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®.

Erbtitux® ( cetuximab)
Solution for intravenous use
Initial U.S. Approval: 2004

WARNING: SERIOUS INFUSION REACTIONS and CARDIOPULMONARY ARREST
See full prescribing information for complete boxed warning.
• Serious infusion reactions, some fatal, occurred in approximately 3% of patients. (5.1)
• Cardiopulmonary arrest and/or sudden death occurred in 2% of patients receiving Erbitux® in combination with radiation therapy. (5.2, 5.6)

RECENT MAJOR CHANGES
Indications and Usage, Colorectal Cancer (1.2) 10/2007

INDICATIONS AND USAGE
Erbtitux® is an epidermal growth factor receptor (EGFR) antagonist indicated for treatment of:

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

Colorectal Cancer
• As a single agent, EGFR-expressing metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens or in patients who are intolerant to irinotecan-based regimens. (1.2, 14.2)
• In combination with irinotecan, EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. Approval is based on objective response rate; no data are available demonstrating an improvement in increased survival. (1.2, 14.2)

DOSEAGE AND ADMINISTRATION
• Premedicate with an H2 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)

DOSEAGE AND ADMINISTRATION
• Initiate Erbitux® one week prior to initiation of radiation therapy. (2.1)
• Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 infusion reactions and non-serious NCI CTC Grade 3-4 infusion reactions. (2.4)
• Permanently discontinue for serious infusion reactions. (2.4)
• Withhold infusion for severe, persistent acniform rash. Reduce dose for recurrent, severe rash. (2.4)

DOSEAGE FORMS AND STRENGTHS
• 100 mg/50 mL, single-use vial (3)
• 200 mg/100 mL, single-use vial (3)

CONTRAINDICATIONS
None (4)

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

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

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

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

See 17 for PATIENT COUNSELING INFORMATION
Revised: 10/2007

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: SERIOUS INFUSION REACTIONS AND CARDIOPULMONARY ARREST
1 INDICATIONS AND USAGE
1.1 Squamous Cell Carcinoma of the Head and Neck (SCCHN)
1.2 Colorectal Cancer
2 DOSAGE AND ADMINISTRATION
2.1 Squamous Cell Carcinoma of the Head and Neck
2.2 Colorectal Cancer
2.3 Recommended Premedication
2.4 Dose Modifications
2.5 Preparation for Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Infusion Reactions
5.2 Cardiopulmonary Arrest
5.3 Pulmonary Toxicity
5.4 Dermatologic Toxicity
5.5 Use of Erbitux® in Combination With Radiation and Cisplatin
5.6 Hyponagmension and Electrolyte Abnormalities
5.7 Epidermal Growth Factor Receptor (EGFR) Expression and Response
6 ADVERSE REACTIONS

6.1 Clinical Trials Experience
6.2 Immunogenicity
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Pharmacology and/or Toxicology
14 CLINICAL STUDIES
14.1 Squamous Cell Carcinoma of the Head and Neck (SCCHN)
14.2 Colorectal Cancer
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

WARNING: SERIOUS INFUSION REACTIONS and CARDIOPULMONARY ARREST

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

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

1 INDICATIONS AND USAGE

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

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

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

1.2 Colorectal Cancer

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

2 DOSAGE AND ADMINISTRATION

2.1 Squamous Cell Carcinoma of the Head and Neck

Erbitux® in combination with radiation therapy:

- The recommended initial dose is 400 mg/m² administered one week prior to initiation of a course of radiation therapy as a 120-minute intravenous infusion (maximum infusion rate 10 mg/min).

- The recommended subsequent weekly dose (all other infusions) is 250 mg/m² infused over 60 minutes (maximum infusion rate 10 mg/min) for the duration of radiation therapy (6–7 weeks). Complete Erbitux® administration 1 hour prior to radiation therapy.

Erbitux® monotherapy:

- The recommended initial dose is 400 mg/m² administered as a 120-minute intravenous infusion (maximum infusion rate 10 mg/min).

