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)

- Retrospective subset analyses of metastatic or advanced colorectal cancer trials have not shown a treatment benefit for Erbitux (cetuximab) in patients whose tumors had KRAS mutations in codon 12 or 13. Use of Erbitux is not recommended for the treatment of colorectal cancer with these mutations. (1.2, 12.1, 14.2)

- 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)
- Initiate Erbitux one week prior to initiation of radiation therapy. Complete Erbitux administration 1 hour prior to platinum-based therapy with 5-FU. (2.1)
- Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 infusion reactions and non-serious NCI CTC Grade 3 infusion reaction. (2.4)
- Permanently discontinue for serious infusion reactions. (2.4)
- Withhold infusion for severe, persistent acneiform rash. Reduce dose for recurrent, severe rash. (2.4)

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

WARNING: SERIOUS INFUSION REACTIONS and CARDIOPULMONARY ARREST

See full prescribing information for complete boxed warning.

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- Permanently discontinue for serious infusion reactions. (2.4)
- Withhold infusion for severe, persistent acneiform rash. Reduce dose for recurrent, severe rash. (2.4)

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1.2 Colorectal Cancer

2 DOSAGE AND ADMINISTRATION

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2.2 Colorectal Cancer
2.3 Recommended Premedication
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Boxed Warning 11/2011

Indications and Usage

Squamous Cell Carcinoma of the Head and Neck (1.1)
Dose and Administration

Squamous Cell Carcinoma of the Head and Neck (2.1)
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Cardiopulmonary Arrest (5.2)
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Recent Major Changes 11/2011

- Boxed Warning
- Indications and Usage
- Dose and Administration
- Warnings and Precautions

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

- Head and Neck Cancer
  - Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy. (1.1, 14.1)
  - Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with 5-FU. (1.1, 14.1)
  - Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy. (1.1, 14.1)

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

- Retrospective subset analyses of metastatic or advanced colorectal cancer trials have not shown a treatment benefit for Erbitux (cetuximab) in patients whose tumors had KRAS mutations in codon 12 or 13. Use of Erbitux is not recommended for the treatment of colorectal cancer with these mutations. (1.2, 12.1, 14.2)

- 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)
- Initiate Erbitux one week prior to initiation of radiation therapy. Complete Erbitux administration 1 hour prior to platinum-based therapy with 5-FU. (2.1)
- Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 infusion reactions and non-serious NCI CTC Grade 3 infusion reaction. (2.4)
- Permanently discontinue for serious infusion reactions. (2.4)
- Withhold infusion for severe, persistent acneiform rash. Reduce dose for recurrent, severe rash. (2.4)

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

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 1-888-FDA-1088 or www.fda.gov/medwatch

- 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: 11/2011

Full Prescribing Information: Contents

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3.1 Injection, for intravenous infusion

4.1 Hypomagnesemia and Electrolyte Abnormalities

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5.2 Cardiopulmonary Arrest

5.3 Pulmonary Toxicity

5.4 Dermatologic Toxicity

5.5 Use of Erbitux in Combination With Radiation and Cisplatin

5.6 Hypomagnesemia and Electrolyte Abnormalities

5.7 Epidermal Growth Factor Receptor (EGFR) Expression and Response

6 Adverse Reactions

6.1 Clinical Trials Experience
6.2 Immunogenicity
6.3 Postmarketing Experience
Erbitux® (cetuximab)

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 and 2 and non-serious NCI CTC Grade 3 infusion reaction.

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) acniform 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 Acanthosis Rash</th>
<th>Erbitux Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st occurrence</td>
<td>Delay infusion 1 to 2 weeks</td>
</tr>
<tr>
<td>2nd occurrence</td>
<td>Reduce dose to 200 mg/m²</td>
</tr>
<tr>
<td>3rd occurrence</td>
<td>Reduce dose to 150 mg/m²</td>
</tr>
<tr>
<td>4th occurrence</td>
<td>Discontinue Erbitux</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, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. Severe (NCI CTC Grades 3 and 4) infusion reactions occurred in 2–5% of 1373 patients in Studies 1, 3, 4, and 5 receiving Erbitux, with fatal outcome in 1 patient. [See Clinical Studies (14.1, 14.2).]

