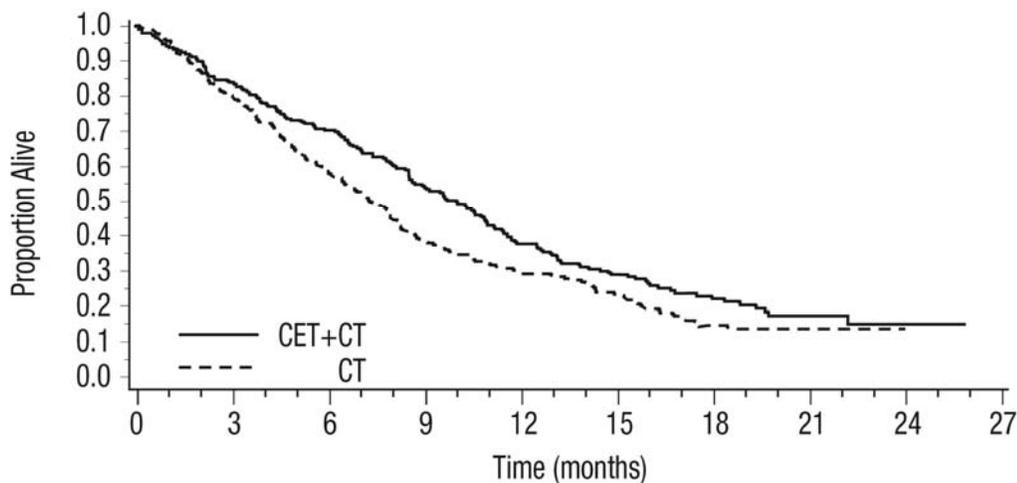
Table 7: Study 2: Clinical Efficacy in Recurrent Locoregional Disease or Metastatic SCCHN

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

^a CI = confidence interval

^b CMH = Cochran-Mantel-Haenszel

527 **Figure 1:** **Kaplan-Meier Curve for Overall Survival in Patients with**
 528 **Recurrent Locoregional Disease or Metastatic Squamous Cell**
 529 **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	0
CT	220	173	127	83	65	47	19	8	1	0	0

531 CT = Platinum-based therapy with 5-FU
 532 CET = EU-approved cetuximab

533 In exploratory subgroup analyses of Study 2 by initial platinum therapy (cisplatin or
 534 carboplatin), for patients (N=284) receiving cetuximab plus cisplatin with 5-FU
 535 compared to cisplatin with 5-FU alone, the difference in median overall survival was
 536 3.3 months (10.6 versus 7.3 months, respectively; HR 0.71; 95% CI 0.54, 0.93). The
 537 difference in median progression-free survival was 2.1 months (5.6 versus 3.5 months,
 538 respectively; HR 0.55; 95% CI 0.41, 0.73). The objective response rate was 39% and
 539 23%, respectively (OR 2.18; 95% CI 1.29, 3.69). For patients (N=149) receiving
 540 cetuximab plus carboplatin with 5-FU compared to carboplatin with 5-FU alone, the
 541 difference in median overall survival was 1.4 months (9.7 versus 8.3 months; HR 0.99;
 542 95% CI 0.69, 1.43). The difference in median progression-free survival was 1.7 months
 543 (4.8 versus 3.1 months, respectively; HR 0.61; 95% CI 0.42, 0.89). The objective
 544 response rate was 30% and 15%, respectively (OR 2.45; 95% CI 1.10, 5.46).

545 Study 3 was a single-arm, multicenter clinical trial in 103 patients with recurrent or
 546 metastatic SCCHN. All patients had documented disease progression within 30 days of a
 547 platinum-based chemotherapy regimen. Patients received a 20-mg test dose of Erbitux on

548 Day 1, followed by a 400 mg/m² initial dose, and 250 mg/m² weekly until disease
549 progression or unacceptable toxicity.

