DRUG NAME: Cetuximab

SYNONYM(S)[1]**:** C225

COMMON TRADE NAME(S): ERBITUX®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Cetuximab is a recombinant chimeric monoclonal antibody that binds to the human epidermal growth factor receptor (EGFR) with high affinity.[1,2] Binding to EGFR blocks phosphorylation and activation of receptor-associated kinases which results in cell growth inhibition, induction of apoptosis, and decreased vascular endothelial growth factor production.[3] Cetuximab also induces internalization and degradation of EGFR, with resulting downregulation of cell surface receptors and reduced EGFR signaling.[4] Mutation of the *K-ras* gene, a part of the EGFR signaling cascade, may affect response to cetuximab, in that mutated *K-ras* in the tumour cell may render EGFR inhibitors ineffective.[5] Cetuximab may also enhance the cytotoxicity of radiation by blocking EGFR signaling.[6] Cetuximab is cell cycle phase-specific, arresting cells in the G1 phase.[1]

PHARMACOKINETICS:

Distribution	exhibits non-linear pharmacokinetics; distributes to normal and tumour cells where EGFR is expressed[2,4]	
	cross blood brain barrier?	no information found
	volume of distribution	2-3 L/m²; likely 2 compartment model
	plasma protein binding	no information found
Metabolism	no information found	
	active metabolite(s)	none
	inactive metabolite(s)	none
Excretion	major route of clearance thought to be internalization and degradation of EGFR complex by hepatocytes and skin[4,7,8]; saturation of elimination pathways occurs at doses between 200-500 mg/m²[1,4,8]	
	urine	no information found
	feces	no information found
	terminal half life	112 h (range 63-230 h)
	clearance[2,9]	20 mL/h/m²
Sex	females exhibit a lower maximal clearance; clinical significance unknown; dose modification unnecessary	

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:
*Colorectal cancer
*Head and neck cancer

*Health Canada approved indication

Other uses:
Lung cancer, non-small cell[3]

SPECIAL PRECAUTIONS:

Contraindications:
- History of hypersensitivity reaction to cetuximab or murine proteins.[7]

Caution:
- ***Severe infusion reactions***, characterized by rapid onset airway obstruction, hypotension, loss of consciousness and/or cardiac arrest have been reported to occur in 2-5% of patients, sometimes with fatal outcome (<1 in 1000).[2] Pre-medication with an H_1 antagonist (e.g., diphenhydramine)[2,10] and corticosteroid [10] prior to the initial dose is recommended. However, approximately 90% of severe reactions have been associated with the first infusion, despite prophylactic pre-medication with antihistamines.[2] Test doses have not been shown to reliably predict risk of reaction and are not recommended.[3] Severe reactions may also occur with subsequent infusions, therefore, caution must be exercised with every infusion.[7] Severe reactions require immediate discontinuation of treatment.[2] See paragraph following **Side Effects** table.
- ***Cardiopulmonary arrest*** and/or sudden death have been reported in 2% of patients treated with concurrent radiation in squamous cell carcinoma of the head and neck,[2] with fatal events reported 1-43 days following the last treatment.[7] Serum electrolytes (including magnesium, potassium and calcium) should be monitored during and after treatment. Caution is suggested for patients with a history of coronary artery disease, congestive heart failure, or arrhythmias.[2]
- ***Interstitial lung disease*** has been reported. Caution is suggested in patients with pre-existing lung disease.[3]
- *Limit* ***sun exposure*** during treatment and for two months following cessation to prevent exacerbation of dermatologic toxicity.[2]

Carcinogenicity: No information found.

Mutagenicity: Not mutagenic or clastogenic in Ames test or mammalian *in vivo* chromosome test.[2]

Fertility: No information found.

Pregnancy: FDA Pregnancy Category C.[2] Animal studies have shown fetal risks, but there are no controlled studies in pregnant women. Cetuximab should be given during pregnancy only if the potential benefit justifies the possible risk to the fetus.

