ERBITUX®

Rx only

(Cetuximab)

For intravenous use only.

WARNING

Infusion Reactions: Severe infusion reactions occurred with the administration of ERBITUX in approximately 3% of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of ERBITUX. Severe infusion reactions are characterized by rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, hypotension and/or cardiac arrest (see **WARNINGS** and **ADVERSE REACTIONS**). Severe infusion reactions require immediate interruption of the ERBITUX infusion and permanent discontinuation from further treatment. (See **WARNINGS: Infusion Reactions** and **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

Cardiopulmonary Arrest: Cardiopulmonary arrest and/or sudden death occurred in 2% (4/208) of patients with squamous cell carcinoma of the head and neck treated with radiation therapy and ERBITUX as compared to none of 212 patients treated with radiation therapy alone. Fatal events occurred within 1 to 43 days after the last ERBITUX treatment. ERBITUX in combination with radiation therapy should be used with caution in head and neck cancer patients with known coronary artery disease, congestive heart failure, and arrhythmias. Although the etiology of these events is unknown, close monitoring of serum electrolytes, including serum magnesium, potassium, and calcium, during and after ERBITUX therapy is recommended. (See **WARNINGS: Cardiopulmonary Arrest**, **PRECAUTIONS: Laboratory Tests: Electrolyte Monitoring**, and **ADVERSE REACTIONS: Electrolyte Depletion**.)

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. Each single-use, 50-mL vial contains 100 mg of Cetuximab at a concentration of 2 mg/mL and 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.

CLINICAL PHARMACOLOGY

General

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. While the mechanism of Cetuximab's anti-tumor effect(s) *in vivo* is unknown, all of these processes may contribute to the overall therapeutic effect of Cetuximab.

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, irinotecan, or irinotecan plus 5-fluorouracil in human tumor xenograft models in mice resulted in an increase in anti-tumor effects compared to radiation therapy or chemotherapy alone.

Human Pharmacokinetics

ERBITUX administered as monotherapy or in combination with concomitant chemotherapy or radiation therapy exhibits nonlinear pharmacokinetics. The pharmacokinetics of Cetuximab were similar in patients with squamous cell carcinoma of

the head and neck (SCCHN) and those with colorectal cancer. The area under the concentration time curve (AUC) increased in a greater than dose proportional manner as the dose increased from 20 to 400 mg/m^2. 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 a 2-hour infusion of 400 mg/m^2 of ERBITUX, the maximum mean serum concentration (Cmax) was 199 μg/mL (range: 70-380 μg/mL) and the mean elimination half-life was 97 hours (range 41-213 hours). A 1-hour infusion of 250 mg/m^2 produced a mean Cmax of 168 μg/mL (range 69-404 μg/mL). 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).

Special Populations

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates including body surface area (BSA), age, gender, race, and hepatic and renal function on the pharmacokinetics of Cetuximab.

Clearance of Cetuximab increased 1.8-fold as BSA increased from 1.3 to 2.3 m^2 (1.8-fold). This finding supports the recommended dosing of Cetuximab on a mg/m^2 basis.

In patients with colorectal cancer, female patients had a 25% lower intrinsic clearance of Cetuximab than male patients. The gender differences in clearance do not necessitate any alteration of dosing because of a similar safety profile. Definitive conclusions regarding comparability in efficacy cannot be made given the small number of patients with objective tumor responses. None of the other patient population covariates explored appeared to have an impact on the pharmacokinetics of Cetuximab. Qualitatively similar, but smaller gender differences in Cetuximab clearance were observed in patients with SCCHN.

ERBITUX has not been studied in pediatric populations.

CLINICAL STUDIES

Squamous Cell Carcinoma of the Head and Neck

Randomized Trial of Radiation Therapy plus Cetuximab vs. Radiation Therapy

The safety and efficacy of ERBITUX were studied in combination with radiation therapy in a randomized, controlled trial of 424 patients with locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) versus radiation therapy alone. In a multicenter, controlled clinical trial, 424 patients with Stage III/IV SCC of the oropharynx, hypopharynx, or larynx with no prior therapy were randomized (1:1) to receive either ERBITUX plus radiation therapy (211 patients) or radiation therapy alone (213 patients). 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. The planned radiation therapy regimen was chosen by the investigator prior to enrollment. For patients with ≥N1 neck disease, a post-radiation therapy neck dissection was recommended. Starting one week before radiation, ERBITUX was administered as a 400-mg/m^2 initial dose, followed by 250 mg/m^2 weekly for the duration of radiation therapy (6-7 weeks). All ERBITUX-treated patients received a 20-mg test dose on Day 1. Cetuximab was administered 1 hour prior to radiation therapy, beginning week 2.