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

2.2 Colorectal Cancer

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

2.3 Recommended Premedication

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

2.4 Dose Modifications

Infusion Reactions

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

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

Dermatologic Toxicity

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

Table 1: Erbitux® Dose Modification Guidelines for Rash

<table>
<thead>
<tr>
<th>Severe Acneform Rash</th>
<th>Erbitux®</th>
<th>Outcome</th>
<th>Erbitux® Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st occurrence</td>
<td>Delay infusion 1 to 2 weeks</td>
<td>Improvement No Improvement</td>
<td>Continue at 250 mg/m²² Discontinue Erbitux®</td>
</tr>
<tr>
<td>2nd occurrence</td>
<td>Delay infusion 1 to 2 weeks</td>
<td>Improvement No Improvement</td>
<td>Reduce dose to 200 mg/m²² Discontinue Erbitux®</td>
</tr>
<tr>
<td>3rd occurrence</td>
<td>Delay infusion 1 to 2 weeks</td>
<td>Improvement No Improvement</td>
<td>Reduce dose to 150 mg/m²² Discontinue Erbitux®</td>
</tr>
<tr>
<td>4th occurrence</td>
<td>Discontinue Erbitux®</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.5 Preparation for Administration

Do not administer Erbitux® as an intravenous push or bolus.

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

100 mg/50 mL, single-use vial

200 mg/100 mL, single-use vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

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

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

Monitor patients for 1 hour following Erbitux® infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (eg, epinephrine,
corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Monitor longer
to confirm resolution of the event in patients requiring treatment for infusion reactions.
Immediately and permanently discontinue Erbitux® in patients with serious infusion
reactions. [See Boxed Warning and Dosage and Administration (2.4).]

5.2 Cardiopulmonary Arrest

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

5.3 Pulmonary Toxicity

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

5.4 Dermatologic Toxicity

Dermatologic toxicities, including acneform rash, skin drying and fissuring, paronychial
inflammation, and infectious sequelae (for example S. aureus sepsis, abscess formation,
cellulitis, blepharitis, cheilitis) occurred in patients receiving Erbitux® therapy. Acneform
rash occurred in 76—88% of 1373 patients receiving Erbitux® in clinical trials. Severe
acneform rash occurred in 1—17% of patients.

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

5.5 Use of Erbitux® in Combination With Radiation and
Cisplatin

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

5.6 Hypomagnesemia and Electrolyte Abnormalities

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

5.7 Epidermal Growth Factor Receptor (EGFR) Expression
and Response

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

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

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

- Infusion reactions [See Boxed Warning and Warnings and Precautions (5.1).]
- Cardiopulmonary arrest [See Boxed Warning and Warnings and Precautions (5.2).]
- Pulmonary toxicity [See Warnings and Precautions (5.3).]
- Dermatologic toxicity [See Warnings and Precautions (5.4).]
- Hypomagnesemia and Electrolyte Abnormalities [See Warnings and Precautions (5.6).]

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

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

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

6.1 Clinical Trials Experience

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

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

Infusion reactions: Infusion reactions, which included pyrexia, chills, rigors, dyspnea, bronchospasm, angioedema, urticaria, hypertension, and hypotension occurred in 15–21% of patients across studies. Grades 3 and 4 infusion reactions occurred in 2–5% of patients; infusion reactions were fatal in 1 patient.
Infections: The incidence of infection was variable across studies, ranging from 13–35%. Sepsis occurred in 1–4% of patients.

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

Squamous Cell Carcinoma of the Head and Neck

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

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>Erbitux® plus Radiation (n=208)</th>
<th>Radiation Therapy Alone (n=212)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1–4</td>
<td>Grades 3 and 4</td>
</tr>
<tr>
<td>% of Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>56</td>
<td>4</td>
</tr>
<tr>
<td>Fever¹</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Infusion Reaction²</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Infection</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Chills¹</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td><strong>Digestive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>49</td>
<td>2</td>
</tr>
<tr>
<td>Emesis</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td><strong>Metabolic/Nutritional</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Loss</td>
<td>84</td>
<td>11</td>
</tr>
<tr>
<td>Dehydration</td>
<td>25</td>
<td>6</td>
</tr>
</tbody>
</table>
Table 2: Incidence of Selected Adverse Events (≥10%) in Patients with Locoregionally Advanced SCCHN