550 The median age was 57 years, 82% were male, 100% Caucasian, and 62% had a
551 Karnofsky performance status of ≥80.

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

554 **14.2 Colorectal Cancer**

555 **Erbix Clinical Trials in *K-Ras* Mutation-negative (Wild-type), EGFR- 556 expressing, Metastatic Colorectal Cancer**

557 Study 4 was a randomized, open-label, multicenter, study of 1217 patients with EGFR-
558 expressing, metastatic colorectal cancer. Patients were randomized (1:1) to receive either
559 EU-approved cetuximab in combination with FOLFIRI or FOLFIRI alone as first-line
560 treatment. Stratification factors were Eastern Cooperative Oncology Group (ECOG)
561 performance status (0 and 1 versus 2) and region (sites in Western Europe versus Eastern
562 Europe versus other).

563 FOLFIRI regimen included 14-day cycles of irinotecan (180 mg/m² administered
564 intravenously on Day 1), folinic acid (400 mg/m² [racemic] or 200 mg/m² [L-form]
565 administered intravenously on Day 1), and 5-FU (400 mg/m² bolus on Day 1 followed by
566 2400 mg/m² as a 46-hour continuous infusion). Cetuximab was administered as a
567 400 mg/m² initial dose on Day 1, Week 1, followed by 250 mg/m² weekly administered
568 1 hour prior to chemotherapy. Study treatment continued until disease progression or
569 unacceptable toxicity occurred.

570 Of the 1217 randomized patients, the median age was 61 years, 60% were male, 86%
571 were Caucasian, and 96% had a baseline ECOG performance status 0–1, 60% had
572 primary tumor localized in colon, 84% had 1–2 metastatic sites and 20% had received
573 prior adjuvant and/or neoadjuvant chemotherapy. Demographics and baseline
574 characteristics were similar between study arms.

575 *K-Ras* mutation status was available for 1079/1217 (89%) of the patients: 676 (63%)
576 patients had *K-Ras* mutation-negative (wild-type) tumors and 403 (37%) patients had
577 *K-Ras* mutation-positive tumors where testing assessed for the following somatic

578 mutations in codons 12 and 13 (exon 2): G12A, G12D, G12R, G12C, G12S, G12V,
579 G13D [see *Warnings and Precautions* (5.7)].

580 Baseline characteristics and demographics in the *K-Ras* mutation-negative (wild-type)
581 subset were similar to that seen in the overall population [see *Warnings and Precautions*
582 (5.7)].

583 The main outcome measure of this trial was progression-free survival assessed by an
584 independent review committee (IRC). Overall survival and response rate were also
585 assessed. A statistically significant improvement in PFS was observed for the cetuximab
586 plus FOLFIRI arm compared with the FOLFIRI arm (median PFS 8.9 vs. 8.1 months,
587 HR 0.85 [95% CI 0.74, 0.99], p-value=0.036). Overall survival was not significantly
588 different at the planned, final analysis based on 838 events [HR=0.93, 95% CI (0.8, 1.1),
589 p-value 0.327].

590 Results of the planned PFS and ORR analysis in all randomized patients and post-hoc
591 PFS and ORR analysis in subgroups of patients defined by *K-Ras* mutation status, and
592 post-hoc analysis of updated OS based on additional follow-up (1000 events) in all
593 randomized patients and in subgroups of patients defined by *K-Ras* mutation status are
594 presented in Table 8 and Figure 2. The treatment effect in the all-randomized population
595 for PFS was driven by treatment effects limited to patients who have *K-Ras* mutation-
596 negative (wild-type) tumors. There is no evidence of effectiveness in the subgroup of
597 patients with *K-Ras* mutation-positive tumors.