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, 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 Study 1. 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. In Study 2, fatal cardiac disorders and/or sudden death occurred in 7 (3%) of 219 patients treated with EU-approved cetuximab and platinum-based therapy with 5-FU as compared to 4 (2%) of 215 patients treated with chemotherapy alone. Five of these 7 patients in the chemotherapy plus cetuximab arm received concomitant cisplatin and 2 patients received concomitant carboplatin. All 4 patients in the chemotherapy-alone arm received cisplatin. Carefully consider use of Erbitux in combination with radiation therapy or platinum-based therapy with 5-FU in head and neck cancer patients with a history

Erbitux® (cetuximab) is indicated in combination with radiation therapy or in combination with platinum-based therapy has failed. [See Clinical Studies (14.1).]

Erbitux, as a single agent, is indicated for the treatment of epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens. Erbitux, as a single agent, is not indicated for the treatment of EGFR-expressing metastatic colorectal cancer in patients who are intolerant to irinotecan-based regimens. [See Warnings and Precautions (5.7), Clinical Studies (14.7, 14.8).]

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 Warnings and Precautions (5.7).]

Retrospective subset analyses of metastatic or advanced colorectal cancer trials have not shown a treatment benefit for Erbitux in patients whose tumors had KRAS mutations in codon 12 or 13. Use of Erbitux is not recommended for the treatment of colorectal cancer with these mutations [See Clinical Pharmacology (12.1), Clinical Studies (14.3)].

Erbitux in combination with platinum-based therapy with 5-FU for the first-line treatment of patients with recurrent locoregional disease or metastatic 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)].

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

Cardiopulmonary Arrest: 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 in Study 1 and in 3% of patients with squamous cell carcinoma of the head and neck treated with European Union (EU)-approved cetuximab in combination with platinum-based therapy with 5-fluorouracil (5-FU) in Study 2. Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after Erbitux administration. [See Warnings and Precautions (5.2, 5.8).]

1 INDICATIONS AND USAGE

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

Erbitux® (cetuximab) 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 is indicated in combination with platinum-based therapy with 5-FU for the first-line treatment of patients with recurrent locoregional disease or metastatic 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 epidermal growth factor receptor (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 Warnings and Precautions (5.7), Clinical Studies (14.7, 14.8)].

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 irinotecin for the treatment of EGFR-expressing, metastatic colorectal carcinoma. [See Warnings and Precautions (5.7), Clinical Studies (14.2)].

Retrospective subset analyses of metastatic or advanced colorectal cancer trials have not shown a treatment benefit for Erbitux in patients whose tumors had KRAS mutations in codon 12 or 13. Use of Erbitux is not recommended for the treatment of colorectal cancer with these mutations [See Clinical Pharmacology (12.1), Clinical Studies (14.3)].

2 DOSAGE AND ADMINISTRATION

2.1 Squamous Cell Carcinoma of the Head and Neck

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

- The recommended initial dose is 400 mg/m² administered one week prior to initiation of a course of radiation therapy or on the day of initiation of platinum-based therapy with 5-FU as a 120-minute intravenous infusion (maximum infusion rate 10 mg/min). Complete Erbitux administration 1 hour prior to platinum-based therapy with 5-FU.
- 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) or until disease progression or unacceptable toxicity when administered in combination with platinum-based therapy with 5-FU. Complete Erbitux administration 1 hour prior to radiation therapy or platinum-based therapy with 5-FU.

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.
ERBITUX® (cetuximab)

5.2 Pulmonary Toxicity

Interstitial lung disease (ILD), including 1 fatality, occurred in 4 of 1570 (<0.5%) patients receiving Erbitux in Studies 1, 3, and 5, as well as other studies, in colorectal cancer and head and neck cancer. 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, infectious sequelae (for example S. aureus sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis, chelitis), and hypertrichosis occurred in patients receiving Erbitux therapy. Acneform rash occurred in 76–88% of 1373 patients receiving Erbitux in Studies 1, 3, 4, and 5. 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 therapy. [See Dosage and Administration (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 365 patients receiving Erbitux in Study 4 and two other clinical trials in colorectal cancer and head and neck cancer, respectively, and was severe (NCI CTC Grades 3 and 4) in 6–17%.