Of the 424 randomized patients, 80% were male and 83% were Caucasian. The median age was 57 years (range 34–83). There were 258 patients enrolled in US sites (61%) and 166 patients (39%) in non-US sites. Ninety percent of patients had baseline Karnofsky Performance Status ≥80; 60% had oropharyngeal, 25% laryngeal, and 15% hypopharyngeal primary tumors; 28% had AJCC T4 tumor stage. The patient characteristics were similar across the study arms. 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 1.

Table 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	24.4 mo	14.9 mo	0.68 (0.52–0.89)	0.005
Overall survival				
Median duration	49.0 mo	29.3 mo	0.74 (0.57–0.97)	0.03

[a] CI = confidence interval

Single-Arm Trial

ERBITUX alone was studied in a single-arm, multicenter clinical trial in 103 patients with recurrent or metastatic SCCHN with documented progression within 30 days after 2–6 cycles of a platinum-based chemotherapy. 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. Upon progression, patients were given the option of receiving ERBITUX plus the platinum regimen that they failed prior to enrollment. Tumor response and progression were assessed by an Independent Radiographic Review Committee (IRC).

The median age was 57 years (range 23–77), 82% were male, 100% Caucasian, and 62% had a Karnofsky performance status of ≥80.

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

Colorectal Cancer

The efficacy and safety of ERBITUX alone or in combination with irinotecan were studied in a randomized, controlled trial (329 patients) and in combination with irinotecan in an open-label, single-arm trial (138 patients). ERBITUX was further evaluated as a single agent in a third clinical trial (57 patients). Safety data from 111 patients treated with single-agent ERBITUX was also evaluated. All trials studied patients with EGFR-expressing, metastatic colorectal cancer, whose disease had progressed after receiving an irinotecan-containing regimen.

Randomized Trial of Monotherapy vs. Combination Therapy

A multicenter, randomized, controlled clinical trial was conducted in 329 patients randomized to receive either ERBITUX plus irinotecan (218 patients) or ERBITUX monotherapy (111 patients). In both arms of the study, ERBITUX was administered as a 400-mg/m^2 initial dose, followed by 250 mg/m^2 weekly until disease progression or unacceptable toxicity. All patients received a 20-mg test dose on Day 1. 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. An IRC, blinded to the treatment arms, assessed both the progression on prior irinotecan and the response to protocol treatment for all patients.

Of the 329 randomized patients, 206 (63%) were male. The median age was 59 years (range 26-84), and the majority was Caucasian (323, 98%). Eighty-eight percent of patients had baseline Karnofsky Performance Status ≥80. Fifty-eight percent of patients had colon cancer and 40% rectal cancer. Approximately two-thirds (63%) of patients had previously failed oxaliplatin treatment.

The efficacy of ERBITUX plus irinotecan or ERBITUX monotherapy was evaluated in all randomized patients.

Analyses were also conducted in two pre-specified subpopulations: irinotecan refractory and irinotecan and oxaliplatin failures. The irinotecan refractory population was defined as randomized patients who had received at least two cycles of irinotecan-based chemotherapy prior to treatment with ERBITUX, and had independent confirmation of disease progression within 30 days of completion of the last cycle of irinotecan-based chemotherapy.

The irinotecan and oxaliplatin failure population was defined as irinotecan refractory patients who had previously been treated with and failed an oxaliplatin-containing regimen.

The objective response rates (ORR) in these populations are presented in Table 2.

Table 2 : Objective Response Rates per Independent Review

Populations	ERBITUX + Irinotecan		ERBITUX Monotherapy		Difference (95% CI[a])	
	n	ORR (%)	N	ORR (%)	%	p-value CMH[b]
All Patients	218	22.9	111	10.8	12.1 (4.1 - 20.2)	0.007
• Irinotecan-Oxaliplatin Failure	80	23.8	44	11.4	12.4 (-0.8 - 25.6)	0.09
• Irinotecan Refractory	132	25.8	69	14.5	11.3 (0.1 - 22.4)	0.07

[a]95% confidence interval for the difference in objective response rates.
[b]Cochran-Mantel-Haenszel test.

The median duration of response in the overall population was 5.7 months in the combination arm and 4.2 months in the monotherapy arm. Compared with patients randomized to ERBITUX alone, patients randomized to ERBITUX and irinotecan experienced a significantly longer median time to disease progression (see Table 3).