Breastfeeding is not recommended due to the potential secretion into breast milk. Discontinue nursing during treatment and for 60 days following the last dose.[2]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[11,12]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	***infusion reactions*** (13-21%, severe 2-5%); sometimes fatal; 90% of severe reactions occur with first infusion; see paragraph following **Side Effects** table
auditory/hearing	deafness (1%)
	ear disorder (1%)
	vertigo (1%)
blood/bone marrow/	anemia (9%, severe 3%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
febrile neutropenia	thrombocytopenia (1%)
cardiovascular (arrhythmia)	atrial fibrillation (1%, severe 1%)
	palpitation (1%)
	tachycardia (2%)
cardiovascular (general)	***cardiopulmonary arrest***; see paragraph in **Caution** section
	hypertension (1%)
	hypotension (1%, severe 1%)
	peripheral edema (5-10%, severe 1%)
coagulation	deep vein thrombophlebitis (1%, severe 1%)
	epistaxis (9%)
	gastrointestinal hemorrhage (3%, severe 1%)
	hemoptysis (2%)
	hemorrhage (1%)
	pulmonary embolus (1%)
	rectal hemorrhage (3%)
constitutional symptoms	***asthenia/malaise*** (48%, severe 10%)
	cachexia (1%)
	chills/rigors (11-13%)[2,3]
	dehydration (2-10%, severe 3%)[2,3]
	fatigue[3] (89%)
	fever (27-30%)[2,3]
	weight loss (7-27%)[2,3]
dermatology/skin	*extravasation hazard: none*[13]
	acneiform rash (76-90%, severe 1-17%); most frequently on face, upper chest, and back[7]; dose modification required if severe; see paragraph following **Side Effects** table
	alopecia (4%); see paragraph following **Side Effects** table
	cellulitis
	cheilitis
	dry skin[3] (49%)
	hair disorder, unspecified (3-4%); see paragraph following **Side Effects** table
	hirsutism (3%)
	hypertrichosis[3]
	nail changes (16-21%)[2,3]; beginning usually after 4-8 weeks; resolving after treatment cessation[14]; see paragraph following **Side Effects** table
	pruritis (11-40%)[2,3]
	radiation dermatitis; see paragraph following **Side Effects** table
	rash, unspecified[3] (89%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	skin necrosis (≤1%)
	sweating (4%)
gastrointestinal	*emetogenic potential: low-moderate*[15]
	anorexia (23%, severe 2%)
	constipation (26-46%, severe 2%)[2,3]
	diarrhea (25-39%, severe 2%)
	dyspepsia (6%, severe 7%)[2,3]
	dysphagia (2%, severe 1%)
	flatulence (3%)
	glossitis (3%)
	hepatomegaly (1%)
	intestinal obstruction (6%)
	jaundice (5%, severe 2%)
	nausea (29%, severe 2%)
	stomatitis (10-25%)[2,3]
	vomiting (25-37%, severe 3%)[2,3]
	xerostomia (2-11%)[2,3]
hepatobiliary/pancreas	ascites (4%, severe 2%)
infection	infection, unspecified (13-35%)
	pneumonia (2%)
	sepsis (1-4%)
	urinary tract infection (6%)
metabolic/laboratory	alkaline phosphatase, increase[3] (5-10%)
	bilirubinemia (2%, severe 1%)
	hypocalcemia (1%); clinically significant (≤1%)[16]
	hypokalemia (5%, severe 1%)
	hypomagnesemia (3-55%, severe 6-17%); progressive magnesium loss (97%)[16]; increasing age associated with increased severity[16]; see paragraph following **Side Effects** table
	hypophosphatemia (1%)
	transaminases, increased[3] (5-10%)
musculoskeletal	joint disorder (1%)
	leg cramps (1%)
	myasthenia (3%)
	weakness[3] (45-48%)
neurology	agitation (1%)
	anxiety (4-14%)[2,3]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	confusion (3-15%, severe 1%)[2,3]
	convulsion (1%)
	depression (7-13%)[2,3]
	dizziness (5%)
	headache (26-33%, severe 2%)[2,3]
	insomnia (10-30%)[2,3]
	neuralgia (1%)
	neuropathy (3%)
	paresthesia (4%)
	somnolence (3%, severe 1%)
ocular/visual	amblyopia (1%)
	blepharitis (≤1%)[3]
	conjunctivitis (7%)
	dry eyes, lacrimation disorder (2%)
	keratitis[3]
pain	***abdominal pain*** (26-59%, severe 9%)[2,3]
	arthralgia (4%)
	back pain (10%, severe 2%)[2,3]
	bone pain (1-15%)[2,3]
	chest pain (4%)[2]
	dysuria (3%)
	myalgia (4%)
	pain, unspecified (17-51%, severe 5%)[2,3]
pulmonary	asthma (1%)
	bronchospasm[3] (≤1%)
	cough (11-29%, severe 1%)[2,3]
	dyspnea (17-48%, severe 7%)[2,3]
	interstitial lung disease (<0.5%), sometimes fatal; see paragraph following **Side Effects** table
	interstitial pneumonitis, sometimes fatal[7]
	pharyngitis (2%)
	pleural effusion (4%, severe 2%)
	rhinitis (5%)
renal/genitourinary	hematuria (3%)
	hydronephrosis (1%)
	incontinence (1%), increased frequency (1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	renal failure (1%)
	urinary retention (1%)
syndromes	flu syndrome (4%)

