HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Erbitux safely and effectively. See full prescribing information for Erbitux.

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

WARNING: SERIOUS INFUSION REACTIONS and CARDIOPULMONARY ARREST

See full prescribing information for complete boxed warning.

- **Serious infusion reactions, some fatal, occurred in approximately 3% of patients. (5.1)**
- **Cardiopulmonary arrest and/or sudden death occurred in 2% of patients receiving Erbitux in combination with radiation therapy. (5.2, 5.6)**

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

Indications and Usage, Colorectal Cancer (1.2)	10/2007
Warnings and Precautions	
Infusion Reactions (5.1)	09/2008
Dermatologic Toxicity (5.4)	09/2008

----------INDICATIONS AND USAGE----------

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

Head and Neck Cancer

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

Colorectal Cancer

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

----------DOSAGE AND ADMINISTRATION----------

- Premedicate with an H_1 antagonist. (2.3)
- Administer 400 mg/m^2 initial dose as a 120-minute intravenous infusion followed by 250 mg/m^2 weekly infused over 60 minutes. (2.1, 2.2)
- 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 Grades 3–4 infusion reactions. (2.4)
- Permanently discontinue for serious infusion reactions. (2.4)
- Withhold infusion for severe, persistent acneform rash. Reduce dose for recurrent, severe rash. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

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

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

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

----------ADVERSE REACTIONS----------

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

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

----------USE IN SPECIFIC POPULATIONS----------

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

* 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/m^2 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/m^2 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/m^2 administered as a 120-minute intravenous infusion (maximum infusion rate 10 mg/min).

- The recommended subsequent weekly dose (all other infusions) is 250 mg/m^2 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/m^2 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/m^2 infused over 60 minutes (maximum infusion rate 10 mg/min) until disease progression or unacceptable toxicity.

2.3 Recommended Premedication

Premedicate with an H_1 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 Grades 3–4 infusion reactions.

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

Dermatologic Toxicity

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

Table 1: Erbitux Dose Modification Guidelines for Rash

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

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 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, infectious sequelae (for example *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis, cheilitis), and hypertrichosis 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 therapy. [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/m^2) 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 Grades 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.

6 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/m^2 initial dose, followed by 250 mg/m^2 weekly). Patients received a median of 8 infusions (range 1–11).

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

Body System Preferred Term	Erbitux plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
	Grades 1–4	Grades 3 and 4	Grades 1–4	Grades 3 and 4
	% of Patients			
Body as a Whole				
Asthenia	56	4	49	5
Fever[1]	29	1	13	1
Headache	19	<1	8	<1
Infusion Reaction[2]	15	3	2	0
Infection	13	1	9	1
Chills[1]	16	0	5	0
Digestive				
Nausea	49	2	37	2
Emesis	29	2	23	4
Diarrhea	19	2	13	1
Dyspepsia	14	0	9	1
Metabolic/Nutritional				
Weight Loss	84	11	72	7
Dehydration	25	6	19	8
Alanine Transaminase, high[3]	43	2	21	1
Aspartate Transaminase, high[3]	38	1	24	1
Alkaline Phosphatase, high[3]	33	<1	24	0

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

Body System Preferred Term	Erbitux plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
	Grades 1–4	Grades 3 and 4	Grades 1–4	Grades 3 and 4
	% of Patients			
Respiratory				
Pharyngitis	26	3	19	4
Skin/Appendages				
Acneform Rash[4]	87	17	10	1
Radiation Dermatitis	86	23	90	18
Application Site Reaction	18	0	12	1
Pruritus	16	0	4	0

[1] Includes cases also reported as infusion reaction.

[2] Infusion reaction is defined as any event described at any time during the clinical study as "allergic reaction" or "anaphylactoid reaction", or any event occurring on the first day of dosing described as "allergic reaction", "anaphylactoid reaction", "fever", "chills", "chills and fever", or "dyspnea".

[3] 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.

[4] 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.

208 Erbitux was administered at the recommended dose and schedule (400 mg/m^2 initial
209 dose, followed by 250 mg/m^2 weekly).

Table 3: Incidence of Selected Adverse Events Occurring in ≥10% of Patients with Advanced Colorectal Carcinoma[1] Treated with Erbitux Monotherapy

	Erbitux plus BSC (n=288)		BSC alone (n=274)	
Body System Preferred Term	**Any Grades[2]**	**Grades 3 and 4**	**Any Grades**	**Grades 3 and 4**
	% of Patients			
Dermatology				
Rash/Desquamation	89	12	16	<1
Dry Skin	49	0	11	0
Pruritus	40	2	8	0
Other-Dermatology	27	1	6	1
Nail Changes	21	0	4	0
Body as a Whole				
Fatigue	89	33	76	26
Fever	30	1	18	<1
Infusion Reactions[3]	20	5		
Rigors, Chills	13	<1	4	0
Pain				
Abdominal Pain	59	14	52	16
Pain-Other	51	16	34	7
Headache	33	4	11	0
Bone Pain	15	3	7	2
Pulmonary				
Dyspnea	48	16	43	12
Cough	29	2	19	1
Gastrointestinal				
Constipation	46	4	38	5
Diarrhea	39	2	20	2
Vomiting	37	6	29	6
Stomatitis	25	1	10	<1
Other-Gastrointestinal	23	10	18	8
Mouth Dryness	11	0	4	0
Infection				
Infection without neutropenia	35	13	17	6

Table 3: Incidence of Selected Adverse Events Occurring in ≥10% of Patients with Advanced Colorectal Carcinoma[1] Treated with Erbitux Monotherapy

	Erbitux plus BSC (n=288)		BSC alone (n=274)	
Body System Preferred Term	**Any Grades[2]**	**Grades 3 and 4**	**Any Grades**	**Grades 3 and 4**
	% of Patients			
Neurology				
Insomnia	30	1	15	1
Confusion	15	6	9	2
Anxiety	14	2	8	1
Depression	13	1	6	<1

[1] Adverse reactions occurring more frequently in Erbitux treated patients compared with controls.

