Cetuximab: Drug information

(For additional information see "Cetuximab: Patient drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

ALERT: US Boxed Warning

Cardiopulmonary arrest:

Cardiopulmonary arrest and/or sudden death occurred in 2% of patients with squamous cell carcinoma of the head and neck treated with radiation and cetuximab and in 3% of patients with squamous cell carcinoma of the head and neck treated with European Union (EU)–approved cetuximab in combination with platinum-based therapy with 5-fluorouracil. Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after cetuximab administration.

Infusion reactions:

Serious infusion reactions occurred with the administration of cetuximab in approximately 3% of patients in clinical trials, with fatal outcomes reported in fewer than 1 in 1,000. Immediately interrupt and permanently discontinue cetuximab infusion for serious infusion reactions.

Brand Names: US

Erbitux

Brand Names: Canada

Erbitux

Pharmacologic Category

Antineoplastic Agent, Epidermal Growth Factor Receptor (EGFR) Inhibitor; Antineoplastic Agent, Monoclonal Antibody

Dosing: Adult

Note: Premedicate with an H_1 antagonist (eg, diphenhydramine) IV 30 to 60 minutes prior to the first dose; premedication for subsequent doses is based on clinical judgment.

Colorectal cancer, metastatic, KRAS wild-type (without mutation): IV:

Initial loading dose: 400 mg/m^2 infused over 120 minutes

Maintenance dose: 250 mg/m^2 infused over 60 minutes weekly until disease progression or unacceptable toxicity

Note: If given in combination with FOLFIRI (irinotecan, fluorouracil, and leucovorin), complete cetuximab infusion 1 hour prior to FOLFIRI.

Head and neck cancer (squamous cell): IV:

Initial loading dose: 400 mg/m^2 infused over 120 minutes

Maintenance dose: 250 mg/m^2 infused over 60 minutes weekly

Note: If given in combination with radiation therapy, administer loading dose 1 week prior to initiation of radiation course; weekly maintenance dose should be completed 1 hour prior to radiation for the duration of radiation therapy (6 to 7 weeks). If given in combination with chemotherapy, administer loading dose on the day of initiation of platinum and fluorouracil-based chemotherapy, cetuximab infusion should be completed 1 hour prior to initiation of chemotherapy; weekly maintenance dose should be completed 1 hour prior to chemotherapy; continue until disease progression or unacceptable toxicity. Monotherapy weekly doses should be continued until disease progression or unacceptable toxicity

Colorectal cancer, advanced, biweekly administration (off-label dosing): IV: 500 mg/m^2 every 2 weeks (initial dose infused over 120 minutes, subsequent doses infused over 60 minutes) in combination with irinotecan (Pfeiffer 2008)

Non-small cell lung cancer (NSCLC), EGFR-expressing, advanced (off-label use): IV: Initial loading dose: 400 mg/m^2, followed by maintenance dose: 250 mg/m^2 weekly in combination with cisplatin and vinorelbine for up to 6 cycles, then as monotherapy until disease progression or unacceptable toxicity (Pirker 2009; Pirker 2012)

Squamous cell skin cancer, unresectable (off-label use): IV: Initial loading dose: 400 mg/m^2, followed by maintenance dose: 250 mg/m^2 weekly until disease progression (Maubec 2011)

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

There are no dosage adjustments provided in the manufacturer's labeling.

Dosing: Hepatic Impairment

There are no dosage adjustments provided in the manufacturer's labeling.

Dosing: Adjustment for Toxicity

Infusion reactions, grade 1 or 2 and nonserious grade 3: Reduce the infusion rate by 50% and continue to use prophylactic antihistamines

Infusion reactions, severe: Immediately and permanently discontinue treatment

Pulmonary toxicity:

Acute onset or worsening pulmonary symptoms: Hold treatment

Interstitial lung disease: Permanently discontinue

Skin toxicity, mild to moderate: No dosage modification required

Acneiform rash, severe (grade 3 or 4):

First occurrence: Delay cetuximab infusion 1 to 2 weeks

If improvement, continue at 250 mg/m^2

If no improvement, discontinue therapy

Second occurrence: Delay cetuximab infusion 1 to 2 weeks

If improvement, continue at reduced dose of 200 mg/m^2

If no improvement, discontinue therapy

Third occurrence: Delay cetuximab infusion 1 to 2 weeks

If improvement, continue at reduced dose of 150 mg/m^2

If no improvement, discontinue therapy

Fourth occurrence: Discontinue therapy

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, Intravenous [preservative free]:

Erbitux: 100 mg/50 mL (50 mL); 200 mg/100 mL (100 mL) [contains galactose-alpha-1,3-galactose]

Generic Equivalent Available (US) No

Administration Administer via IV infusion; loading dose over 2 hours, weekly maintenance dose over 1 hour. Do not administer as IV push or bolus. Do not shake or dilute. Administer via infusion pump or syringe pump. Following the infusion, an observation period (1 hour) is recommended; longer observation time (following an infusion reaction) may be required. Premedication with an H_1 antagonist prior to the initial dose is recommended. The maximum infusion rate is 10 mg/minute. Administer through a low protein-binding 0.22 micrometer in-line filter.

For biweekly administration (off-label frequency and dose), the initial dose was infused over 120 minutes and subsequent doses infused over 60 minutes (Pfeiffer 2007; Pfeiffer 2008).

Use

Colorectal cancer, metastatic: Treatment of *KRAS* wild-type (without mutation), epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer as determined by approved tests (in combination with FOLFIRI [irinotecan, fluorouracil, and leucovorin] as first-line treatment, in combination with irinotecan [in patients refractory to irinotecan-based chemotherapy], or as a single agent in patients who have failed irinotecan- and oxaliplatin-based chemotherapy or who are intolerant to irinotecan).

Limitation of use: Cetuximab is not indicated for the treatment of *RAS*-mutant colorectal cancer or when results of the *RAS* mutation tests are unknown.

Head and neck cancer, squamous cell: Treatment of squamous cell cancer of the head and neck (as a single agent for recurrent or metastatic disease after platinum-based chemotherapy failure; in combination with radiation therapy as initial treatment of locally or regionally advanced disease; in combination with platinum and fluorouracil-based chemotherapy as first-line treatment of locoregional or metastatic disease).

Use: Off-Label

Non-small cell lung cancer, EGFR-expressing, advanced; Squamous cell skin cancer, unresectable

Medication Safety Issues

Sound-alike/look-alike issues:

Cetuximab may be confused with bevacizumab

Adverse Reactions

>10%:

Central nervous system: Fatigue (91%), malaise (≤73%), pain (59%), peripheral sensory neuropathy (45%; grades 3/4: 1%), headache (19% to 38%), insomnia (27%), confusion (18%), chills (≤16%), rigors (≤16%), anxiety (14%), depression (14%)

Dermatologic: Desquamation (95%), acneiform eruption (15% to 88%; grades 3/4: 1% to 18%), radiodermatitis (86%), xeroderma (14% to 57%), pruritus (14% to 47%), skin rash (28% to 44%), changes in nails (31%), acne vulgaris (14% to 22%), paronychia (20%), palmar-plantar erythrodysesthesia (19%), skin fissure (19%), alopecia (12%)

Endocrine & metabolic: Weight loss (15% to 84%), hypomagnesemia (6% to 55%), dehydration (13% to 25%), hypocalcemia (12%), hypokalemia (12%)

Gastrointestinal: Diarrhea (19% to 72%), nausea (49% to 64%), abdominal pain (59%), constipation (53%), vomiting (40%), stomatitis (31% to 32%), anorexia (25% to 30%), dyspepsia (14% to 16%), xerostomia (12%)

Hematologic & oncologic: Neutropenia (49%; grades 3/4: 31%), leukopenia (grades 3/4: 17%)

Hepatic: Increased serum ALT (43%), increased serum AST (38%), increased serum alkaline phosphatase (33%)

Infection: Infection (13% to 44%), infection without neutropenia (38%)

Local: Application site reaction (18%)

Neuromuscular & skeletal: Weakness (≤73%), ostealgia (15%), arthralgia (14%)

Ophthalmic: Conjunctivitis (10% to 18%)

Respiratory: Dyspnea (49%), cough (30%), pharyngitis (26%)

Miscellaneous: Fever (22% to 29%), infusion related reaction (10% to 18%; grades 3/4: 2% to 5%)

1% to 10%:

Cardiovascular: Cardiorespiratory arrest (2% to 3%), ischemic heart disease (2%)

Dermatologic: Hypertrichosis

Gastrointestinal: Dysgeusia (10%)

Immunologic: Antibody development (5%)

Infection: Sepsis (1% to 4%)

Renal: Renal failure (1%: colorectal cancer patients; frequency not defined in other populations)

<1%, postmarketing, and/or case reports: Abscess, aseptic meningitis, blepharitis, bronchospasm, bullous pemphigoid, cardiac arrhythmia, cellulitis, cheilitis, corneal ulcer, electrolyte disturbance, hoarseness, hypotension, interstitial pulmonary disease, keratitis, loss of consciousness, mucosal inflammation, myocardial infarction, pulmonary embolism, shock, skin infection, Stevens-Johnson syndrome, stridor, toxic epidermal necrolysis

Contraindications

There are no contraindications listed in the manufacturer's US labeling.