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

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 after 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, EGFR immunohistochemical evidence of EGFR tumor expression prior to study entry is a requirement for patients enrolled in the colorectal cancer clinical studies who were 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.

6 ADVERSE REACTIONS

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

- Infusion reactions [See Boxed Warning, Warnings and Precautions (5.1.)
- Cardiopulmonary arrest [See Boxed Warning, 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 Studies 1, 3, 4, and 5, 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 4) or Phase 2 (Studies 3 and 5) trials treated at the recommended dose and schedule for medians of 7 to 14 weeks. [See Clinical Studies (14)].

Infusion reactions: Infusion reactions, which included pyrexia, chills, rigor, 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

Erbitux in Combination with Radiation Therapy

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>Preferred Term</th>
<th>Grades 1–4</th>
<th>Grades 3 and 4</th>
<th>Grades 1–4</th>
<th>Grades 3 and 4</th>
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</thead>
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<td>Body as a Whole</td>
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<td>Asthenia</td>
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<td>5</td>
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<td>13</td>
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<td>Headache</td>
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<td>Infusion Reactiona</td>
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<td>Chillsa</td>
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<td>Alamine Transaminase, highb</td>
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<td>Respiratory</td>
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<td>Pharyngitis</td>
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<td>Skin/Appenages</td>
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<td>Acneiform Rasha</td>
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<td>Application Site Reaction</td>
<td>18</td>
<td>0</td>
<td>12</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>16</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

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 events, the number of subjects with tested samples varied from 205–206 for Erbitux 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".

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.
for the initial dose, followed by 250 mg/m² weekly. Patients received a median of 17 infusions (range 1–89).

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

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Grades 1–4&lt;br&gt;(n=219)</th>
<th>Grades 3 and 4&lt;br&gt;(n=219)</th>
<th>Grades 1–4&lt;br&gt;(n=215)</th>
<th>Grades 3 and 4&lt;br&gt;(n=215)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>54</td>
<td>4</td>
<td>47</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26</td>
<td>5</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22</td>
<td>0</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Infusion Reaction a</td>
<td>10</td>
<td>2</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection b</td>
<td>44</td>
<td>11</td>
<td>27</td>
<td>8</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>25</td>
<td>5</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>12</td>
<td>4</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>12</td>
<td>7</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>11</td>
<td>5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acneiform Rash b</td>
<td>70</td>
<td>9</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>28</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Acne</td>
<td>22</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis Acneiform</td>
<td>15</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dry Skin</td>
<td>14</td>
<td>0</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>12</td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

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

* a Injection – this term excludes sepsis-related events which are presented separately.

a Acneform rash defined as any event described as “acne”, “dermatitis acneform”, “dry skin”, “exfoliative rash”, “rash”, “rash erythematous”, “rash macular”, “rash papular”, or “rash pustular”.

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

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

Table 4 contains selected adverse events in 562 patients receiving best supportive care (BSC) alone or with Erbitux monotherapy for metastatic colorectal cancer in Study 4. Erbitux was administered at the recommended dose and schedule (400 mg/m² initial dose, followed by 250 mg/m² weekly).

Table 4: 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>Any Grades</th>
<th>Grades 3 and 4</th>
<th>Any Grades</th>
<th>Grades 3 and 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash/Desquamation</td>
<td>89</td>
<td>12</td>
<td>16</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Dry Skin</td>
<td>49</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>40</td>
<td>2</td>
<td>8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other-Dermatology</td>
<td>27</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nail Changes</td>
<td>21</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>89</td>
<td>33</td>
<td>76</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>30</td>
<td>1</td>
<td>18</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Infusion Reactionc</td>
<td>20</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigors, Chills</td>
<td>13</td>
<td>&lt;1</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>59</td>
<td>14</td>
<td>52</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Pain-Other</td>
<td>51</td>
<td>16</td>
<td>34</td>
<td>7</td>
<td></td>
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<tr>
<td>Headache</td>
<td>33</td>
<td>4</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bone Pain</td>
<td>15</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>48</td>
<td>16</td>
<td>43</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>29</td>
<td>2</td>
<td>19</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>46</td>
<td>4</td>
<td>38</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>39</td>
<td>2</td>
<td>20</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>37</td>
<td>6</td>
<td>29</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>25</td>
<td>1</td>
<td>10</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Other-Gastrointestinal</td>
<td>23</td>
<td>10</td>
<td>18</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Mouth Dryness</td>
<td>11</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection without neutropenia</td>
<td>35</td>
<td>13</td>
<td>17</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Neurology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>30</td>
<td>1</td>
<td>15</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>15</td>
<td>6</td>
<td>9</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>14</td>
<td>2</td>
<td>8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>13</td>
<td>1</td>
<td>6</td>
<td>&lt;1</td>
<td></td>
</tr>
</tbody>
</table>