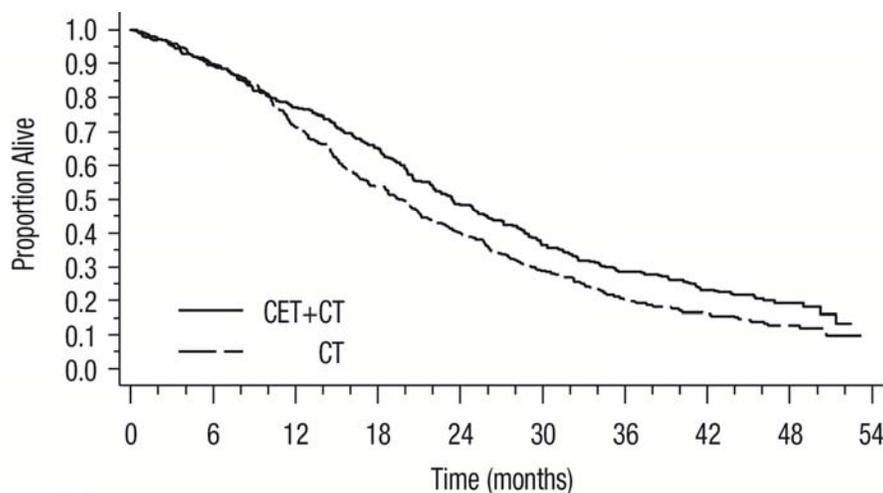
Table 8: Clinical Efficacy in First-line EGFR-expressing, Metastatic Colorectal Cancer (All Randomized and *K-Ras* Status)

	All Randomized		<i>K-Ras</i> Mutation-negative (Wild-type)		<i>K-Ras</i> Mutation-positive	
	EU- Approved Cetuximab plus FOLFIRI (n=608)	FOLFIRI (n=609)	EU- Approved Cetuximab plus FOLFIRI (n=320)	FOLFIRI (n=356)	EU- Approved Cetuximab plus FOLFIRI (n=216)	FOLFIRI (n=187)
Progression-Free Survival						
Number of Events (%)	343 (56)	371 (61)	165 (52)	214 (60)	138 (64)	112 (60)
Median (months) (95% CI)	8.9 (8.0, 9.4)	8.1 (7.6, 8.8)	9.5 (8.9, 11.1)	8.1 (7.4, 9.2)	7.5 (6.7, 8.7)	8.2 (7.4, 9.2)
HR (95% CI)	0.85 (0.74, 0.99)		0.70 (0.57, 0.86)		1.13 (0.88, 1.46)	
p-value ^a	0.0358					
Overall Survival^b						
Number of Events (%)	491 (81)	509 (84)	244 (76)	292 (82)	189 (88)	159 (85)
Median (months) (95% CI)	19.6 (18, 21)	18.5 (17, 20)	23.5 (21, 26)	19.5 (17, 21)	16.0 (15, 18)	16.7 (15, 19)
HR (95% CI)	0.88 (0.78, 1.0)		0.80 (0.67, 0.94)		1.04 (0.84, 1.29)	
Objective Response Rate						
ORR (95% CI)	46% (42, 50)	38% (34, 42)	57% (51, 62)	39% (34, 44)	31% (25, 38)	35% (28, 43)

598 ^a Based on the Stratified Log-rank test.

599 ^b Post-hoc updated OS analysis, results based on an additional 162 events.

600 **Figure 2:** **Kaplan-Meier Curve for Overall Survival in the *K-Ras***
 601 **Mutation-negative (Wild-type) Population in Study 4**



Patients at Risk		0	6	12	18	24	30	36	42	48	54
CET+CT		320	282	237	198	144	108	82	65	21	4
CT		356	313	247	179	132	92	64	48	18	2

602

603 Study 5 was a multicenter, open-label, randomized, clinical trial conducted in
 604 572 patients with EGFR-expressing, previously treated, recurrent mCRC. Patients were
 605 randomized (1:1) to receive either Erbitux plus best supportive care (BSC) or BSC alone.
 606 Erbitux was administered as a 400 mg/m² initial dose, followed by 250 mg/m² weekly
 607 until disease progression or unacceptable toxicity.

