

ERBITUX- cetuximab solution
ImClone LLC

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 use

Initial U.S. Approval: 2004

WARNING: INFUSION REACTIONS and CARDIOPULMONARY ARREST

See full prescribing information for complete boxed warning.

- ERBITUX can cause serious and fatal infusion reactions. (5.1, 6) Immediately interrupt and permanently discontinue ERBITUX for serious infusion reactions. (2.4)
- Cardiopulmonary arrest or sudden death occurred in patients with squamous cell carcinoma of the head and neck receiving ERBITUX with radiation therapy or with a cetuximab product with platinum-based therapy and fluorouracil. Monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after ERBITUX administration. (5.2, 5.6)

RECENT MAJOR CHANGES

Dosage and Administration,

Dosage Modifications for Adverse Reactions (2.4)

6/2018

Warnings and Precautions, Infusion Reactions (5.1)

6/2018

Warnings and Precautions, Embryo-Fetal Toxicity (5.8)

5/2018

INDICATIONS AND USAGE

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

Head and Neck Cancer

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

Colorectal Cancer

K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer as determined by an FDA-approved test

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

Limitations of Use: ERBITUX is not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown. (5.7)

DOSAGE AND ADMINISTRATION

- Premedicate with an H₁ receptor 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, 2.4)
- Initiate ERBITUX one week prior to initiation of radiation therapy. Complete ERBITUX administration 1 hour prior to irinotecan, platinum-based therapy with fluorouracil or FOLFIRI. (2.1, 2.2)

DOSAGE FORMS AND STRENGTHS

- Injection: 100 mg/50 mL (2 mg/mL) or 200 mg/100 mL (2 mg/mL) in a single-dose vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Infusion Reactions: Monitor patients following infusion. Immediately stop and permanently discontinue ERBITUX for serious infusion reactions. (2.4, 5.1)
- Cardiopulmonary Arrest: Monitor serum electrolytes during and after ERBITUX. (5.2, 5.6)
- Pulmonary Toxicity: Interrupt or permanently discontinue for acute onset or worsening of pulmonary symptoms. (2.4, 5.3)
- Dermatologic Toxicity: Monitor for dermatologic toxicities or infectious sequelae. Limit sun exposure. (2.4, 5.4)
- Hypomagnesemia and Accompanying Electrolyte Abnormalities: Monitor during treatment and for at least 8 weeks following the completion. Replete electrolytes as necessary. (5.6)
- Increased tumor progression, increased mortality, or lack of benefit observed in patients with Ras-mutant mCRC. (5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of potential risk to the fetus and to use effective contraception. (5.8, 8.1, 8.3)

----- **ADVERSE REACTIONS** -----

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

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: INFUSION REACTIONS and CARDIOPULMONARY ARREST

1 INDICATIONS AND USAGE

- 1.1 Squamous Cell Carcinoma of the Head and Neck (SCCHN)
- 1.2 K-Ras Wild-type, EGFR-expressing Colorectal Cancer (CRC)

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosage for Squamous Cell Carcinoma of the Head and Neck (SCCHN)
- 2.2 Recommended Dosage for Colorectal Cancer (CRC)
- 2.3 Premedication
- 2.4 Dosage Modifications for Adverse Reactions
- 2.5 Preparation for Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Infusion Reactions
- 5.2 Cardiopulmonary Arrest
- 5.3 Pulmonary Toxicity
- 5.4 Dermatologic Toxicity
- 5.5 Risks Associated with Use in Combination with Radiation and Cisplatin
- 5.6 Hypomagnesemia and Accompanying Electrolyte Abnormalities
- 5.7 Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with Ras-Mutant mCRC
- 5.8 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS

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

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation

8.3 Females and Males of Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

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

14.2 K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (CRC)

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

WARNING: INFUSION REACTIONS and CARDIOPULMONARY ARREST

Infusion Reactions: ERBITUX can cause serious and fatal infusion reactions [see *Warnings and Precautions (5.1), Adverse Reactions (6)*]. Immediately interrupt and permanently discontinue ERBITUX for serious infusion reactions [see *Dosage and Administration (2.4)*].

Cardiopulmonary Arrest: Cardiopulmonary arrest or sudden death occurred in patients with squamous cell carcinoma of the head and neck receiving ERBITUX with radiation therapy or a cetuximab product with platinum-based therapy and fluorouracil. Monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after ERBITUX administration [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 (SCCHN).
- in combination with platinum-based therapy with fluorouracil for the first-line treatment of patients with recurrent locoregional disease or metastatic SCCHN.
- as a single agent for the treatment of patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed.

1.2 K-Ras Wild-type, EGFR-expressing Colorectal Cancer (CRC)

ERBITUX is indicated for the treatment of K-Ras wild-type, epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC) as determined by an FDA-approved test [see *Dosage and Administration (2.2)*]:

- in combination with FOLFIRI (irinotecan, fluorouracil, leucovorin) for first-line treatment,
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who

are intolerant to irinotecan.

Limitations of Use: ERBITUX is not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown [see *Warnings and Precautions (5.7)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Squamous Cell Carcinoma of the Head and Neck (SCCHN)

In combination with radiation therapy or platinum-based therapy and fluorouracil

- The recommended initial dose is 400 mg/m² administered one week prior to initiating a course of radiation therapy or on the first day of platinum-based therapy and fluorouracil as a 120-minute intravenous infusion.
- The recommended subsequent dosage (all other infusions) is 250 mg/m² weekly as a 60-minute infusion for the duration of radiation therapy (6–7 weeks) or until disease progression or unacceptable toxicity when administered in combination with platinum-based therapy and fluorouracil.
- Complete ERBITUX administration 1 hour prior to radiation therapy or platinum-based therapy with fluorouracil.

Monotherapy

- The recommended initial dose is 400 mg/m² administered as a 120-minute intravenous infusion.
- The recommended subsequent dosage (all other infusions) is 250 mg/m² weekly as a 60-minute infusion until disease progression or unacceptable toxicity.

2.2 Recommended Dosage for Colorectal Cancer (CRC)

Determine EGFR-expression status using FDA-approved tests prior to initiating treatment. Also confirm the absence of a Ras mutation prior to initiation of treatment with ERBITUX. Information on FDA-approved tests for the detection of K-Ras mutations in patients with metastatic CRC is available at: <http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm301431.htm>.

- The recommended initial dose, either as monotherapy or in combination with irinotecan or FOLFIRI (irinotecan, fluorouracil, leucovorin), is 400 mg/m² administered as a 120-minute intravenous infusion.
- The recommended subsequent dosage, either as monotherapy or in combination with irinotecan or FOLFIRI, is 250 mg/m² weekly as a 60-minute infusion until disease progression or unacceptable toxicity.
- Complete ERBITUX administration 1 hour prior to irinotecan or FOLFIRI.

2.3 Premedication

Premedicate with a histamine-1 (H₁) receptor antagonist intravenously 30–60 minutes prior to the first dose or subsequent doses as deemed necessary [see *Warnings and Precautions (5.1)*].