Table 3: Time to Progression per Independent Review

Populations	ERBITUX + Irinotecan (median)	ERBITUX Monotherapy (median)	Hazard Ratio (95% CI[a])	Log-rank p-value
All Patients	4.1 mo	1.5 mo	0.54 (0.42 – 0.71)	<0.001
• Irinotecan-Oxaliplatin Failure	2.9 mo	1.5 mo	0.48 (0.31 - 0.72)	<0.001
• Irinotecan Refractory	4.0 mo	1.5 mo	0.52 (0.37 - 0.73)	<0.001

[a]Hazard ratio of ERBITUX + irinotecan: ERBITUX monotherapy with 95% confidence interval.

Single-Arm Trials

ERBITUX, in combination with irinotecan, was also studied in a single-arm, multicenter, open-label clinical trial in 138 patients with EGFR-expressing metastatic colorectal cancer who had progressed following an irinotecan-containing regimen using the same dose and schedule of ERBITUX as in the randomized trial (above). Patients received the same dose and schedule for irinotecan as the patient had previously failed. Of 138 patients enrolled, 74 patients had documented progression to irinotecan as determined by

an IRC. The overall response rate was 15% for the overall population and 12% for the irinotecan-failure population. The median durations of response were 6.5 and 6.7 months, respectively.

ERBITUX was also studied as a single agent in a multicenter, open-label, single-arm clinical trial in patients with EGFR-expressing, metastatic colorectal cancer who progressed following an irinotecan-containing regimen. Of 57 patients enrolled, 28 patients had documented progression to irinotecan. The overall response rate was 9% for the all-treated group and 14% for the irinotecan-failure group. The median duration of response was 4.2 months for both groups.

EGFR Expression and Response

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

Patients enrolled in the colorectal cancer clinical studies were required to have immunohistochemical evidence of EGFR 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.

INDICATIONS AND USAGE

Head and Neck Cancer

ERBITUX, in combination with radiation therapy, is indicated for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck.

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.

Colorectal Cancer

ERBITUX, used in combination with irinotecan, is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy.

ERBITUX administered as a single agent is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy.

The effectiveness of ERBITUX for the treatment of EGFR-expressing, metastatic colorectal carcinoma is based on objective response rates (see **CLINICAL STUDIES**). Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with ERBITUX for the treatment of EGFR-expressing, metastatic colorectal carcinoma.

CONTRAINDICATIONS

None.

WARNINGS

Infusion Reactions (See BOXED WARNING: Infusion Reactions, ADVERSE REACTIONS: Infusion Reactions, and DOSAGE AND ADMINISTRATION: Dose Modifications.)

Severe infusion reactions occurred with the administration of ERBITUX in approximately 3% (46/1485) of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of ERBITUX despite the use of prophylactic antihistamines. These reactions were characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, hypotension, and/or cardiac arrest. Caution must be exercised with every ERBITUX infusion, as there were patients who experienced their first severe infusion reaction during later infusions. A 1-hour observation period is recommended following the ERBITUX infusion. Longer observation periods may be required in patients who experience infusion reactions.

Severe infusion reactions require the immediate interruption of ERBITUX therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

In clinical trials, mild to moderate infusion reactions were managed by slowing the infusion rate of ERBITUX and by continued use of antihistamine medications (eg, diphenhydramine) in subsequent doses (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Cardiopulmonary Arrest (See BOXED WARNING: Cardiopulmonary Arrest, PRECAUTIONS: Laboratory Tests: Electrolyte Monitoring, and ADVERSE REACTIONS: Electrolyte Depletion.)

In a randomized, controlled trial in patients with squamous cell carcinoma of the head and neck (SCCHN), cardiopulmonary arrest and/or sudden death occurred in 4/208 patients (2%) treated with radiation therapy and ERBITUX as compared to none of 212 patients treated with radiation therapy alone. 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. ERBITUX in combination with radiation therapy should be used with caution in head and neck cancer patients with a history of coronary artery disease, congestive heart failure, and arrhythmias. Although the etiology of these events is unknown, close monitoring of serum electrolytes, including serum magnesium, potassium, and calcium, during and after ERBITUX therapy is recommended.

Pulmonary Toxicity

Interstitial lung disease (ILD) was reported in 3 of 774 (<0.5%) patients with advanced colorectal cancer and in 1 of 796 patients with head and neck cancer receiving ERBITUX in clinical studies. Among these four cases, interstitial pneumonitis with non-cardiogenic pulmonary edema resulting in death was reported in one patient with colon cancer. In two of the remaining cases, the patients had pre-existing fibrotic lung disease and experienced an acute exacerbation of their disease while receiving ERBITUX in combination with irinotecan. The onset of symptoms occurred between the fourth and eleventh doses of treatment in all reported cases.