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

b Adverse events 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, pruritus, sweating, tremors, shaking, cough, visual disturbances, or other) recorded by the investigator as infusion-related.

BSC = best supportive care

Erbitux in Combination with Irinotecan

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 Grades 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% (40 of 1001) of evaluable patients without apparent effect on the safety or antitumor activity of Erbitux.
ERBITUX® (cetuximab)

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.

6.3 Postmarketing Experience

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

- Aseptic meningitis

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

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

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

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, in combination with irinotecan, were evaluated in pediatric patients with refractory solid tumors in an open-label, single-arm, dose-finding study. Erbitux was administered once weekly, at doses up to 250 mg/m², to 27 patients ranging from 1 to 12 years old; and in 19 patients ranging from 13 to 18 years old. No new safety signals were identified in pediatric patients. The pharmacokinetic profiles of cetuximab between the two age groups were similar at the 75 and 150 mg/m² single dose levels. The volume of the distribution appeared to be independent of dose and approximated the vascular space of 2–3 L/m². Following a single dose of 250 mg/m², the geometric mean AUC 0-inf (in vivo) of cetuximab was 110 hours (range 69 to 188 hours) for the younger age group, and 82 hours (range 55 to 117 hours) for the adolescent age group.

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.

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 1 (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 solution with no preservatives, which contains 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic hexahydrate, 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. Signal transduction through the EGFR results in activation of wild-type KRAS protein. However, in cells with activating KRAS somatic mutations, the mutant KRAS protein is continuously active and appears independent of EGFR regulation.

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 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 is similar in patients with SCCHN and those with colorectal cancer. Erbitux had an approximately 22% (90% confidence interval: 6%, 38%) higher systemic exposure relative to the EU-approved cetuximab used in Study 2 based on a population pharmacokinetic analysis. [See Clinical Studies (14.1)]

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/scherichia 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.
ERBITUX® (cetuximab)

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 until 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 99% 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; 26% 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 5.

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

<table>
<thead>
<tr>
<th></th>
<th>Erbitux + Radiation</th>
<th>Radiation Alone</th>
<th>Hazard Ratio (95% CI)</th>
<th>Stratified Log-rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoregional Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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 an open label, randomized, multicenter, controlled trial of 442 patients with recurrent locoregional disease or metastatic SCCHN conducted outside the U.S. using an EU-approved cetuximab as the clinical trial material. Erbitux provides approximately 22% higher exposure relative to the EU-approved cetuximab used in Study 2; these pharmacokinetic data, together with the results of Study 2 and other clinical trial data establish the efficacy of Erbitux at the recommended dose [see Clinical Pharmacology (12.3)].

Patients with no prior therapy for recurrent locoregional disease or metastatic SCCHN were randomized (1:1) to receive EU-approved cetuximab plus cisplatin or carboplatin and 5-FU, or cisplatin or carboplatin and 5-FU alone. Choice of cisplatin or carboplatin was at the discretion of the treating physician. Stratification factors were Karnofsky Performance Status (<60 versus ≥80) and previous chemotheraphy. Cisplatin (100 mg/m², Day 1) or carboplatin (AUC 5. Day 1) plus intravenous 5-FU (1000 mg/m²/d, Days 1–4) were administered every 3 weeks (1 cycle) for a maximum of 6 cycles in the absence of disease progression or unacceptable toxicity. Cetuximab was administered at a 400 mg/m² initial dose, followed by a 250 mg/m² weekly dose in combination with chemotherapy. Patients demonstrating at least stable disease on cetuximab in combination with chemotherapy were to continue cetuximab monotherapy at 250 mg/m² weekly, in the absence of disease progression or unacceptable toxicity after completion of 6 planned courses of platinum-based therapy. For patients where treatment was delayed because of the toxic effects of chemotherapy, weekly cetuximab could be continued as monotherapy until disease progression or unacceptable toxicity.