608 Of the 572 randomized patients, the median age was 63 years, 64% were male, 89% were
 609 Caucasian, and 77% had baseline ECOG performance status of 0–1. Demographics and
 610 baseline characteristics were similar between study arms. All patients were to have
 611 received and progressed on prior therapy including an irinotecan-containing regimen and
 612 an oxaliplatin-containing regimen.

613 *K-Ras* status was available for 453/572 (79%) of the patients: 245 (54%) patients had
 614 *K-Ras* mutation-negative (wild-type) tumors and 208 (46%) patients had *K-Ras* mutation-
 615 positive tumors where testing assessed for the following somatic mutations in codons
 616 12 and 13 (exon 2): G12A, G12D, G12R, G12C, G12S, G12V, G13D [see *Warnings and*
 617 *Precautions* (5.7)].

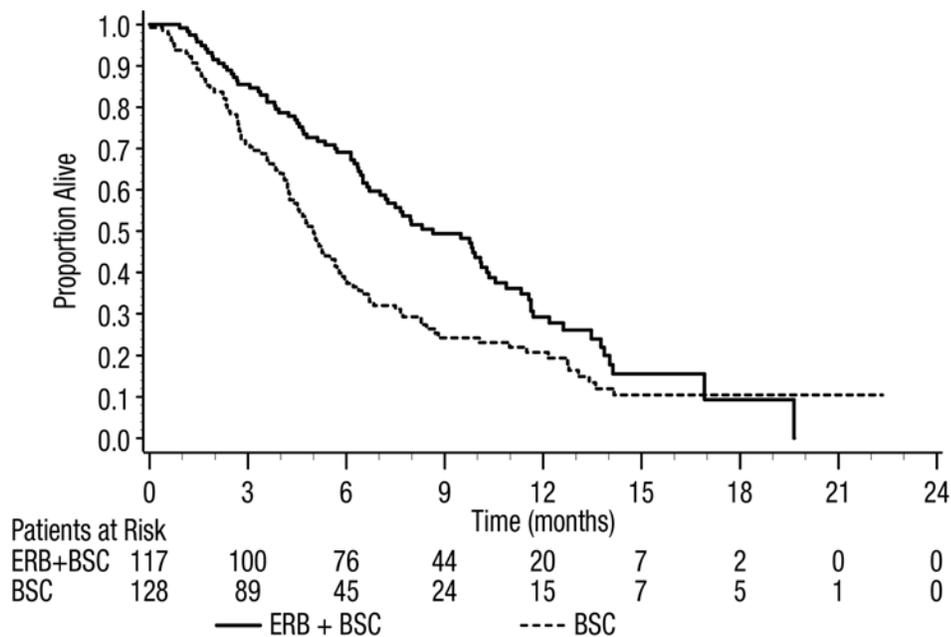
618 The main outcome measure of the study was overall survival. Results are presented in
 619 Table 9 and Figure 3.

Table 9: Overall Survival in Previously Treated EGFR-expressing, Metastatic Colorectal Cancer (All Randomized and *K-Ras* Status)

	All Randomized		<i>K-Ras</i> Mutation-negative (Wild-type)		<i>K-Ras</i> Mutation-positive	
	Erbitux plus BSC (N=287)	BSC (N=285)	Erbitux plus BSC (N=117)	BSC (N=128)	Erbitux plus BSC (N=108)	BSC (N=100)
Median (months) (95% CI)	6.1 (5.4, 6.7)	4.6 (4.2, 4.9)	8.6 (7.0, 10.3)	5.0 (4.3, 5.7)	4.8 (3.9, 5.6)	4.6 (3.6, 4.9)
HR (95% CI)	0.77 (0.64, 0.92)		0.63 (0.47, 0.84)		0.91 (0.67, 1.24)	
p-value ^a	0.0046					

620 ^a Based on the Stratified Log-rank test.