In the event of acute onset or worsening pulmonary symptoms, ERBITUX therapy should be interrupted and a prompt investigation of these symptoms should occur. If ILD is confirmed, ERBITUX should be discontinued and the patient should be treated appropriately.

Dermatologic Toxicity (See ADVERSE REACTIONS: Dermatologic Toxicity and DOSAGE AND ADMINISTRATION: Dose Modifications.)

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.

In clinical studies of ERBITUX, dermatologic toxicities, including acneform rash, skin drying and fissuring, and inflammatory and infectious sequelae (eg, blepharitis, cheilitis, cellulitis, cyst) were reported. In patients with head and neck cancer treated with ERBITUX plus radiation, acneform rash was reported in 87% as compared with 10% in patients treated with radiation therapy alone. The incidence of severe acneform rash was markedly increased in the ERBITUX plus radiation arm (17% versus 1%). In patients with head and neck cancer treated with ERBITUX monotherapy, acneform rash was reported in 76% of patients and was severe in 1%. In patients with advanced colorectal cancer, acneform rash was reported in 89% (686/774) of all treated patients, and was severe in 11% (84/774). Subsequent to the development of severe dermatologic toxicities, complications including *S. aureus* sepsis and abscesses requiring incision and drainage were reported.

Patients developing dermatologic toxicities while receiving ERBITUX should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future ERBITUX infusions should be instituted in case of severe acneform rash (see **DOSAGE AND ADMINISTRATION**, Table 6). Treatment with topical and/or oral antibiotics should be considered; topical corticosteroids are not recommended.

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, delayed, accelerated (concomitant boost) fractionation radiation therapy, and cisplatin (100 mg/m^2) conducted in patients with locally advanced squamous cell

carcinoma of the head and neck. 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 (myocardial infarction in one patient and arrhythmia, diminished cardiac output, and hypotension in the other patient).

PRECAUTIONS

General

ERBITUX therapy should be used with caution in patients with known hypersensitivity to Cetuximab, murine proteins, or any component of this product.

It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving ERBITUX as sunlight can exacerbate any skin reactions that may occur.

Use of ERBITUX in Combination with Radiation Therapy

ERBITUX plus radiation therapy should be used with caution in patients with a known history of coronary artery disease, arrhythmias and congestive heart failure. Close monitoring of serum electrolytes, including serum magnesium, potassium, and calcium, during and after ERBITUX therapy is recommended. (See **BOXED WARNING**, **WARNINGS: Cardiopulmonary Arrest**, and **PRECAUTIONS: Laboratory Tests: Electrolyte Monitoring.**)

EGF Receptor Testing

Head and Neck Cancer

Pretreatment assessment for evidence of EGFR expression is not required for patients with squamous cell carcinoma of the head and neck (SCCHN).

Colorectal Cancer

Patients enrolled in the colorectal cancer clinical studies were required to have immunohistochemical evidence of EGFR expression using the DakoCytomation EGFR pharmDx™ test kit. Assessment for EGFR expression should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. Refer to the

DakoCytomation test kit package insert for full instructions on assay performance. (See **CLINICAL STUDIES: EGFR Expression and Response**.)

Laboratory Tests: Electrolyte Monitoring

Patients should be periodically monitored for hypomagnesemia, and accompanying hypocalcemia and hypokalemia, during and following the completion of ERBITUX therapy. Monitoring should continue for a period of time commensurate with the half-life and persistence of the product; ie, 8 weeks. (See **ADVERSE REACTIONS: Electrolyte Depletion.**)

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to test Cetuximab for carcinogenic potential. No mutagenic or clastogenic potential of Cetuximab was observed in the *Salmonella-Escherichia coli* (Ames) assay or in the *in vivo* rat micronucleus test. A 39-week toxicity study in cynomolgus monkeys receiving 0.4 to 4 times the human dose of Cetuximab (based on total body surface area) revealed a tendency for impairment of menstrual cycling in treated female monkeys, including increased incidences of irregularity or absence of cycles, when compared to control animals, and beginning from week 25 of treatment and continuing through the 6-week recovery period. Serum testosterone levels and analysis of sperm counts, viability, and motility were not remarkably different between Cetuximab-treated and control male monkeys. It is not known if Cetuximab can impair fertility in humans.