2.4 Dosage Modifications for Adverse Reactions

Reduce, delay, or discontinue ERBITUX to manage adverse reactions as described in Table 1.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity ^a	Dosage Modification
Infusion reactions [see <i>Warnings and Precautions (5.1)</i>]	Grade 1 or 2	Reduce the infusion rate by 50%.
	Grade 3 or 4	Immediately and permanently, discontinue ERBITUX.
		Delay infusion 1 to 2 weeks; if

Dermatologic toxicities and infectious sequelae (e.g., acneiform rash, mucocutaneous disease) [see Warnings and Precautions (5.4)]	1 st occurrence; Grade 3 or 4	condition improves, continue at 250 mg/m ² . If no improvement, discontinue ERBITUX.
	2 nd occurrence; Grade 3 or 4	Delay infusion 1 to 2 weeks; if condition improves, continue at 200 mg/m ² . If no improvement, discontinue ERBITUX.
	3 rd occurrence; Grade 3 or 4	Delay infusion 1 to 2 weeks; if condition improves, continue at 150 mg/m ² . If no improvement, discontinue ERBITUX.
	4 th occurrence; Grade 3 or 4	Discontinue ERBITUX.
Pulmonary toxicity [see Warnings and Precautions (5.3)]	Acute onset or worsening pulmonary symptoms	Delay infusion 1 to 2 weeks; if condition improves, continue at the dose that was being administered at the time of occurrence. If no improvement in 2 weeks or interstitial lung disease (ILD) is confirmed, discontinue ERBITUX.

^a National Cancer Institute (NCI) Common Toxicity Criteria (CTC), version 2.0.

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

Injection: 100 mg/50 mL (2 mg/mL) or 200 mg/100 mL (2 mg/mL) as a clear, colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

ERBITUX can cause serious and fatal infusion reactions. Infusion reactions of any grade occurred in 8.4% of 1373 patients who received ERBITUX across clinical trials. Severe (Grades 3 and 4) infusion reactions occurred in 2.2% of patients [see Adverse Reactions (6.1)]. Signs and symptoms included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest.

[The risk of anaphylactic reactions may be increased in patients with a history of tick bites, red meat

allergy, or in the presence of IgE antibodies directed against galactose- α -1,3-galactose (alpha-gal).

Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines. Infusion reactions may occur during or several hours following completion of the infusion.

Premedicate with a histamine-1(H₁) receptor antagonist as recommended [see *Dosage and Administration (2.3)*]. Monitor patients for at least 1 hour following each ERBITUX infusion, in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis. In patients requiring treatment for infusion reactions, monitor for more than 1 hour to confirm resolution of the reaction. Interrupt the infusion and upon recovery, resume the infusion at a slower rate or permanently discontinue ERBITUX based on severity [see *Dosage and Administration (2.4)*].

5.2 Cardiopulmonary Arrest

ERBITUX can cause cardiopulmonary arrest. Cardiopulmonary arrest or sudden death occurred in 2% of 208 patients treated with radiation therapy and ERBITUX in BONNER. 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 EXTREME, fatal cardiac disorders and/or sudden death occurred in 3% of 219 patients treated with a cetuximab product in combination with platinum-based therapy and fluorouracil.

Carefully consider use of ERBITUX with radiation therapy or platinum-based therapy with fluorouracil in patients with SCCHN with a history of coronary artery disease, congestive heart failure, or arrhythmias. Monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after ERBITUX [see *Warnings and Precautions (5.6)*].

5.3 Pulmonary Toxicity

ERBITUX can cause interstitial lung disease (ILD). ILD, including 1 fatality, occurred in <0.5% of 1570 patients receiving ERBITUX in clinical trials.

Monitor patients for signs and symptoms of pulmonary toxicity. Interrupt or permanently discontinue ERBITUX for acute onset or worsening of pulmonary symptoms. Permanently discontinue ERBITUX for confirmed ILD [see *Dosage and Administration (2.4)*].

5.4 Dermatologic Toxicity

ERBITUX can cause dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychia inflammation, infectious sequelae (for example, *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis.

Acneiform rash occurred in 82% of the 1373 patients who received ERBITUX across clinical trials. Severe (Grades 3 or 4) acneiform rash occurred in 9.7% of patients [see *Adverse Reactions (6.1)*]. Acneiform rash usually developed within the first two weeks of therapy; the rash lasted more than 28 days after stopping ERBITUX in most patients.

Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing, has been observed in patients who received ERBITUX. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (e.g., Stevens-Johnson syndrome or toxic epidermal necrolysis).

Monitor patients receiving ERBITUX for dermatologic toxicities and infectious sequelae. Instruct patients to limit sun exposure during ERBITUX therapy. Withhold, reduce dose or permanently discontinue ERBITUX based on severity of acneiform rash or mucocutaneous disease [see *Dosage and*

Administration (2.4)].

5.5 Risks Associated with Use in Combination with Radiation and Cisplatin

In a controlled study, 940 patients with locally advanced SCCHN were randomized 1:1 to receive either ERBITUX in combination with radiation therapy and cisplatin or radiation therapy and cisplatin alone. The addition of ERBITUX resulted in an increase in the incidence of Grade 3 and 4 mucositis, radiation recall syndrome, acneiform rash, cardiac events, and electrolyte disturbances compared to radiation and cisplatin alone. Adverse reactions with fatal outcome were reported in 4% of patients in the ERBITUX combination arm and 3% in the control arm. In the ERBITUX arm, 2% experienced myocardial ischemia compared to 0.9% in the control arm. The main efficacy outcome of the study was progression-free survival (PFS). The addition of ERBITUX to radiation and cisplatin did not improve PFS. ERBITUX is not indicated for the treatment of SCCHN in combination with radiation and cisplatin.

5.6 Hypomagnesemia and Accompanying Electrolyte Abnormalities

ERBITUX can cause hypomagnesemia. Hypomagnesemia occurred in 55% of 365 patients receiving ERBITUX in Study CA225-025 and two other clinical trials in patients with colorectal cancer (CRC) or head and neck cancer, including Grades 3 and 4 in 6% to 17%.

In EXTREME, where a cetuximab product was administered in combination with platinum-based therapy, the addition of cetuximab to cisplatin and fluorouracil resulted in an increased incidence of hypomagnesemia of any grade (14%) and of Grade 3 or 4 hypomagnesemia (7%). Hypomagnesemia of any grade occurred in 4% of patients who received cetuximab, carboplatin, and fluorouracil. No patient experienced Grade 3 or 4 hypomagnesemia [*see Adverse Reactions (6.1)*].

Hypomagnesemia and accompanying electrolyte abnormalities can occur days to months after initiating ERBITUX. Monitor patients weekly during treatment for hypomagnesemia, hypocalcemia, and hypokalemia, and for at least 8 weeks following the completion of ERBITUX. Replete electrolytes as necessary.