Adapted from standard reference[2] unless specified otherwise.

An ***acneiform rash*** consisting of a diffuse, erythematous, follicular-based reaction with or without comedones[17] usually develops within the first two weeks of therapy.[2] Resolution follows cessation of treatment in the majority of cases but may be prolonged (i.e., greater than 28 days) in up to half of affected patients. Dose modification may be required if severe. Monitor for the development of inflammatory or infectious complications and treat as necessary. Treatment with topical corticosteroids, and topical (i.e., clindamycin) and/or oral (i.e., tetracyclines) antibiotics may be required.[14,18,19] Topical retinoids or benzoyl peroxide may worsen the condition and should be avoided.[14] Very rare cases of skin necrosis have been reported. Limit sun exposure during treatment and for 2 months following cessation of treatment.[2]

Hair alterations are typically a delayed effect, occurring 2-3 months after treatment. Hair can be brittle, fine, or curly. Frontal alopecia, increased facial hair, and eyelash trichomegaly have been reported.[14]

Onset of ***hypomagnesemia*** and accompanying hypocalcemia and hypokalemia may occur days to months after initiation of treatment,[2,7,16] and may result from magnesium wasting through urinary excretion.[16,20] Hypomagnesemia can manifest as severe fatigue, irritability, paresthesias, cramps, and hypocalcemia.[7,16,20] Monitor electrolytes during treatment and continue for at least 8 weeks following completion of treatment. Replenish electrolytes as necessary.[2,16,20]

Infusion reactions may include pyrexia, chills, rigors, dyspnea, bronchospasm, angioedema, urticaria, hypertension, and hypotension. Severe, potentially fatal, infusion reactions characterized by rapid onset airway obstruction, hypotension, loss of consciousness, and/or cardiac arrest have been reported to occur in 2-5% of patients, sometimes with fatal outcome (<1 in 1000).[2] A one-hour observation period is recommended following the end of the first and second infusions. The observation period may be discontinued for subsequent infusions if no infusion reaction occurs for 2 consecutive infusions.[21] Mild to moderate infusion reactions may be managed with a slower infusion rate and prophylactic antihistamines, for subsequent dosing. Severe reactions require immediate and permanent discontinuation of cetuximab.[2]

Adverse pulmonary effects, including interstitial lung disease, interstitial pneumonitis, and exacerbation of pre-existing fibrotic lung disease, have been reported, usually occurring between the fourth and 11th doses of cetuximab.[7] Acute onset or worsening pulmonary symptoms should be investigated, and cetuximab discontinued, if interstitial lung disease is confirmed.[2] Caution is suggested with pre-existing lung disease.[3]