<table>
<thead>
<tr>
<th>Body System</th>
<th>Erbitux® plus Radiation (n=208)</th>
<th>Radiation Therapy Alone (n=212)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1–4</td>
<td>Grades 3 and 4</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Skin/Appendages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acneform Rash</td>
<td>87</td>
<td>17</td>
</tr>
<tr>
<td>Radiation Dermatitis</td>
<td>86</td>
<td>23</td>
</tr>
<tr>
<td>Application Site Reaction</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>16</td>
<td>0</td>
</tr>
</tbody>
</table>

1 Includes cases also reported as infusion reaction.
2 Infusion reaction is defined as any event described at any time during the clinical study as “allergic reaction” or “anaphylactoid reaction”, or any event occurring on the first day of dosing described as “allergic reaction”, “anaphylactoid reaction”, “fever”, “chills”, “chills and fever”, or “dyspnea”.
3 Acneform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.

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

Late Radiation Toxicity

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

Colorectal Cancer

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

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

<table>
<thead>
<tr>
<th>Body System</th>
<th>Preferred Term</th>
<th>Erbitux® plus BSC (n=288)</th>
<th>BSC alone (n=274)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grades 2</td>
<td>Grades 3 and 4</td>
<td>Any Grades</td>
</tr>
<tr>
<td></td>
<td>% of Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatology</td>
<td>89</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Dry Skin</td>
<td>49</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>40</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Other-Dermatology</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Nail Changes</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>Fatigue</td>
<td>89</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Infusion Reactions 3</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Rigors, Chills</td>
<td>13</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pain</td>
<td>Abdominal Pain</td>
<td>59</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Pain-Other</td>
<td>51</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>33</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Bone Pain</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Dyspnea</td>
<td>48</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Constipation</td>
<td>46</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>39</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>37</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Other-Gastrointestinal</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Mouth Dryness</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>Infection without neutropenia</td>
<td>35</td>
<td>13</td>
</tr>
</tbody>
</table>
### Table 3: Incidence of Selected Adverse Events Occurring in ≥10% of Patients with Advanced Colorectal Carcinoma Treated with Erbitux® Monotherapy

<table>
<thead>
<tr>
<th>Body System</th>
<th>Erbitux® plus BSC (n=288)</th>
<th>BSC alone (n=274)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grades 2</td>
<td>Grades 3 and 4</td>
<td>Any Grades</td>
</tr>
<tr>
<td>Neurology</td>
<td></td>
<td>% of Patients</td>
</tr>
<tr>
<td>Insomnia</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Confusion</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Anxiety</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Depression</td>
<td>13</td>
<td>1</td>
</tr>
</tbody>
</table>

1. Adverse reactions occurring more frequently in Erbitux® treated patients compared with controls.
2. Adverse events were graded using the NCI CTC, V 2.0.
3. Infusion reaction is defined as any event (chills, rigors, dyspnea, tachycardia, bronchospasm, chest tightness, swelling, urticaria, hypotension, flushing, rash, hypertension, nausea, angioedema, pain, pruritus, sweating, tremors, shaking, cough, visual disturbances, or other) recorded by the investigator as infusion related.

BSC = best supportive care

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

#### 6.2 Immunogenicity

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

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

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

10 OVERDOSAGE

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

11 DESCRIPTION

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.3 Pharmacokinetics

Erbitux® administered as monotherapy or in combination with concomitant chemotherapy or radiation therapy exhibits nonlinear pharmacokinetics. The area under the concentration time curve (AUC) increased in a greater than dose proportional manner while clearance of cetuximab decreased from 0.08 to 0.02 L/h/m² as the dose increased from 20 to 200 mg/m², and at doses >200 mg/m², it appeared to plateau. The volume of the distribution for cetuximab appeared to be independent of dose and approximated the vascular space of 2–3 L/m².
Following the recommended dose regimen (400 mg/m² initial dose; 250 mg/m² weekly dose), concentrations of cetuximab reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 µg/mL, respectively. The mean half-life of cetuximab was approximately 112 hours (range 63–230 hours). The pharmacokinetics of cetuximab were similar in patients with SCCHN and those with colorectal cancer.