Pregnancy Category C

Animal reproduction studies have not been conducted with Cetuximab. However, the EGFR has been implicated in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. In addition, human IgG1 is known to cross the placental barrier; therefore Cetuximab has the potential to be transmitted from the mother to the developing fetus. It is not known whether ERBITUX can cause fetal harm when administered to a pregnant woman or whether ERBITUX can affect reproductive capacity. There are no adequate and well-

controlled studies of ERBITUX in pregnant women. ERBITUX should only be given to a pregnant woman, or any woman not employing adequate contraception if the potential benefit justifies the potential risk to the fetus. All patients should be counseled regarding the potential risk of ERBITUX treatment to the developing fetus prior to initiation of therapy. If the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus and/or the potential risk for loss of the pregnancy.

Nursing Mothers

It is not known whether ERBITUX is secreted in human milk. Because human IgG is secreted in human milk, the potential for absorption and harm to the infant after ingestion exists. Based on the mean half-life of Cetuximab after multiple dosing of 114 hours [range 75-188 hours] (see **CLINICAL PHARMACOLOGY: Human Pharmacokinetics**), women should be advised to discontinue nursing during treatment with ERBITUX and for 60 days following the last dose of ERBITUX.

Pediatric Use

The safety and effectiveness of ERBITUX in pediatric patients have not been established.

Geriatric Use

Of the 424 patients with head and neck cancer who received ERBITUX with radiation therapy or radiation therapy alone, 110 patients were 65 years of age or older [65 (30%) in the radiation therapy alone arm, 45 (21%) in the radiation and ERBITUX arm]. In a subgroup analysis of patients less than 65 years of age, the hazard ratio of the radiation and ERBITUX arm versus radiation therapy alone arm for duration of locoregional control was 0.68 (95% confidence interval 0.50–0.93), and in patients age 65 years and older the hazard ratio was 0.87 (95% confidence interval 0.56–1.37). For overall survival, the hazard ratio in patients less than 65 years of age was 0.68 (95% confidence interval 0.49–0.94), and in patients age 65 years and older the hazard ratio was 1.15 (95% confidence interval 0.72–1.84).

Of the 774 patients who received ERBITUX with irinotecan or ERBITUX monotherapy in four advanced colorectal cancer studies, 253 patients (33%) were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

ADVERSE REACTIONS

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 adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Potential immunogenic responses to Cetuximab were assessed using either a double antigen radiometric assay or an enzyme-linked immunosorbant assay. Due to limitations in assay performance and sampling timing, the incidence of antibody development in patients receiving ERBITUX has not been adequately determined. The incidence of antibodies to Cetuximab was measured by collecting and analyzing serum pre-study, prior to selected infusions and during treatment follow-up. Patients were considered evaluable if they had a negative pre-treatment sample and a post-treatment sample. Non-neutralizing anti-Cetuximab antibodies were detected in 5% (49 of 1001) of evaluable patients. In patients positive for anti-Cetuximab antibody, the median time to onset was 44 days (range 8-281 days). Although the number of sero-positive patients is limited, there does not appear to be any relationship between the appearance of antibodies to Cetuximab and the safety or antitumor activity of ERBITUX.

The observed incidence of anti-Cetuximab antibody responses may be influenced by the low sensitivity of available assays, inadequate to reliably detect lower antibody titers. Other factors which might influence the incidence of anti-Cetuximab antibody response include sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Cetuximab with the incidence of antibodies to other products may be misleading.

Electrolyte Depletion

In 244 patients evaluated in ongoing, controlled clinical trials, the incidence of hypomagnesemia, both overall and severe (NCI-CTC Grades 3 and 4), was increased in patients receiving ERBITUX alone or in combination with chemotherapy as compared to those receiving best supportive care or chemotherapy alone. Approximately one-half of these patients receiving ERBITUX experienced hypomagnesemia and 10-15%

experienced severe hypomagnesemia. The onset of electrolyte abnormalities has been reported to occur from days to months after initiation of ERBITUX. Electrolyte repletion was necessary in some patients and in severe cases, intravenous replacement was required. The time to resolution of electrolyte abnormalities is not well known, hence monitoring during and after ERBITUX treatment is recommended. (See **PRECAUTIONS: Laboratory Tests: Electrolyte Monitoring**.)

Infusion Reactions (see BOXED WARNING: Infusion Reactions)

In clinical trials, severe, potentially fatal infusion reactions were reported. These events include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. In major clinical studies in advanced SCCHN, severe infusion reactions (Grade 3 or 4) were observed in 3% of patients receiving ERBITUX plus radiation and 4% of patients receiving ERBITUX monotherapy. In studies in advanced colorectal cancer, severe infusion reactions were observed in 3% of patients receiving ERBITUX plus irinotecan and 2% of patients receiving ERBITUX monotherapy. Grade 1 and 2 infusion reactions, including chills, fever, and dyspnea usually occurring on the first day of initial dosing, were observed in 16% of patients receiving ERBITUX plus irinotecan and 19% of patients receiving ERBITUX monotherapy. (See **WARNINGS: Infusion Reactions** and **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

In the clinical studies described above, a 20-mg test dose was administered intravenously over 10 minutes prior to the loading dose to all patients. The test dose did not reliably identify patients at risk for severe allergic reactions.