[2] Adverse events were graded using the NCI CTC, V 2.0.

[3] Infusion reaction is defined as any event (chills, rigors, dyspnea, tachycardia, bronchospasm, chest tightness, swelling, urticaria, hypotension, flushing, rash, hypertension, nausea, angioedema, pain, pruritus, sweating, tremors, shaking, cough, visual disturbances, or other) recorded by the investigator as infusion related.

BSC = best supportive care

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% (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

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 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/m^2 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/m^2 as the dose increased from 20 to 200 mg/m^2, and at doses >200 mg/m^2, 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/m^2.

Following the recommended dose regimen (400 mg/m^2 initial dose; 250 mg/m^2 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/m^2 initial dose beginning one week prior to initiation of radiation therapy, followed by 250 mg/m^2 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

	Erbitux + Radiation (n=211)	Radiation Alone (n=213)	Hazard Ratio (95% CI[a])	Stratified Log-rank p-value
Locoregional control				
Median duration (months)	24.4	14.9	0.68 (0.52–0.89)	0.005
Overall survival				
Median duration (months)	49.0	29.3	0.74 (0.57–0.97)	0.03

[a] CI = confidence interval

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

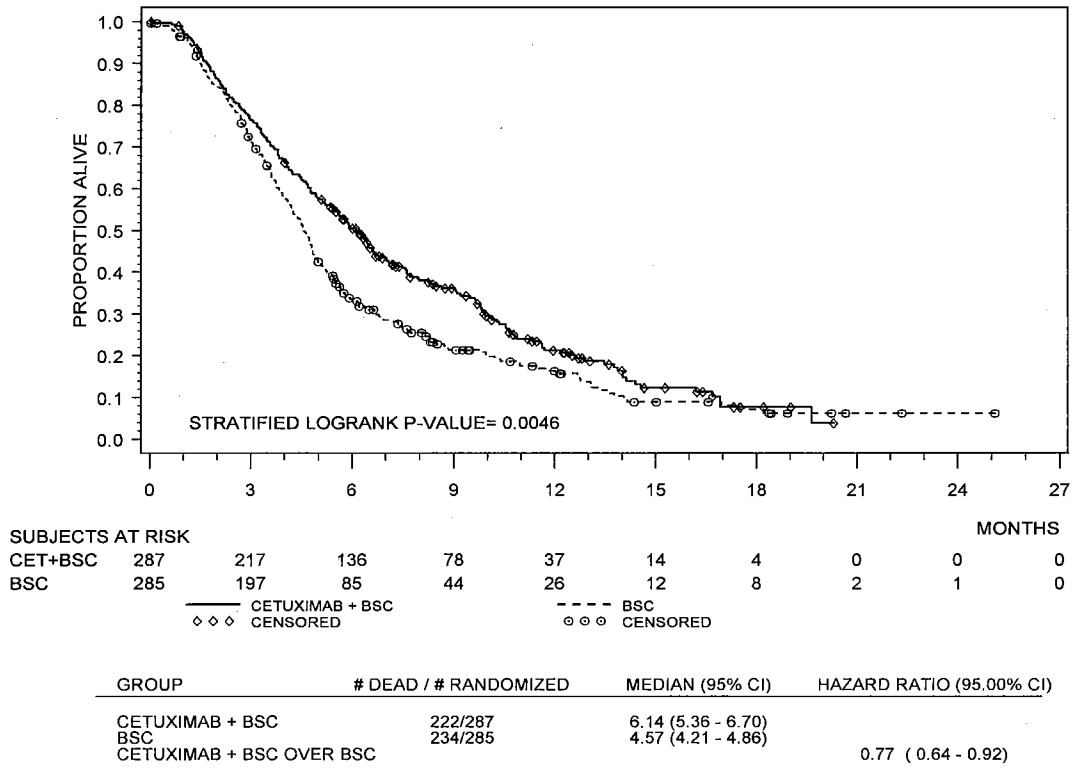
14.2 Colorectal Cancer

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/m^2 initial dose, followed by 250 mg/m^2 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



GROUP	# DEAD / # RANDOMIZED	MEDIAN (95% CI)	HAZARD RATIO (95.00% CI)
CETUXIMAB + BSC	222/287	6.14 (5.36 - 6.70)	
BSC	234/285	4.57 (4.21 - 4.86)	
CETUXIMAB + BSC OVER BSC			0.77 (0.64 - 0.92)

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/m^2 initial dose, followed by 250 mg/m^2 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/m^2 every 3 weeks, 180 mg/m^2 every 2 weeks, or 125 mg/m^2 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 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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