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

### 13 NONCLINICAL TOXICOLOGY

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

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

#### 13.2 Animal Pharmacology and/or Toxicology

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

14 CLINICAL STUDIES

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

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

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

The main outcome measure of this trial was duration of locoregional control. Overall survival was also assessed. Results are presented in Table 4.
Table 4: Study 1: Clinical Efficacy in Locoregionally Advanced SCCHN

<table>
<thead>
<tr>
<th>Locoregional control</th>
<th>Erbitux® + Radiation (n=211)</th>
<th>Radiation Alone (n=213)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Stratified Log-rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration (months)</td>
<td>24.4</td>
<td>14.9</td>
<td>0.68 (0.52–0.89)</td>
<td>0.005</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration (months)</td>
<td>49.0</td>
<td>29.3</td>
<td>0.74 (0.57–0.97)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

CI = confidence interval

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

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

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

14.2 Colorectal Cancer

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

Of the 572 randomized patients, the median age was 63 years, 64% were male, 89% were Caucasian, and 77% had baseline ECOG Performance Status of 0–1. All patients were to have received and progressed on prior therapy including an irinotecan-containing regimen and an oxaliplatin-containing regimen.
The main outcome measure of the study was overall survival. The results are presented in Figure 1.

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

<table>
<thead>
<tr>
<th>SUBJECTS AT RISK</th>
<th>MONTHS</th>
<th>PROPORTION ALIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CETX+BSC</td>
<td>287</td>
<td>0.98</td>
</tr>
<tr>
<td>BSC</td>
<td>285</td>
<td>0.97</td>
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<th>SUBJECTS AT RISK</th>
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<th>PROPORTION ALIVE</th>
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</thead>
<tbody>
<tr>
<td>CETX+BSC</td>
<td>217</td>
<td>0.94</td>
</tr>
<tr>
<td>BSC</td>
<td>197</td>
<td>0.93</td>
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<th>SUBJECTS AT RISK</th>
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<th>PROPORTION ALIVE</th>
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</thead>
<tbody>
<tr>
<td>CETX+BSC</td>
<td>136</td>
<td>0.90</td>
</tr>
<tr>
<td>BSC</td>
<td>85</td>
<td>0.89</td>
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<th>SUBJECTS AT RISK</th>
<th>MONTHS</th>
<th>PROPORTION ALIVE</th>
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<tbody>
<tr>
<td>CETX+BSC</td>
<td>78</td>
<td>0.87</td>
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<tr>
<td>BSC</td>
<td>44</td>
<td>0.86</td>
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<th>PROPORTION ALIVE</th>
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<tr>
<td>CETX+BSC</td>
<td>37</td>
<td>0.84</td>
</tr>
<tr>
<td>BSC</td>
<td>26</td>
<td>0.83</td>
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<th>PROPORTION ALIVE</th>
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</thead>
<tbody>
<tr>
<td>CETX+BSC</td>
<td>14</td>
<td>0.81</td>
</tr>
<tr>
<td>BSC</td>
<td>12</td>
<td>0.80</td>
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<th>SUBJECTS AT RISK</th>
<th>MONTHS</th>
<th>PROPORTION ALIVE</th>
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</thead>
<tbody>
<tr>
<td>CETX+BSC</td>
<td>4</td>
<td>0.79</td>
</tr>
<tr>
<td>BSC</td>
<td>8</td>
<td>0.78</td>
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<th>MONTHS</th>
<th>PROPORTION ALIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CETX+BSC</td>
<td>0</td>
<td>0.77</td>
</tr>
<tr>
<td>BSC</td>
<td>2</td>
<td>0.76</td>
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<table>
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<th>SUBJECTS AT RISK</th>
<th>MONTHS</th>
<th>PROPORTION ALIVE</th>
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</thead>
<tbody>
<tr>
<td>CETX+BSC</td>
<td>0</td>
<td>0.75</td>
</tr>
<tr>
<td>BSC</td>
<td>1</td>
<td>0.74</td>
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<table>
<thead>
<tr>
<th>SUBJECTS AT RISK</th>
<th>MONTHS</th>
<th>PROPORTION ALIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CETX+BSC</td>
<td>0</td>
<td>0.73</td>
</tr>
<tr>
<td>BSC</td>
<td>0</td>
<td>0.72</td>
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</table>