5.7 Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with Ras-Mutant mCRC

ERBITUX is not indicated for the treatment of patients with CRC that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either K-Ras or N-Ras and hereafter is referred to as “Ras” or when the Ras status is unknown.

Retrospective subset analyses of Ras-mutant and wild-type populations across several randomized clinical trials, including CRYSTAL, were conducted to investigate the role of Ras mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies. Use of cetuximab in patients with Ras mutations resulted in no clinical benefit with treatment related toxicity. Confirm Ras mutation status in tumor specimens prior to initiating ERBITUX [*see Indications and Usage (1.2)*].

5.8 Embryo-Fetal Toxicity

Based on animal data and its mechanism of action, ERBITUX can cause fetal harm when administered to a pregnant woman. There are no available data for ERBITUX exposure in pregnant women. In an animal reproduction study, intravenous administration of cetuximab once weekly to pregnant cynomolgus monkeys during the period of organogenesis resulted in an increased incidence of embryoletality and abortion. Disruption or depletion of EGFR in animal models results in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ERBITUX and for 2 months after the last dose of ERBITUX [*see Use in Specific Populations (8.1, 8.3)*].

6 ADVERSE REACTIONS

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

- Infusion reactions [see Warnings and Precautions (5.1)].
- Cardiopulmonary arrest [see 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)].

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 described in Warnings and Precautions reflect exposure to ERBITUX in 1373 patients with SCCHN or CRC enrolled in clinical trials and treated at the recommended dosage for a median of 7 to 14 weeks [see Clinical Studies (14)].

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

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

In Combination with Radiation Therapy

The safety of ERBITUX in combination with radiation therapy compared to radiation therapy alone was evaluated in BONNER. The data described below reflect exposure to ERBITUX in 420 patients with locally or regionally advanced SCCHN. ERBITUX was administered at the recommended dosage (400 mg/m² initial dose, followed by 250 mg/m² weekly). Patients received a median of 8 infusions (range 1 to 11) [see Clinical Studies (14.1)].

Table 2 provides the frequency and severity of adverse reactions in BONNER.

Table 2: Selected Adverse Reactions in $\geq 10\%$ of Patients with Locoregionally Advanced SCCHN (BONNER)^a

Adverse Reaction	ERBITUX with Radiation (n=208)		Radiation Therapy Alone (n=212)	
	Grades 1–4 ^b	Grades 3 and 4	Grades 1–4	Grades 3 and 4
General				
Asthenia	56	4	49	5
Fever ^c	29	1	13	1
Headache	19	<1	8	<1
Chills ^c	16	0	5	0
Infusion Reaction ^d	15	3	2	0
Infection	13	1	9	1
Gastrointestinal				
Nausea	49	2	37	2
Emesis	29	2	23	4
Diarrhea	19	2	13	1
Dyspepsia	14	0	9	1
Metabolism and Nutrition				
Weight Loss	84	11	72	7
Dehydration	25	6	19	8
Increased Alanine				

Transaminase ^e	43	2	21	1
Increased Aspartate Transaminase ^e	38	1	24	1
Increased Alkaline Phosphatase ^e	33	<1	24	0
Respiratory				
Pharyngitis	26	3	19	4
Dermatologic				
Acneiform Rash ^f	87	17	10	1
Radiation Dermatitis	86	23	90	18
Application Site Reaction	18	0	12	1
Pruritus	16	0	4	0

^a Adverse reactions occurring in $\geq 10\%$ of patients in the ERBITUX combination arm and at a higher incidence ($\geq 5\%$) compared to the radiation alone arm.

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

^c Includes cases also reported as infusion reaction.

^d Infusion reaction 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”.

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

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

The overall incidence of late radiation toxicities (any grade) was higher for patients receiving 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 with radiation treatment groups.

In Combination with Platinum-based Therapy and Fluorouracil

The safety of a cetuximab product in combination with platinum-based therapy and fluorouracil or platinum-based therapy and fluorouracil alone was evaluated in EXTREME. The data described below reflect exposure to a cetuximab product in 434 patients with recurrent locoregional disease or metastatic SCCHN. Because ERBITUX provides approximately 22% higher exposure relative to the cetuximab product, the data provided below may underestimate the incidence and severity of adverse reactions anticipated with ERBITUX for this indication; however, the tolerability of the recommended dose is supported by safety data from additional studies of ERBITUX [see *Clinical Pharmacology (12.3)*]. Cetuximab was administered intravenously at a dosage of 400 mg/m² for the initial dose, followed by 250 mg/m² weekly. Patients received a median of 17 infusions (range 1 to 89) [see *Clinical Studies (14.1)*].

Table 3 provides the frequency and severity of adverse reactions in EXTREME.

Table 3: Selected Adverse Reactions in $\geq 10\%$ of Patients with Recurrent Locoregional Disease or Metastatic SCCHN (EXTREME)^a

Adverse Reaction	Cetuximab with Platinum-based Therapy and fluorouracil (n=219)		Platinum-based Therapy and fluorouracil Alone (n=215)	
	Grades	Grades	Grades	Grades

	1–4 ^b	3 and 4	1–4	3 and 4
Eye				
Conjunctivitis	10	0	0	0
Gas trointes tinal				
Nausea	54	4	47	4
Diarrhea	26	5	16	1
General and Administration Site				
Pyrexia	22	0	13	1
Infusion Reaction ^c	10	2	<1	0
Infections				
Infection ^d	44	11	27	8
Metabolism and Nutrition				
Anorexia	25	5	14	1
Hypocalcemia	12	4	5	1
Hypokalemia	12	7	7	5
Hypomagnesemia	11	5	5	1
Dermatologic				
Acneiform Rash ^e	70	9	2	0
Rash	28	5	2	0
Acne	22	2	0	0
Dermatitis Acneiform	15	2	0	0
Dry Skin	14	0	<1	0
Alopecia	12	0	7	0

^a Adverse reactions occurring in ≥10% of patients in the cetuximab combination arm and at a higher incidence (≥5%) compared to the platinum-based therapy and fluorouracil alone arm.

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

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

^d Infection excludes sepsis-related events which are presented separately.

^e Acneiform rash defined as “acne”, “dermatitis acneiform”, “dry skin”, “exfoliative rash”, “rash”, “rash erythematous”, “rash macular”, “rash papular”, or “rash pustular”.

Chemotherapy = cisplatin and fluorouracil or carboplatin and fluorouracil

For cardiac disorders, approximately 9% of patients in both treatment arms in EXTREME experienced a cardiac event. The majority of these events occurred in patients who received cisplatin and fluorouracil with or without cetuximab. Cardiac disorders were observed in 11% and 12% of patients who received cisplatin and fluorouracil with or without cetuximab, respectively, and 6% and 4% in patients who received carboplatin and fluorouracil with or without cetuximab, respectively. In both arms, the incidence of cardiovascular events was higher in the cisplatin and fluorouracil containing subgroup. Death attributed to cardiovascular events or sudden death was reported in 3% of the patients in the cetuximab with platinum-based therapy and fluorouracil arm and in 2% of the patients in the platinum-based therapy and fluorouracil alone arm.