Head and Neck Cancer

Except where indicated, the data described below reflect exposure to ERBITUX in 208 patients with locally or regionally advanced SCCHN who received ERBITUX in combination with radiation and as monotherapy in 103 patients with recurrent or metastatic SCCHN. Of the 103 patients receiving ERBITUX monotherapy, 53 continued to a second phase with the combination of ERBITUX plus chemotherapy.

Patients receiving ERBITUX plus radiation therapy received a median of 8 doses (range 1-11 infusions). The population had a median age of 56; 81% were male and 84% Caucasian.

Patients receiving ERBITUX monotherapy, received a median of 11 doses (range 1–45 infusions). The population had a median age of 57; 82% were male and 100% Caucasian.

The most **serious adverse reactions** associated with ERBITUX in combination with radiation therapy in patients with head and neck cancer were:

- Infusion reaction (3%) (see **BOXED WARNINGS**, **WARNINGS**, and **DOSAGE AND ADMINISTRATION: Dose Modifications**);
- Cardiopulmonary arrest (2%) (see **BOXED WARNINGS**, **WARNINGS**);
- Dermatologic toxicity (2.5%) (see **WARNINGS** and **DOSAGE AND ADMINISTRATION: Dose Modifications**);
- Mucositis (6%);
- Radiation dermatitis (3%);
- Confusion (2%);
- Diarrhea (2%).

Fourteen (7%) patients receiving ERBITUX plus radiation therapy and 5 (5%) patients receiving ERBITUX monotherapy, discontinued treatment primarily because of adverse events.

The most common adverse events seen in 208 patients receiving ERBITUX in combination with radiation therapy were acneform rash (87%), mucositis (86%), radiation dermatitis (86%), weight loss (84%), xerostomia (72%), dysphagia (65%), asthenia (56%), nausea (49%), constipation (35%), and vomiting (29%).

The most common adverse events seen in 103 patients receiving ERBITUX monotherapy were acneform rash (76%), asthenia (45%), pain (28%), fever (27%), and weight loss (27%).

The data in Table 4 are based on the experience of 208 patients with locoregionally advanced SCCHN treated with ERBITUX plus radiation therapy compared to 212 patients treated with radiation therapy alone.

Table 4: 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				
Mucositis/Stomatitis	93	56	94	52
Xerostomia	72	5	71	3
Dysphagia	65	26	63	30
Nausea	49	2	37	2
Constipation	35	5	30	5
Vomiting	29	2	23	4
Anorexia	27	2	23	2
Diarrhea	19	2	13	1
Dyspepsia	14	0	9	1
Metabolic/Nutritional				
Weight Loss	84	11	72	7
Dehydration	25	6	19	8
Respiratory				
Pharyngitis	26	3	19	4
Cough Increased	20	<1	19	0
Skin/Appendages				
Acneform Rash[3]	87	17	10	1
Radiation Dermatitis	86	23	90	18
Application Site Reaction	18	0	12	1
Pruritus	16	0	4	0

Table 4: 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			

[1] Includes cases also reported as infusion reaction.

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

[3] Acneform rash is defined as any event described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis".

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%), brain (11% versus 9%), lung (11% versus 8%), spinal cord (4% versus 3%), and bone (4% versus 5%). The incidence of Grade 3 or 4 late radiation toxicities were generally similar between the radiation therapy alone and the ERBITUX plus radiation treatment groups.

Colorectal Cancer

Except where indicated, the data described below reflect exposure to ERBITUX in 774 patients with advanced metastatic colorectal cancer. ERBITUX was studied in combination with irinotecan (n=354) or as monotherapy (n=420). Patients receiving ERBITUX plus irinotecan received a median of 12 doses [with 88/354 (25%) treated for over 6 months], and patients receiving ERBITUX monotherapy received a median of 7 doses [with 36/420 (9%) treated for over 6 months]. The population had a median age of 59 and was 59% male and 91% Caucasian. The range of dosing for patients receiving ERBITUX plus irinotecan was 1-84 infusions, and the range of dosing for patients receiving ERBITUX monotherapy was 1-63 infusions.