621 **Figure 3: Kaplan-Meier Curve for Overall Survival in Patients with**
 622 ***K-Ras* Mutation-negative (Wild-type) Metastatic Colorectal**
 623 **Cancer in Study 5**



624

625 Study 6 was a multicenter, clinical trial conducted in 329 patients with EGFR-expressing
 626 recurrent mCRC. Tumor specimens were not available for testing for *K-Ras* mutation
 627 status. Patients were randomized (2:1) to receive either Erbitux plus irinotecan
 628 (218 patients) or Erbitux monotherapy (111 patients). Erbitux was administered as a
 629 400 mg/m² initial dose, followed by 250 mg/m² weekly until disease progression or

630 unacceptable toxicity. In the Erbitux plus irinotecan arm, irinotecan was added to Erbitux
631 using the same dose and schedule for irinotecan as the patient had previously failed.
632 Acceptable irinotecan schedules were 350 mg/m² every 3 weeks, 180 mg/m² every
633 2 weeks, or 125 mg/m² weekly times four doses every 6 weeks. Of the 329 patients, the
634 median age was 59 years, 63% were male, 98% were Caucasian, and 88% had baseline
635 Karnofsky performance status ≥80. Approximately two-thirds had previously failed
636 oxaliplatin treatment.

637 The efficacy of Erbitux plus irinotecan or Erbitux monotherapy, based on durable
638 objective responses, was evaluated in all randomized patients and in two pre-specified
639 subpopulations: irinotecan refractory patients, and irinotecan and oxaliplatin failures. In
640 patients receiving Erbitux plus irinotecan, the objective response rate was
641 23% (95% confidence interval 18%–29%), median duration of response was 5.7 months,
642 and median time to progression was 4.1 months. In patients receiving Erbitux
643 monotherapy, the objective response rate was 11% (95% confidence interval 6%–18%),
644 median duration of response was 4.2 months, and median time to progression was
645 1.5 months. Similar response rates were observed in the pre-defined subsets in both the
646 combination arm and monotherapy arm of the study.

647 **16 HOW SUPPLIED/STORAGE AND HANDLING**

648 Erbitux[®] (cetuximab) is supplied at a concentration of 2 mg/mL as a 100 mg/50 mL,
649 single-use vial or as a 200 mg/100 mL, single-use vial as a sterile, injectable liquid
650 containing no preservatives.

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

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

653 Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). **Do not freeze.** Increased
654 particulate formation may occur at temperatures at or below 0° C. This product contains
655 no preservatives. Preparations of Erbitux in infusion containers are chemically and
656 physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at
657 controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining
658 solution in the infusion container after 8 hours at controlled room temperature or after
659 12 hours at 2° C to 8° C. Discard any unused portion of the vial.

660 **17 PATIENT COUNSELING INFORMATION**

661 Advise patients:

- 662 • To report signs and symptoms of infusion reactions such as fever, chills, or breathing
663 problems.
- 664 • Of the potential risks of using Erbitux during pregnancy or nursing and of the need
665 to use adequate contraception in both males and females during and for 6 months
666 following the last dose of Erbitux therapy.
- 667 • That nursing is not recommended during, and for 2 months following the last dose of
668 Erbitux therapy.
- 669 • To limit sun exposure (use sunscreen, wear hats) while receiving and for 2 months
670 following the last dose of Erbitux.

671 Erbitux[®] is a registered trademark of ImClone LLC a wholly-owned subsidiary of
672 Eli Lilly and Company.

673 Manufactured by ImClone LLC a wholly-owned subsidiary of Eli Lilly and Company,
674 Branchburg, NJ 08876 USA

675 Distributed and marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

676 Co-marketed by Eli Lilly and Company, Indianapolis, IN 46285 USA



Bristol-Myers Squibb

The logo for Eli Lilly, consisting of the word "Lilly" written in a red, cursive script font.

677 Copyright © 2004–2013 ImClone LLC a wholly-owned subsidiary of Eli Lilly and
678 Company, and Bristol-Myers Squibb Company. All rights reserved.

679 1236886B3

Rev March 2013