K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (mCRC)

In Combination with FOLFIRI

The safety of a cetuximab product in combination with FOLFIRI or FOLFIRI alone was evaluated in CRYSTAL. The data described below reflect exposure to a cetuximab product in 667 patients with K-Ras wild-type, EGFR-expressing, mCRC. ERBITUX provides approximately 22% higher exposure compared to this product; however, the safety data from CRYSTAL is consistent in incidence and severity of adverse reactions with those seen for ERBITUX in this indication. Cetuximab was

administered intravenously at a dosage of 400 mg/m² initial dose, followed by 250 mg/m² weekly. Patients received a median of 24 infusions (range 1 to 224) [see *Clinical Studies (14.2)*].

Serious adverse reactions included pulmonary embolism, which was reported in 4.4% of patients treated with cetuximab with FOLFIRI as compared to 3.4% of patients treated with FOLFIRI alone.

Table 4 provides the frequency and severity of adverse reactions in CRYSTAL.

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

Adverse Reaction	Cetuximab with FOLFIRI (n=317)		FOLFIRI Alone (n=350)	
	Grades 1–4 ^b	Grades 3 and 4	Grades 1–4	Grades 3 and 4
Hematologic				
Neutropenia	49	31	42	24
Eye				
Conjunctivitis	18	<1	3	0
Gas trointes tinal				
Diarrhea	66	16	60	10
Stomatitis	31	3	19	1
Dyspepsia	16	0	9	0
General and Administration Site				
Pyrexia	26	1	14	1
Weight Decreased	15	1	9	1
Infusion Reaction ^c	14	2	<1	0
Infections				
Paronychia	20	4	<1	0
Metabolism and Nutrition				
Anorexia	30	3	23	2
Dermatologic				
Acne-like Rash ^d	86	18	13	<1
Rash	44	9	4	0
Dermatitis Acneiform	26	5	<1	0
Dry Skin	22	0	4	0
Acne	14	2	0	0
Pruritus	14	0	3	0
Palmar-plantar Erythrodysesthesia Syndrome	19	4	4	<1
Skin Fissures	19	2	1	0

^a Adverse reactions occurring in ≥10% of patients in the cetuximab combination arm and at a higher incidence (≥5%) compared to the FOLFIRI alone arm.

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

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

angina”, “shock”, “sudden death”, “syncope”, or “systolic hypertension”.

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

As Monotherapy

The safety of ERBITUX with best supportive care (BSC) or BSC alone was evaluated in Study CA225-025. The data described below reflect exposure to ERBITUX in 242 patients with K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer (mCRC) [see Warnings and Precautions (5.8)].

ERBITUX was administered intravenously at the recommended dosage (400 mg/m² initial dose, followed by 250 mg/m² weekly). Patients received a median of 17 infusions (range 1 to 51) [see Clinical Studies (14.2)].

Table 5 provides the frequency and severity of adverse reactions in Study CA225-025.

Table 5: Selected Adverse Reactions in ≥10% of Patients with K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer Treated with ERBITUX Monotherapy (Study CA225-025)^a

Adverse Reaction	ERBITUX with BSC (n=118)		BSC alone (n=124)	
	Grades 1–4 ^b	Grades 3 and 4	Grades 1–4	Grades 3 and 4
Dermatologic				
Rash/Desquamation	95	16	21	1
Dry Skin	57	0	15	0
Pruritus	47	2	11	0
Other-Dermatology	35	0	7	2
Nail Changes	31	0	4	0
General				
Fatigue	91	31	79	29
Fever	25	3	16	0
Infusion Reactions ^c	18	3	0	0
Rigors, Chills	16	1	3	0
Pain				
Pain-Other	59	18	37	10
Headache	38	2	11	0
Bone Pain	15	4	8	2
Pulmonary				
Dyspnea	49	16	44	13
Cough	30	2	19	2
Gastrointestinal				
Nausea	64	6	50	6
Constipation	53	3	38	3
Diarrhea	42	2	23	2
Vomiting	40	5	26	5
Stomatitis	32	1	10	0
Other	22	12	16	5

Dehydration	13	5	3	0
Mouth Dryness	12	0	6	0
Taste Disturbance	10	0	5	0
Infection				
Infection without neutropenia	38	11	19	5
Musculoskeletal				
Arthralgia	14	3	6	0
Neurological				
Neuropathy-sensory	45	1	38	2
Insomnia	27	0	13	0
Confusion	18	6	10	2
Anxiety	14	1	5	1
Depression	14	0	5	0

^a Adverse reactions occurring in $\geq 10\%$ of patients in the ERBITUX with BSC arm and at a higher incidence ($\geq 5\%$) compared to the BSC alone arm.

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

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

In Combination with Irinotecan

ERBITUX at the recommended dosage was administered in combination with irinotecan in 354 patients with EGFR-expressing recurrent mCRC in Study CP02-9923 and BOND.

The most common adverse reactions were acneiform rash (88%), asthenia/malaise (73%), diarrhea (72%), and nausea (55%). The most common Grades 3–4 adverse reactions included diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneiform rash (14%).

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection 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 cetuximab in the studies below with the incidence of antibodies to cetuximab in other studies or to other products may be misleading.

An ELISA methodology was used to characterize the incidence of anti-cetuximab antibodies. The incidence of anti-cetuximab binding antibodies in 105 patients (from studies I4E-MC-JXBA, I4E-MC-JXBB, and I4E-MC-JXBD) with at least one post-baseline blood sample (≥ 4 weeks post first ERBITUX administration) was $< 5\%$.

6.3 Postmarketing Experience

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

- *Neurologic*: Aseptic meningitis
- *Gastrointestinal*: Mucosal inflammation
- *Dermatologic*: Stevens-Johnson syndrome, toxic epidermal necrolysis, life-threatening and fatal bullous mucocutaneous disease

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action [see *Clinical Pharmacology (12.1)*], ERBITUX can cause fetal harm when administered to a pregnant woman. There are no available data for ERBITUX exposure in pregnant women. In an animal reproduction study, intravenous administration of cetuximab once weekly to pregnant cynomolgus monkeys during the period of organogenesis resulted in an increased incidence of embryoletality and abortion. Disruption or depletion of EGFR in animal models results in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development (see *Data*). Human IgG is known to cross the placental barrier; therefore, cetuximab may be transmitted from the mother to the developing fetus. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20% respectively.

Data

Animal Data

Pregnant cynomolgus monkeys were administered cetuximab intravenously once weekly during the period of organogenesis (gestation day [GD] 20-48) at dose levels 0.4 to 4 times the recommended dose of ERBITUX based on body surface area (BSA). Cetuximab was detected in the amniotic fluid and in the serum of embryos from treated dams on GD 49. While no fetal malformations occurred in offspring, there was an increased incidence of embryoletality and abortions at doses approximately 1 to 4 times the recommended dose of ERBITUX based on BSA.