Canadian labeling: Known severe hypersensitivity to cetuximab or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

• Cardiopulmonary arrest: **[US Boxed Warning]: In patients with squamous cell head and neck cancer, cardiopulmonary arrest and/or sudden death has occurred in 2% of patients receiving radiation therapy in combination with cetuximab and in 3% of patients receiving combination chemotherapy (platinum and fluorouracil-based) with cetuximab. Closely monitor serum electrolytes (magnesium, potassium, calcium) during and after cetuximab treatment** (monitor for at least 8 weeks after treatment). Use with caution in patients with a history of coronary artery disease, heart failure, and arrhythmias; fatalities have been reported.

• Dermatologic toxicity: Acneiform rash has been reported in 76% to 88% of patients (severe in 1% to 17%), usually developing within the first 2 weeks of therapy; may require dose modification; generally resolved after discontinuation in most patients, although persisted beyond 28 days in some patients. Acneiform rash should be treated with topical and/or oral antibiotics; topical corticosteroids are not recommended. In colorectal cancer, the presence of acneiform rash correlates with treatment response and prolonged survival (Cunningham, 2004). Life-threatening and fatal bullous mucocutaneous disease (with blisters, erosions, and skin sloughing) has been observed with cetuximab; etiology is not determined; may be due to epidermal growth factor receptor (EGFR) inhibition or to idiosyncratic immune-related effects (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis). Other dermatologic toxicities, including dry skin, fissures, hypertrichosis, paronychial inflammation, and skin infections, have been reported; related ocular toxicities (blepharitis, conjunctivitis, keratitis, ulcerative keratitis with decreased visual acuity) may also occur. Monitor closely for dermatologic toxicities and potential infectious sequelae. Sunlight may exacerbate skin reactions (limit sun exposure).

• Electrolyte abnormality: Hypomagnesemia is common (may be severe); the onset of electrolyte disturbance may occur within days to months after initiation of treatment; monitor magnesium, calcium, and potassium during treatment and for at least 8 weeks after completion. May require electrolyte replacement.

• Infusion reactions: **[US Boxed Warning]: In clinical trials, serious infusion reactions have**

been reported in approximately 3% of patients; fatal outcome has been reported rarely (less than 1 in 1,000); interrupt infusion promptly and permanently discontinue for serious infusion reactions. Reactions have included airway obstruction (bronchospasm, stridor, hoarseness), hypotension, loss of consciousness, shock, myocardial infarction (MI), and/or cardiac arrest. Premedicate with anintravenous (IV) H_1 antagonist 30 to 60 minutes prior to the first dose; premedication for subsequent doses is based on clinical judgment and with consideration of prior reaction to the initial infusion. The use of nebulized albuterol-based premedication to prevent infusion reaction has been reported (Tra, 2008). Approximately 90% of reactions occur with the first infusion despite the use of prophylactic antihistamines. Immediate treatment for anaphylactic/anaphylactoid reactions should be available during administration. The manufacturer recommends monitoring patients for at least 1 hour following completion of infusion, or longer if a reaction occurs. Mild to moderate infusion reactions (chills, fever, dyspnea) are managed by slowing the infusion rate (by 50%) and administering antihistamines. Patients with preexisting IgE antibody against cetuximab (specific for galactose-α-1,3-galactose) are reported to have a higher incidence of severe hypersensitivity reaction. Severe hypersensitivity reaction has been reported more frequently in patients living in the middle south area of the United States, including North Carolina and Tennessee (Chung, 2008; O'Neil, 2007).

• Interstitial lung disease: Has been reported; use with caution in patients with preexisting lung disease. Interrupt treatment for acute onset or worsening of pulmonary symptoms. Permanently discontinue with confirmed interstitial lung disease.