The most **serious adverse reactions** associated with ERBITUX were:

- Infusion reaction (3%) (see **BOXED WARNING**, **WARNINGS**, and **DOSAGE AND ADMINISTRATION: Dose Modifications**);
- Dermatologic toxicity (1%) (see **WARNINGS** and **DOSAGE AND ADMINISTRATION: Dose Modifications**);
- Interstitial lung disease (0.4%) (see **WARNINGS**);
- Fever (5%);
- Sepsis (3%);
- Kidney failure (2%);
- Pulmonary embolus (1%);
- Dehydration (5%) in patients receiving ERBITUX plus irinotecan, 2% in patients receiving ERBITUX monotherapy;
- Diarrhea (6%) in patients receiving ERBITUX plus irinotecan, 0.2% in patients receiving ERBITUX monotherapy.

Thirty-seven (10%) patients receiving ERBITUX plus irinotecan and 17 (4%) patients receiving ERBITUX monotherapy discontinued treatment primarily because of adverse events.

The most common adverse events seen in 354 patients receiving ERBITUX plus irinotecan were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), nausea (55%), abdominal pain (45%), and vomiting (41%).

The most common adverse events seen in 420 patients receiving ERBITUX monotherapy were acneform rash (90%), asthenia/malaise (48%), nausea (29%), fever (27%), constipation (26%), abdominal pain (26%), headache (26%), and diarrhea (25%).

Data in patients with advanced colorectal carcinoma in Table 5 are based on the experience of 354 patients treated with ERBITUX plus irinotecan and 420 patients treated with ERBITUX monotherapy.

Table 5: Incidence of Adverse Events (≥10%) in Patients with Advanced Colorectal Carcinoma

Body System Preferred Term[1]	ERBITUX plus Irinotecan (n=354)		ERBITUX Monotherapy (n=420)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
	% of Patients			
Body as a Whole				
Asthenia/Malaise[2]	73	16	48	10
Abdominal Pain	45	8	26	9
Fever[3]	34	4	27	<1
Pain	23	6	17	5
Infusion Reaction[4]	19	3	21	2
Infection	16	1	14	1
Back Pain	16	3	10	2
Headache	14	2	26	2
Digestive				
Diarrhea	72	22	25	2
Nausea	55	6	29	2
Vomiting	41	7	25	3
Anorexia	36	4	23	2
Constipation	30	2	26	2
Stomatitis	26	2	10	<1
Dyspepsia	14	0	6	0
Hematic/Lymphatic				
Leukopenia	25	17	<1	0
Anemia	16	5	9	3
Metabolic/Nutritional				
Weight Loss	21	0	7	1
Peripheral Edema	16	1	10	1
Dehydration	15	6	10	3
Nervous				
Insomnia	12	0	10	<1
Depression	10	0	7	0
Respiratory				
Dyspnea[3]	23	2	17	7
Cough Increased	20	0	11	1

Table 5: Incidence of Adverse Events (≥10%) in Patients with Advanced Colorectal Carcinoma

Body System Preferred Term[1]	ERBITUX plus Irinotecan (n=354)		ERBITUX Monotherapy (n=420)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
	% of Patients			
Skin/Appendages				
Acneform Rash[5]	88	14	90	8
Alopecia	21	0	4	0
Skin Disorder	15	1	4	0
Nail Disorder	12	<1	16	<1
Pruritus	10	1	11	<1
Conjunctivitis	14	1	7	<1

[1] Adverse events that occurred (toxicity Grades 1 through 4) in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX plus irinotecan or in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX monotherapy.

[2] Asthenia/malaise is defined as any event described as “asthenia”, “malaise”, or “somnolence”.

[3] Includes cases also reported as infusion reaction.

[4] 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”.

[5] Acneform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.

Dermatologic Toxicity and Related Disorders

Non-suppurative acneform rash described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis” was observed in patients receiving ERBITUX plus radiation, ERBITUX plus irinotecan, or ERBITUX monotherapy. One or more of the dermatological adverse events were reported in 87% (17% Grade 3 or 4) of patients receiving ERBITUX plus radiation and in 76% (1% Grade 3 or 4) receiving ERBITUX monotherapy during treatment for advanced SCCHN. In studies of advanced colorectal cancer, dermatological adverse events were reported in 88% (14% Grade 3) of patients receiving ERBITUX plus irinotecan and in 90% (8% Grade 3) of patients receiving ERBITUX monotherapy. Acneform rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities and was characterized by multiple follicular- or pustular-appearing lesions. Skin drying and fissuring were common in some instances, and were associated with inflammatory and infectious

sequelae (eg, blepharitis, cellulitis, cyst). Two cases of *S. aureus* sepsis were reported. The onset of acneform rash was generally within the first two weeks of therapy. Although in a majority of the patients the event resolved following cessation of treatment, in nearly half of the cases, the event continued beyond 28 days. (See **WARNINGS: Dermatologic Toxicity** and **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

A related nail disorder, occurring in 12% of patients (0.4% Grade 3), was characterized as a paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers, with the great toes and thumbs as the most commonly affected digits.