In mice, EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/postnatal survival and development. Reduction or elimination of embryo-fetal or maternal EGFR signaling can prevent implantation, can cause embryo-fetal loss during various stages of gestation (through effects on placental development), and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos/neonates of mice with disrupted EGFR signaling.

8.2 Lactation

Risk Summary

There is no information regarding the presence of ERBITUX in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG antibodies can be excreted in human milk. Due to the potential for serious adverse reactions in breastfed infants from ERBITUX, advise women not to breastfeed during treatment with ERBITUX and for 2 months after the last dose of ERBITUX.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating ERBITUX [see *Use in Specific Population (8.1)*].

Contraception

Based on its mechanism of action, ERBITUX can cause harm to the fetus when administered to a pregnant woman [see *Use in Specific Populations (8.1)*].

Females

Advise females of reproductive potential to use effective contraception during treatment with ERBITUX and for 2 months after the last dose of ERBITUX.

Infertility

Females

Based on animal studies, ERBITUX may impair fertility in females of reproductive potential [see *Nonclinical Toxicology (13.1)*].

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 pharmacokinetics of cetuximab between the two age groups were similar following a single dose of 75 mg/m² and 150 mg/m². The volume of the distribution appears to be independent of dose and approximates the vascular space of 2 L/m² to 3 L/m². Following a single dose of 250 mg/m², the mean AUC_{0-inf} (CV%) was 17.7 mg*h/mL (34%) in the younger age group (1–12 years, n=9) and 13.4 mg*h/mL (38%) in the adolescent group (13–18 years, n=6). The mean half-life of cetuximab was 110 hours (69 to 188 hours) in the younger group and 82 hours (55 to 117 hours) in the adolescent group.

8.5 Geriatric Use

Of the 1662 patients with advanced colorectal cancer who received ERBITUX with irinotecan, with FOLFIRI or as monotherapy in six studies (BOND, IMCL-CP02-9923, IMCL-CP02-0141, IMCL-CP02-0144, CA225-025 and CRYSTAL), 35% of 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.

11 DESCRIPTION

Cetuximab is an epidermal growth factor receptor (EGFR) antagonist. It 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 (cetuximab) injection for intravenous use, is a sterile, preservative-free, clear, colorless solution, which may contain a small amount of visible, white, amorphous cetuximab particulates in a single-dose vial. Each 1 mL of solution contains 2 mg of cetuximab, sodium chloride (8.48 mg), sodium phosphate dibasic heptahydrate (1.88 mg), sodium phosphate monobasic monohydrate (0.41 mg), and Water for Injection, USP at pH of 7.0 to 7.4.

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- α . *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 Ras proteins, but in cells with activating Ras somatic mutations, the resulting mutant Ras proteins are continuously active regardless 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 L/h/m² to 0.02 L/h/m² as the dose increased from 20 mg/m² to 200 mg/m² and plateaued at doses >200 mg/m².

The systemic exposure of cetuximab after ERBITUX administration was 22% (90% CI: 6%, 38%) higher than that of another cetuximab product used in EXTREME and CRYSTAL.

Distribution

The volume of the distribution for cetuximab appeared to be independent of dose and approximated the vascular space of 2–3 L/m².

Elimination

Following the recommended dosage (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 μ g/mL to 235 μ g/mL and 41 μ g/mL to 85 μ g/mL, respectively. The mean half-life of cetuximab was approximately 112 hours (63 to 230 hours).

Specific Population

Age, sex, race, hepatic and renal function had no clinically significant effect on the pharmacokinetics of cetuximab. Clearance of cetuximab increased 1.8-fold as body surface area increased from 1.3 m² to 2.3 m², which is consistent with the recommended dosing of cetuximab on mg/m² basis.

Drug Interaction Studies

No pharmacokinetic interaction was observed between cetuximab and irinotecan, cetuximab and cisplatin, and cetuximab and carboplatin.

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 recommended dose of ERBITUX (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 on week 25 and continued through the 6-week recovery period. No effects of cetuximab were observed on measured male fertility parameters (i.e., serum testosterone levels and analysis of sperm counts, viability, and motility) as compared to control male monkeys.

14 CLINICAL STUDIES

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

In Combination with Radiation Therapy

BONNER (NCT00004227) 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 in combination with 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 intravenously as a 400 mg/m² initial dose beginning one week prior to initiation of radiation therapy, followed by 250 mg/m² weekly administered 1 hour prior to radiation therapy for the duration of radiation therapy (6–7 weeks). The main efficacy outcome measure was duration of locoregional control. Another outcome measure was overall survival (OS).

Of the 424 randomized patients, the median age was 57 years, 80% were male, 83% were White, and 90% had baseline Karnofsky performance status ≥80. There were 258 patients enrolled in U.S. 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.

Efficacy results are presented in Table 6.

Table 6: Efficacy Results in Locoregionally Advanced SCCHN in BONNER

	ERBITUX plus 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.

In Combination with Platinum-based Therapy with Fluorouracil

EXTREME (NCT00122460) was an open-label, randomized, multicenter, controlled trial of 442 patients with recurrent locoregional disease or metastatic SCCHN. Patients with no prior therapy for recurrent locoregional disease or metastatic SCCHN were randomized (1:1) to receive a cetuximab product in combination with platinum-based therapy and fluorouracil or platinum-based therapy and fluorouracil alone. Choice of cisplatin or carboplatin was at the discretion of the investigator. Stratification factors were Karnofsky performance status (<80 versus ≥80) and previous chemotherapy. Cisplatin (100 mg/m² intravenously on Day 1) or carboplatin (AUC 5 mg/mL*min intravenously on Day 1) and fluorouracil (1000 mg/m²/day intravenously on 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 intravenously at a 400 mg/m² initial dose, followed by a 250 mg/m² weekly

dose. In the absence of disease progression or unacceptable toxicity after completion of 6 planned courses of platinum-based therapy, weekly cetuximab as monotherapy could be continued until disease progression or unacceptable toxicity. If chemotherapy was delayed because of adverse reactions, weekly cetuximab was continued. If chemotherapy was discontinued for adverse reactions, weekly cetuximab as monotherapy could be continued until disease progression or unacceptable toxicity. The main efficacy outcome measure was OS. Other outcome measures were PFS and objective response rate (ORR).

Of the 442 randomized patients, the median age was 57 years, 90% were male, 98% were White, 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. Sixty-four percent of patients received cisplatin therapy and 34% received carboplatin as initial therapy. Approximately fifteen percent of the patients in the cisplatin alone arm switched to carboplatin during the treatment period.

Efficacy results are presented in Table 7 and Figure 1.