Disease-related concerns:

• Colorectal cancer and *RAS* mutation status: Cetuximab is only indicated for patients with EGFR-expressing metastatic colorectal cancer without *RAS* (*KRAS* or *NRAS*) mutations. Determine *RAS* mutation status prior to treatment (with an approved test). Patients with a codon 12 and 13 (exon 2), codon 59 and 61 (exon 3), and codon 117 and 146 (exon 4) *RAS* mutation are unlikely to benefit from EGFR inhibitor therapy (while experiencing toxicities) and should not receive cetuximab treatment; cetuximab is not effective for colorectal cancer with *RAS* mutations. Cetuximab is also reported to be ineffective in patients with *BRAF* V600E mutation (Di Nicolantonio, 2008). The American Society of Clinical Oncology (ASCO) provisional clinical opinion (Allegra, 2009) recommends genotyping tumor tissue for KRAS mutation in all patients with metastatic colorectal cancer (genotyping may be done on archived specimens).

• EGFR expression testing: In trials for colorectal cancer, evidence of EGFR expression was required, although the response rate did not correlate with either the percentage of cells positive for EGFR or the intensity of expression. EGFR expression has been detected in nearly all patients with head and neck cancer; therefore, laboratory evidence of EGFR expression is not necessary for head and neck cancers.

Concurrent drug therapy issues:

• Combination with cisplatin and radiation therapy: In a study of radiation therapy **and** cisplatin with or without cetuximab in patients with squamous cell head and neck cancer, an increase in the incidence of adverse reactions (eg, grade 3/4 mucositis, radiation recall, acneiform rash, electrolyte abnormalities, and cardiac events including ischemia) was noted in patients receiving cetuximab, including fatal reactions. There was no improvement in the primary end point of progression-free survival.

Other warnings/precautions:

• Anti-cetuximab antibodies: Non-neutralizing anti-cetuximab antibodies were detected in 5% of evaluable patients. Relationship between the appearance of antibodies and the safety or antitumor activity of the molecule is unknown.

Metabolism/Transport Effects

None known.

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

There are no known significant interactions.

Pregnancy Risk Factor

C (show table)

Pregnancy Implications

Adverse events were observed in animal reproduction studies. Human IgG is known to cross the placenta. Because cetuximab inhibits epidermal growth factor (EGF), a component of fetal development, adverse effects on pregnancy would be expected. The manufacturer recommends that males and females use effective contraception during therapy and for 6 months following the last dose of cetuximab.

Breast-Feeding Considerations

It is not known if cetuximab is excreted in breast milk. IgG antibodies can be detected in breast milk. Due to the potential for serious adverse reactions in the nursing infant, the manufacturer recommends that the decision to discontinue cetuximab or discontinue breast-feeding should take into account the benefits of treatment to the mother. If breast-feeding is interrupted for cetuximab treatment, based on the half-life, breast-feeding should not be resumed for at least 60 days following the last cetuximab dose.

Monitoring Parameters

Vital signs during infusion and observe for at least 1 hour postinfusion. Patients developing dermatologic toxicities should be monitored for the development of complications. Periodic monitoring of serum magnesium, calcium, and potassium are recommended to continue over an interval consistent with the half-life (8 weeks); monitor closely (during and after treatment) for cetuximab plus radiation therapy. *KRAS* genotyping of tumor tissue in patients with colorectal cancer

Mechanism of Action

Recombinant human/mouse chimeric monoclonal antibody which binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands. Binding 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. EGFR signal transduction results in *RAS* wild-type activation; cells with *RAS* mutations appear to be unaffected by EGFR inhibition.

Pharmacodynamics/Kinetics

Distribution: V_d: ~2 to 3 L/m^2

Half-life elimination: ~112 hours (range: 63 to 230 hours)

Pricing: US

Solution (Erbitux Intravenous)

100 mg/50 mL (50 mL): $688.38

200 mg/100 mL (100 mL): $1376.76

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names

Cetuxim (BD); Erbitux (AE, AR, AT, AU, BE, BG, BR, CH, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EE, ES, FI, FR, GB, GR, GT, HK, HN, HR, HU, ID, IE, IL, IS, IT, JO, JP, KR, KW, LB, LT, LU, LV, MT, MY, NI, NL, NO, NZ, PA, PE, PH, PL, PT, QA, RO, RU, SE, SG, SI, SK, SV, TH, TR, TW, UA, VE, VN, ZA)

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