OVERDOSAGE

Single doses of ERBITUX higher than 500 mg/m^2 have not been tested. There is no experience with overdosage in human clinical trials.

DOSAGE AND ADMINISTRATION

General

Premedication with an H_1 antagonist (eg, 50 mg of diphenhydramine IV) is recommended. Appropriate medical resources for the treatment of severe infusion reactions should be available during ERBITUX infusions. (See **WARNINGS: Infusion Reactions**.)

Squamous Cell Carcinoma of the Head and Neck

The recommended dose of ERBITUX, in combination with radiation therapy, is 400 mg/m^2 as an initial loading dose (first infusion) administered as a 120-minute IV infusion (maximum infusion rate 5 mL/min) one week prior to initiation of a course of radiation therapy. The recommended weekly maintenance dose (all other infusions) is 250 mg/m^2 infused over 60 minutes (maximum infusion rate 5 mL/min) weekly for the duration of radiation therapy (6-7 weeks). In clinical studies, Cetuximab was administered 1 hour prior to radiation therapy.

The recommended dosing regimen for single-agent ERBITUX in the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck is a 400-mg/m^2 initial dose followed by 250 mg/m^2 weekly until disease progression or unacceptable toxicity.

Colorectal Cancer

The recommended dose of ERBITUX, in combination with irinotecan, or as monotherapy, is 400 mg/m^2 as an initial loading dose (first infusion) administered as a 120-minute IV infusion (maximum infusion rate 5 mL/min). The recommended weekly maintenance dose (all other infusions) is 250 mg/m^2 infused over 60 minutes (maximum infusion rate 5 mL/min).

Dose Modifications

Infusion Reactions

If the patient experiences a mild or moderate (Grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced by 50%.

ERBITUX should be immediately and permanently discontinued in patients who experience severe (Grade 3 or 4) infusion reactions. (See **WARNINGS** and **ADVERSE REACTIONS.)**

Dermatologic Toxicity and Related Disorders

Dosage modifications for dermatologic toxicity are recommended for severe acneform rash (NCI CTC Grades 3 or 4), as specified in Table 6. ERBITUX dosage modification is not recommended for severe radiation dermatitis. (See **WARNINGS** and **ADVERSE REACTIONS**.)

Table 6: ERBITUX Dose Modification Guidelines

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		

Preparation for Administration

DO NOT ADMINISTER ERBITUX AS AN IV PUSH OR BOLUS.

ERBITUX must be administered with the use of a low protein binding 0.22-micrometer in-line filter.

ERBITUX is supplied as a 50-mL, single-use vial containing 100 mg of Cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. 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.**

PREPARE INFUSION USING APPROPRIATE ASEPTIC TECHNIQUE. ERBITUX SHOULD BE ADMINISTERED VIA INFUSION PUMP OR SYRINGE PUMP.

Infusion Pump:

- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented needle or pin may be used).
- Fill ERBITUX into a sterile evacuated container or bag such as glass containers, polyolefin bags (eg, Baxter Intravia), ethylene vinyl acetate bags (eg, Baxter Clintec), DEHP plasticized PVC bags (eg, Abbott Lifecare), or PVC bags.
- Repeat procedure until the calculated volume has been put into the container. Use a new needle for each vial.
- Administer through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
- Affix the infusion line and prime it with ERBITUX before starting the infusion.
- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.

Syringe Pump:

- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented needle or pin may be used).
- Place the syringe into the syringe driver of a syringe pump and set the rate.
- Administer through a low protein binding 0.22-micrometer in-line filter rated for syringe pump use (placed as proximal to the patient as practical).
- Connect up the infusion line and start the infusion after priming the line with ERBITUX.
- Repeat procedure until the calculated volume has been infused.

- Use a new needle and filter for each vial.
- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.

ERBITUX should be piggybacked to the patient's infusion line.

Following the ERBITUX infusion, a 1-hour observation period is recommended. Longer observation periods may be required in those who experience infusion reactions.

HOW SUPPLIED

ERBITUX® (Cetuximab) is supplied as a single-use, 50-mL vial containing 100 mg of Cetuximab as a sterile, preservative-free, injectable liquid. Each carton contains one ERBITUX vial (NDC 66733-948-23).

Stability and Storage

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° to 8° C. Discard any unused portion of the vial.

ERBITUX® is a registered trademark of ImClone Systems Incorporated.

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

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