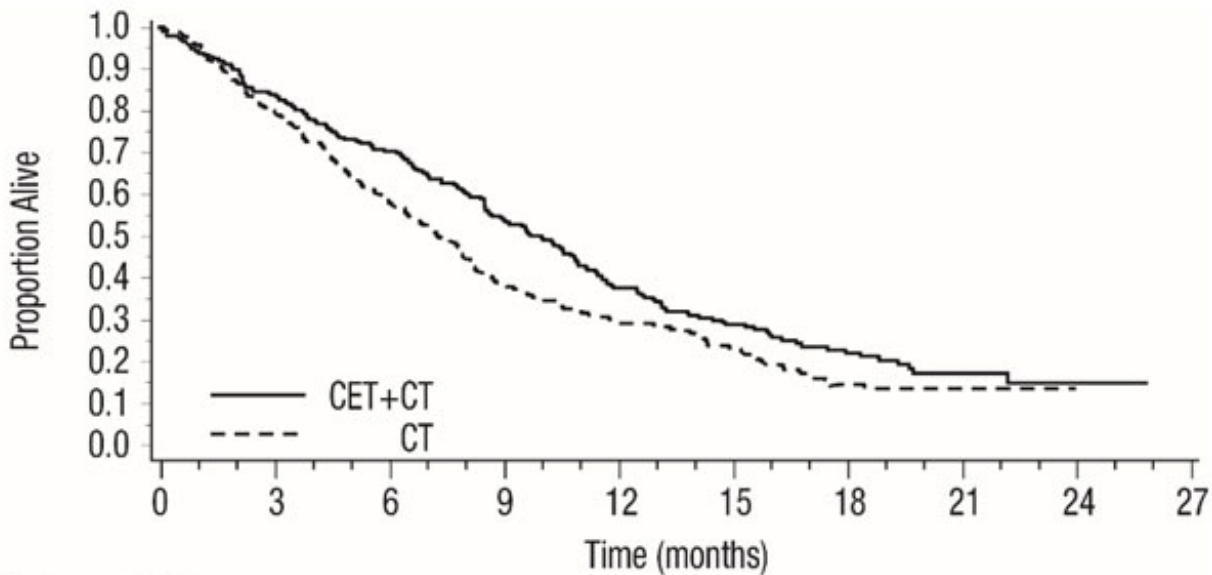
Table 7: Efficacy Results in Recurrent Locoregional Disease or Metastatic SCCHN in EXTREME

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

^a CI = confidence interval.

^b CMH = Cochran-Mantel-Haenszel.

Figure 1: Kaplan-Meier Curves for Overall Survival in Patients with Recurrent Locoregional Disease or Metastatic SCCHN in EXTREME



Patients at Risk		0	3	6	9	12	15	18	21	24	27
CET+CT	222	184	153	118	82	57	30	15	3	0	0
CT	220	173	127	83	65	47	19	8	1	0	0

CT = Platinum-based therapy with fluorouracil

CET = another cetuximab product

In exploratory subgroup analyses by initial platinum therapy (cisplatin or carboplatin), for patients (N=284) receiving cetuximab in combination with cisplatin and fluorouracil compared to cisplatin and fluorouracil alone, the difference in median OS was 3.3 months (10.6 versus 7.3 months; HR 0.71; 95% CI 0.54, 0.93). The difference in median PFS was 2.1 months (5.6 versus 3.5 months; HR 0.55; 95% CI 0.41, 0.73). The ORR was 39% and 23%, respectively (OR 2.18; 95% CI 1.29, 3.69).

For patients (N=149) receiving cetuximab in combination with carboplatin and fluorouracil compared to carboplatin and fluorouracil alone, the difference in median OS was 1.4 months (9.7 versus 8.3 months; HR 0.99; 95% CI 0.69, 1.43). The difference in median PFS was 1.7 months (4.8 versus 3.1 months, respectively; HR 0.61; 95% CI 0.42, 0.89). The ORR was 30% and 15%, respectively (OR 2.45; 95% CI 1.10, 5.46).

As Monotherapy

EMR 62202-016 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 were administered intravenously a 20-mg test dose of ERBITUX on Day 1, followed by a 400 mg/m² initial dose, and 250 mg/m² weekly until disease progression or unacceptable toxicity.

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

The ORR was 13% (95% CI 7%, 21%). Median duration of response (DoR) was 5.8 months (range 1.2 to 5.8 months).

14.2 K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (CRC)

In Combination with FOLFIRI

CRYSTAL (NCT00154102) was a randomized, open-label, multicenter, study of 1217 patients with EGFR-expressing, mCRC. Patients were randomized (1:1) to receive either a cetuximab product in combination with FOLFIRI or FOLFIRI alone as first-line treatment. Stratification factors were Eastern

Cooperative Oncology Group (ECOG) performance status (0 and 1 versus 2) and region (Western Europe versus Eastern Europe versus other).

FOLFIRI regimen included 14-day cycles of irinotecan (180 mg/m² intravenously on Day 1), folinic acid (400 mg/m² [racemic] or 200 mg/m² [L-form] intravenously on Day 1), and fluorouracil (400 mg/m² bolus on Day 1 followed by 2400 mg/m² as a 46-hour continuous infusion). Cetuximab was administered intravenously as a 400 mg/m² initial dose, followed by 250 mg/m² weekly administered 1 hour prior to chemotherapy. Study treatment continued until disease progression or unacceptable toxicity. The main efficacy outcome measure was PFS assessed by an independent review committee (IRC). Other outcome measures were OS and ORR.

Of the 1217 randomized patients, the median age was 61 years, 60% were male, 86% were White, and 96% had a baseline ECOG performance status 0–1, 60% had primary tumor localized in colon, 84% had 1–2 metastatic sites and 20% had received prior adjuvant and/or neoadjuvant chemotherapy.

Demographics and baseline characteristics were similar between study arms.

K-Ras mutation status was available for 89% of the patients: 63% had K-Ras wild-type tumors and 37% had K-Ras mutant tumors where testing assessed for the following somatic mutations in codons 12 and 13 (exon 2): G12A, G12D, G12R, G12C, G12S, G12V, G13D. Baseline characteristics and demographics in the K-Ras wild-type subset were similar to that seen in the overall population.

A statistically significant improvement in PFS was observed for the cetuximab with FOLFIRI arm compared with the FOLFIRI arm (median PFS 8.9 vs. 8.1 months, HR 0.85 [95% CI 0.74, 0.99], p-value=0.036). OS was not significantly different at the planned, final analysis based on 838 events (HR=0.93, 95% CI [0.8, 1.1], p-value 0.327).