<table>
<thead>
<tr>
<th>SUBJECTS AT RISK</th>
<th>MONTHS</th>
<th>PROPORTION ALIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CETX+BSC OVER BSC</td>
<td>7</td>
<td>0.71</td>
</tr>
<tr>
<td>BSC OVER BSC</td>
<td>5</td>
<td>0.70</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GROUP</th>
<th># DEAD / # RANDOMIZED</th>
<th>MEDIAN (95% CI) HAZARD RATIO (95.00% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CETX+BSC</td>
<td>222/287</td>
<td>6.14 (5.16 - 8.70) 0.77 (0.64 - 0.92)</td>
</tr>
<tr>
<td>BSC</td>
<td>254/285</td>
<td>4.97 (4.21 - 4.86) 0.77 (0.64 - 0.92)</td>
</tr>
<tr>
<td>CETX+BSC OVER BSC</td>
<td>234/285</td>
<td>4.97 (4.21 - 4.86) 0.77 (0.64 - 0.92)</td>
</tr>
</tbody>
</table>

Study 4 was a multicenter, clinical trial conducted in 329 patients with EGFR-expressing recurrent metastatic colorectal cancer. Patients were randomized (2:1) to receive either Erbitux® plus irinotecan (218 patients) or Erbitux® monotherapy (111 patients). Erbitux® was administered as a 400-mg/m² initial dose, followed by 250 mg/m² weekly until disease progression or unacceptable toxicity. In the Erbitux® plus irinotecan arm, irinotecan was added to Erbitux® using the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m² every 3 weeks, 180 mg/m² every 2 weeks, or 125 mg/m² weekly times four doses every 6 weeks. Of the 329 patients, the median age was 59 years, 63% were male, 98% were Caucasian, and 88% had baseline Karnofsky Performance Status ≥80. Approximately two-thirds had previously failed oxaliplatin treatment.
The efficacy of Erbitux® plus irinotecan or Erbitux® monotherapy, based on durable objective responses, was evaluated in all randomized patients and in two pre-specified subpopulations: irinotecan refractory patients, and irinotecan and oxaliplatin failures. In patients receiving Erbitux® plus irinotecan, the objective response rate was 23% (95% confidence interval 18%–29%), median duration of response was 5.7 months, and median time to progression was 4.1 months. In patients receiving Erbitux® monotherapy, the objective response rate was 11% (95% confidence interval 6%–18%), median duration of response was 4.2 months, and median time to progression was 1.5 months. Similar response rates were observed in the pre-defined subsets in both the combination arm and monotherapy arm of the study.

16 **HOW SUPPLIED/STORAGE AND HANDLING**

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

| NDC 66733-948-23 | 100 mg/50 mL, single-use vial, individually packaged in a carton |
| NDC 66733-958-23 | 200 mg/100 mL, single-use vial, individually packaged in a carton |

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

17 **PATIENT COUNSELING INFORMATION**

Advise patients:

- To report signs and symptoms of infusion reactions such as fever, chills, or breathing problems.
• Of the potential risks of using Erbitux\textsuperscript{®} during pregnancy or nursing and of the need
to use adequate contraception in both males and females during and for 6 months
following the last dose of Erbitux\textsuperscript{®} therapy.

• That nursing is not recommended during, and for 2 months following the last dose of
Erbitux\textsuperscript{®} therapy.

• To limit sun exposure (use sunscreen, wear hats) while receiving and for 2 months
following the last dose of Erbitux\textsuperscript{®}.

Erbitux\textsuperscript{®} is a registered trademark of ImClone Systems Incorporated.

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

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