Of the 442 randomized patients, the median age was 57 years, 96% were male, 98% were Caucasian, and 88% had baseline Karnofsky Performance Status ≥80. Thirty-four percent of patients had oropharyngeal, 25% laryngeal, 20% oral cavity, and 14% hypopharyngeal primary tumors. Fifty-three percent of patients had recurrent locoregional disease only and 47% had metastatic disease. Fifty-eight percent had AJCC Stage IV disease and 21% had Stage III disease. Forty-four percent of patients received cisplatin therapy and 34% received carboplatin as initial therapy. Approximately fifteen percent of the patients in the cisplatin arm switched to carboplatin during the treatment period.

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

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

<table>
<thead>
<tr>
<th></th>
<th>EU-Approved Cetuximab + Platinum-based Therapy + 5-FU (n=222)</th>
<th>Platinum-based Therapy + 5-FU (n=220)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Stratified Log-rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>10.1 7.4 0.80 (0.64, 0.98)</td>
<td>3.5 2.3 0.63 (0.36, 1.04)</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Subjects at Risk (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%–16%), 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.

Lack of Efficacy of Anti-EGFR Monoclonal Antibodies in Patients with mCRC Containing KRAS Mutations

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

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

<table>
<thead>
<tr>
<th>Population (n: ITT)</th>
<th>Treatment</th>
<th>Number of Patients with KRAS Results (% ITT)</th>
<th>Number of Patients with KRAS mutant (mAb vs control)</th>
<th>Effect of mAb on Endpoints: KRAS Mutant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line treatment mCRC (1198)</td>
<td>FOLFOX ± Erbitux</td>
<td>540 (45%)</td>
<td>105/67</td>
<td>PFS: no difference OS: no difference ORR: decreased</td>
</tr>
<tr>
<td>1st line treatment mCRC (337)</td>
<td>FOLFOX-4 ± Erbitux</td>
<td>233 (69%)</td>
<td>52/47</td>
<td>ORR: decreased PFS: decreased OS: no difference</td>
</tr>
<tr>
<td>1st line treatment mCRC (1053)</td>
<td>oxaliplatin or irinotecan-based chemotherapy, bevacizumab ± panitumumab</td>
<td>664 (81%)</td>
<td>135/125</td>
<td>PFS: decreased OS: no difference ORR: increased ODDS: decreased</td>
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<tr>
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<td>oxaliplatin or irinotecan</td>
<td>47/39</td>
<td>ORR: decreased PFS: decreased OS: decreased</td>
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</tr>
</tbody>
</table>

* mAb: EGFR monoclonal antibody; PFS: progression-free survival; ORR: overall response rate; OS: overall survival.
* Results from the primary efficacy endpoint are in bold. A given endpoint is designated as “decreased” if there was a numerically smaller result and as “increased” if there was a numerically higher result in the mAb group than in the control group.

### Study 4

3rd line treatment mCRC (572)  
BSC ± Erbitux  
3rd line treatment mCRC (463)  
BSC ± Panitumumab

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

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* mAb: EGFR monoclonal antibody; PFS: progression-free survival; ORR: overall response rate; OS: overall survival.
* Results from the primary efficacy endpoint are in bold. A given endpoint is designated as “decreased” if there was a numerically smaller result and as “increased” if there was a numerically higher result in the mAb group than in the control group.

### 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, injectable liquid containing no preservatives.

### 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 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 therapy.
- That nursing is not recommended during, and for 2 months following the last dose of Erbitux therapy.
- To limit sun exposure (use sunscreen, wear hats) while receiving and for 2 months following the last dose of Erbitux.

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

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

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

Bristol-Myers Squibb

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