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

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

	All Randomized		K-Ras Wild-type		K-Ras Mutant	
	Cetuximab with FOLFIRI (n=608)	FOLFIRI (n=609)	Cetuximab with FOLFIRI (n=320)	FOLFIRI (n=356)	Cetuximab with FOLFIRI (n=216)	FOLFIRI (n=187)
Progression-Free Survival						
Number of Events (%)	343 (56)	371 (61)	165 (52)	214 (60)	138 (64)	112 (60)
Median (months) (95% CI)	8.9 (8.0, 9.4)	8.1 (7.6, 8.8)	9.5 (8.9, 11.1)	8.1 (7.4, 9.2)	7.5 (6.7, 8.7)	8.2 (7.4, 9.2)
HR (95% CI)	0.85 (0.74, 0.99)		0.70 (0.57, 0.86)		1.13 (0.88, 1.46)	
p-value ^a	0.0358					
Overall Survival^b						
Number of Events (%)	491 (81)	509 (84)	244 (76)	292 (82)	189 (88)	159 (85)
Median (months) (95% CI)	19.6 (18, 21)	18.5 (17, 20)	23.5 (21, 26)	19.5 (17, 21)	16.0 (15, 18)	16.7 (15, 19)
HR (95% CI)	0.88 (0.78, 1.0)		0.80 (0.67, 0.94)		1.04 (0.84, 1.29)	

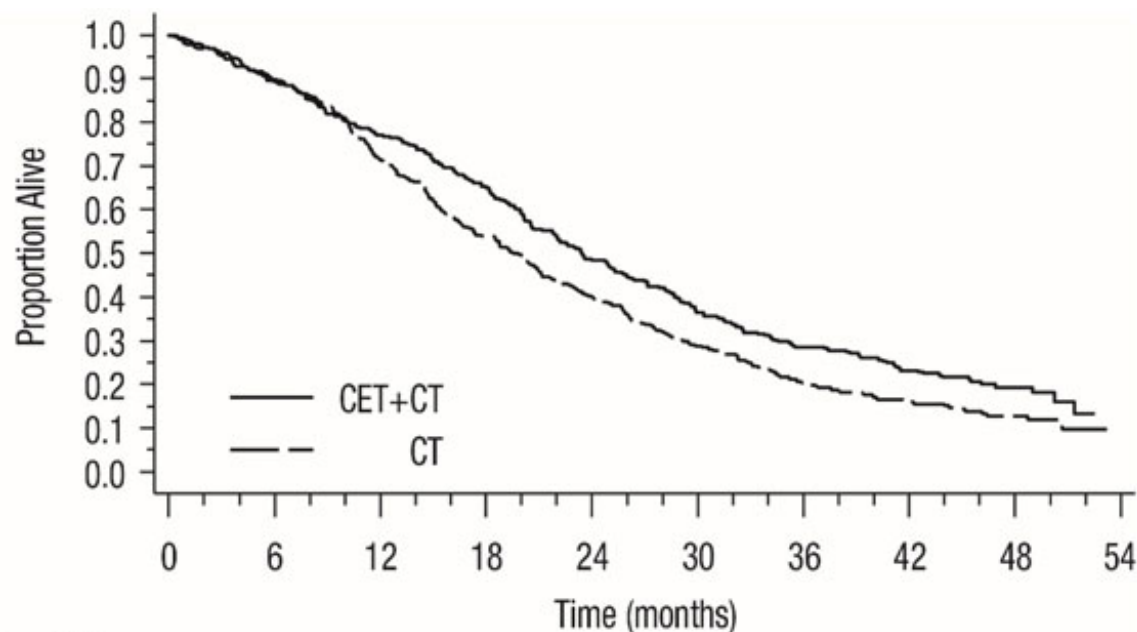
Objective Response Rate

ORR (95% CI)	46% (42, 50)	38% (34, 42)	57% (51, 62)	39% (34, 44)	31% (25, 38)	35% (28, 43)
--------------	-----------------	-----------------	-----------------	-----------------	-----------------	-----------------

^a Based on the Stratified Log-rank test.

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

Figure 2: Kaplan-Meier Curves for Overall Survival in the K-Ras Wild-type Population in CRYSTAL



Patients at Risk

CET+CT	320	282	237	198	144	108	82	65	21	4
CT	356	313	247	179	132	92	64	48	18	2

As Monotherapy

Study CA225-025 (NCT00079066) was a multicenter, open-label, randomized, clinical trial conducted in 572 patients with EGFR-expressing, previously treated, recurrent mCRC. Patients were randomized (1:1) to receive either ERBITUX with best supportive care (BSC) or BSC alone. ERBITUX was administered intravenously as a 400 mg/m² initial dose, followed by 250 mg/m² weekly until disease progression or unacceptable toxicity. The main efficacy outcome measure was OS.

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

K-Ras status was available for 79% of the patients: 54% had K-Ras wild-type tumors and 46% had K-Ras mutant tumors where testing assessed for the following somatic mutations in codons 12 and 13 (exon 2): G12A, G12D, G12R, G12C, G12S, G12V, G13D.

Efficacy results are presented in Table 9 and Figure 3.

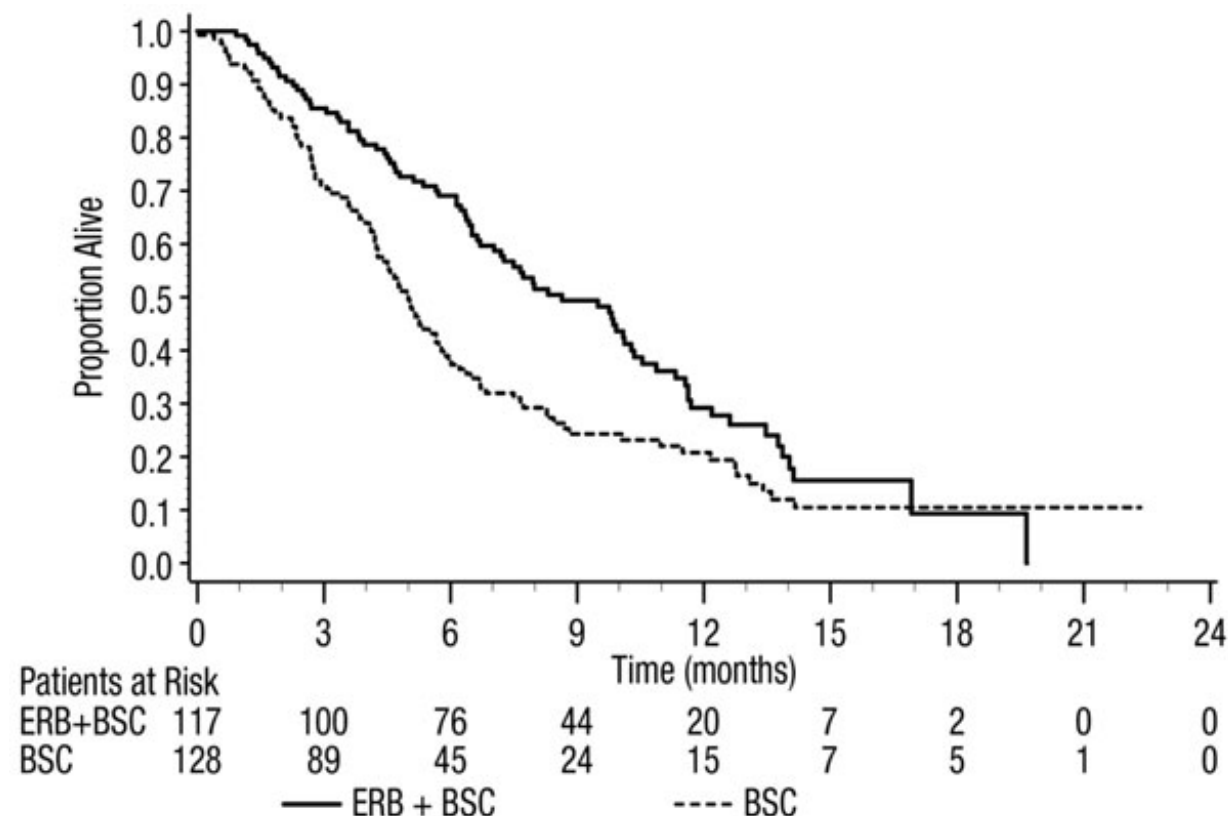
Table 9: Overall Survival in Previously Treated EGFR-expressing, Metastatic Colorectal Cancer in Study CA225-025 (All Randomized and K-Ras Status)

	All Randomized		K-Ras Wild-type		K-Ras Mutant	
	ERBITUX		ERBITUX		ERBITUX	

	with BSC (N=287)	BSC (N=285)	with BSC (N=117)	BSC (N=128)	with BSC (N=108)	BSC (N=100)
Median (months) (95% CI)	6.1 (5.4, 6.7)	4.6 (4.2, 4.9)	8.6 (7.0, 10.3)	5.0 (4.3, 5.7)	4.8 (3.9, 5.6)	4.6 (3.6, 4.9)
HR (95% CI)	0.77 (0.64, 0.92)		0.63 (0.47, 0.84)		0.91 (0.67, 1.24)	
p-value ^a	0.0046					

^a Based on the Stratified Log-rank test.

Figure 3: Kaplan-Meier Curves for Overall Survival in Patients with K-Ras Wild-type Metastatic Colorectal Cancer in Study CA225-025



In Combination with Irinotecan

BOND was a multicenter, clinical trial conducted in 329 patients with EGFR-expressing recurrent mCRC. Tumor specimens were not available for testing for K-Ras mutation status. Patients were randomized (2:1) to receive either ERBITUX in combination with irinotecan (218 patients) or ERBITUX monotherapy (111 patients). ERBITUX was administered intravenously as a 400 mg/m² initial dose, followed by 250 mg/m² weekly until disease progression or unacceptable toxicity. In the ERBITUX with irinotecan arm, irinotecan was added to ERBITUX using the same dosage for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m² every 3 weeks, 180 mg/m² every 2 weeks, or 125 mg/m² weekly times four doses every 6 weeks. The efficacy of ERBITUX with irinotecan or ERBITUX monotherapy, based on durable objective responses, was evaluated in all randomized patients and in two pre-specified subpopulations: irinotecan refractory and irinotecan and oxaliplatin failures.

Of the 329 patients, the median age was 59 years, 63% were male, 98% were White, and 88% had baseline Karnofsky performance status \geq 80. Approximately two-thirds had previously failed oxaliplatin treatment.

In patients receiving ERBITUX with irinotecan, the ORR was 23% (95% CI 18%, 29%), median DoR was 5.7 months, and median time to progression was 4.1 months. In patients receiving ERBITUX monotherapy, the ORR was 11% (95% CI 6%, 18%), median DoR 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ERBITUX[®] (cetuximab) injection is a sterile, preservative-free, clear, colorless solution in a 2 mg/mL single-dose vial supplied as follows:

- 100 mg/50 mL individually packaged in a carton (NDC 66733-948-23)
- 200 mg/100 mL individually packaged in a carton (NDC 66733-958-23)

Storage and Handling

- Store vials under refrigeration at 2° C to 8° C (36° F to 46° F).
- Do not freeze or shake.
- Increased particulate formation may occur at temperatures at or below 0° C (32° 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

Infusion Reactions

Advise patients that the risk of serious infusion reactions may be increased in patients who have had a tick bite or red meat allergy. Advise patients to contact their healthcare provider and to report signs and symptoms of infusion reactions, including late onset infusion reactions, such as fever, chills, or breathing problems [see *Warnings and Precautions (5.1)*].

Cardiopulmonary Arrest

Advise patients of the risk of cardiopulmonary arrest or sudden death and to report any history of coronary artery disease, congestive heart failure, or arrhythmias [see *Warnings and Precautions (5.2)*].

Pulmonary Toxicity

Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath [see *Warnings and Precautions (5.3)*].

Dermatologic Toxicities

Advise patients to limit sun exposure during ERBITUX treatment and for 2 months after the last dose of ERBITUX. Advise patients to notify their healthcare provider of any sign of acne-like rash, (which can include itchy, dry, scaly, or cracking skin and inflammation, infection or swelling at the base of the nails or loss of the nails), conjunctivitis, blepharitis, or decreased vision [see *Warnings and Precautions (5.4)*].

Embryo-Fetal Toxicity

Advise female patients of reproductive potential of the potential risk to a fetus and to use effective contraception during ERBITUX treatment and for 2 months after the last dose of ERBITUX. Advise patients to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.8), Use in Specific Populations (8.3)*].

Lactation

Advise patients not to breastfeed during ERBITUX treatment and for 2 months after the last dose of ERBITUX [see *Use in Specific Populations (8.2)*].

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

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

Eli Lilly and Company, Indianapolis, IN 46285, USA

US License No. 1827

Copyright © 2004, 2019, ImClone LLC a wholly-owned subsidiary of Eli Lilly and Company. All rights reserved.

ERB-0005-USPI-20190423

PACKAGE LABEL- Erbitux 50 mL (2mg/mL) Vial Carton

NDC 66733-948-23

ERBITUX[®]

CETUXIMAB

Injection

For intravenous use

Rx only

100 mg/50 mL

(2 mg/mL)

DO NOT DILUTE

Lilly



PACKAGE LABEL- Erbitux 100 mL (2mg/mL) Vial Carton

NDC 66733-958-23

ERBITUX®

CETUXIMAB

Injection

For intravenous use

Rx only

200 mg/100 mL

(2 mg/mL)

DO NOT DILUTE

Lilly



ERBITUX

cetuximab solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:66733-948
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
cetuximab (UNII: PQX0D8J21J) (cetuximab - UNII:PQX0D8J21J)	cetuximab	2 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	8.48 mg in 1 mL
SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE (UNII: 70WT22SF4B)	1.88 mg in 1 mL
SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE (UNII: 593YOG76RN)	0.41 mg in 1 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
WATER (UNII: 059QF0K00R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:66733-948-23	1 in 1 CARTON	02/12/2004	
1		50 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125084	02/12/2004	

ERBITUX

cetuximab solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:66733-958
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
cetuximab (UNII: PQX0D8J21J) (cetuximab - UNII:PQX0D8J21J)	cetuximab	2 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	8.48 mg in 1 mL
SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE (UNII: 70WT22SF4B)	1.88 mg in 1 mL
SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE (UNII: 593YOG76RN)	0.41 mg in 1 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
WATER (UNII: 059QF0K00R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:66733-958-23	1 in 1 CARTON	10/02/2007	
1		100 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125084	10/02/2007	

Labeler - ImClone LLC (832474493)

Revised: 2/2020

ImClone LLC