Nail changes, particularly affecting the great toes and thumbs,[7] may present as tender, erythematous, and edematous lateral nail folds with prominent granulation tissue and occasionally a seropurulent discharge. Bacterial colonization or superinfection can occur. Avoid trauma to the area as it may promote the inflammatory changes. Changes are usually delayed, developing after 4-8 weeks of therapy. Spontaneous healing has been reported during treatment, but changes typically resolve within a few days after cessation of treatment.[14]

Severe cases of ***radiation dermatitis*** have been reported, with early erythema, followed by epidermolysis, progressing to dermatitis with necrosis.[22] The likelihood of severe radiation dermatitis increases with radiation dose.[12,23] Severe radiation dermatitis reactions appear to completely resolve with little or no persistent scarring.[23] The overall incidence of ***late radiation toxicities*** (any grade) is higher with concurrent therapy; however, the incidence of Grade 3 or 4 toxicities appears to be similar (approximately 20% in both groups).[2,6,24]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
cisplatin[2]	no interaction		
doxorubicin[2]	no interaction		
gemcitabine[2]	no interaction		
irinotecan[2]	no interaction		
paclitaxel[2]	no interaction		

SUPPLY AND STORAGE:

***Injection*:** ImClone Systems Incorporated supplies cetuximab as 100 and 200 mg ready-to-use, single-use (preservative free) vials in a concentration of 2 mg/mL. Refrigerate.[2]

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information: The presence of white particulates in the vials will not affect the quality of the product. Administer using a 0.2 or 0.22 micron low protein binding in-line filter.[2]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous[2]	do NOT use
Intermittent infusion	***weekly dosing: loading dose over 2 h, maintenance doses over 1 h;[25,26] maximum rate = 10 mg/min[25]*** ***or*** ***2- weekly dosing: initial dose over 2 h for first infusion, subsequent infusions over 1 h[27-29]*** (See Dosage Guidelines for more information)
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found

BCCA administration guideline noted in ***bold***, ***italics***

Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	***2 weeks:[9,27-30]***	***500 mg/m² IV for one dose starting on day 1, until progression or unacceptable toxicity***
	1 week[2]:	400 mg/m² IV loading dose for one dose starting on day 1, followed by 250 mg/m² IV starting on day 1 of each subsequent cycle until progression or unacceptable toxicity
Concurrent radiation:	***5-7 weeks:[2,26]***	***400 mg/m² IV loading dose for one dose starting on day minus 7 from radiation start date, followed by 250 mg/m² IV weekly starting on day 1.*** * For maintenance doses, the ideal timing of cetuximab relative to radiation is not clear. Although the manufacturer[31,32] recommends to complete cetuximab infusion 1 hour before radiation, its long half-life may provide adequate serum levels irrespective of its timing relative to radiation on the day that radiation is given.[33,34] Refer to protocol by which patient is being treated.
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"	
Dosage in renal failure:	no adjustment required[2]	
Dosage in hepatic failure:	no adjustment required[2]	
Dosage in dialysis:	no information found	

Children: no information found

REFERENCES:

1. Baselga J. The EGFR as a target for anticancer therapy - focus on cetuximab. Eur J Cancer 2001;37:S16-S22.
2. ImClone Systems Incorporated and Bristol-Myers Squibb Company. ERBITUX® product monograph. Branchburg, NJ, USA; March 2009.
3. Rose BD editor. Cetuximab. UpToDate 17.1 ed. Waltham, Massachusetts: UpToDate®; 2009.
4. Dirks NL, Nolting A, Kovar A, et al. Population pharmacokinetics of cetuximab in patients with squamous cell carcinoma of the head and neck. J Clin Pharmacol 2008;48:267-278.

5. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008;359(17):1757-1765.
6. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354(6):567-578.
7. McEvoy GK, editor. AHFS 2008 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc. p. 977-980.
8. Tan AR, Moore DF, Hidalgo M, et al. Pharmacokinetics of cetuximab after administration of escalating single dosing and weekly fixed dosing in patients with solid tumors. Clin Cancer Res 2006;12(21):6517-6522.
9. Tabernero J, Pfeiffer P, Cervantes A. Administration of cetuximab every 2 weeks in the treatment of metastatic colorectal cancer: an effective, more convenient alternative to weekly administration? Oncologist 2008;13(2):113-119.
10. Wilke H, Glynne-Jones R, Thaler J, et al. Cetuximab plus irinotecan in heavily pretreated metastatic colorectal cancer progressing on irinotecan: MABEL study. J Clin Oncol 2008;26(33):5335-5343.
11. Sanjay Rao MD. Personal communication. BC Cancer Agency Gastrointestinal Tumour Group; 12 May 2009.
12. Frances Wong MD. Personal communication. Radiation Oncologist, BC Cancer Agency; 13 May 2009.
13. BC Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; 01 December 2007.
14. Dick SE, Crawford GH. Managing cutaneous side effects of epidermal growth factor receptor (HER1/EGFR) inhibitors. Comm Onc 2005;2(6):492-496.
15. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 March 2008.
16. Tejpar S, Piessevaux H, Claes K, et al. Magnesium wasting associated with epidermal-growth-factor receptor-targeting antibodies in colorectal cancer: a prospective study. Lancet Oncol 2007;8(5):387-394.
17. Payne AS, James WD, Weiss RB. Dermatologic toxicity of chemotherapeutic agents. Semin Oncol 2006;33:86-97.
18. Lynch Jr TJ, Kim ES, Eaby B, et al. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. The Oncologist 2007;12:610-621.
19. Thomas M. Cetuximab: adverse event profile and recommendations for toxicity management. Clin J Oncol Nurs 2005;9(3):332-8.
20. Schrag D, Chung KY, Flombaum C, et al. Cetuximab therapy and symptomatic hypomagnesemia. J Natl Cancer Inst 2005;97(16):1221-1224.
21. BC Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-60: Physician Coverage for Medical Emergencies During Delivery of Selected Chemotherapy Drugs. Vancouver, British Columbia: BC Cancer Agency; 1 March 2012.
22. Budach W, Bolke E, Homey B. Severe Cutaneous Reaction during Radiation Therapy with Concurrent Cetuximab. N Engl J Med 2007;357(5):514-515.
23. Giro C, Berger B, Bolke E, et al. High rate of severe radiation dermatitis during radiation therapy with concurrent cetuximab in head and neck cancer: results of a survey in EORTC institutes. Radiother Oncol 2009;90:166-171.
24. Bernier J, Bonner J, Vermorken JB, et al. Consensus guidelines for the management of radiation dermatitis and coexisting acne-like rash in patients receiving radiotherapy plus EGFR inhibitors for the treatment of squamous cell carcinoma of the head and neck. Ann Oncol 2008;19(1):142-149.
25. ImClone Systems Incorporated and Bristol-Myers Squibb Company. ERBITUX® product monograph. Branchburg, NJ, USA; June 2009.
26. BC Cancer Agency Head and Neck Tumour Group. (UHNCETRT) BCCA Protocol Summary for Combined Cetuximab and Radiation Treatment for Locally Advanced Squamous Cell Carcinoma of the Head and Neck. Vancouver, British Columbia: BC Cancer Agency; 1 January 2008.
27. BC Cancer Agency Gastrointestinal Tumour Group. (UGIAVCETIR) BCCA Protocol Summary Third Line Treatment of Metastatic Colorectal Cancer Using Cetuximab in Combination with Irinotecan. Vancouver, British Columbia: BC Cancer Agency; 1 August 2009.
28. Pfeiffer P, Nielsen D, Bjerregaard J, et al. Biweekly cetuximab and irinotecan as third-line therapy in patients with advanced colorectal cancer after failure to irinotecan, oxaliplatin and 5-fluorouracil. Ann Oncol 2008;19(6):1141-1145.
29. Martin-Martorell P, Rosello S, Rodriguez-Braun E, et al. Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. Br J Cancer 2008;99:455-458.
30. Roca J, Alonso V, Pericay C, et al. Cetuximab given every 2 weeks (q2w) plus irinotecan, as feasible option, for previously treated patients (pts) with metastatic colorectal cancer (MCRC). J Clin Oncol (Meeting Abstracts) 2008;26(15_suppl):15122.
31. ImClone LLC (distributed by Bristol-Myers Squibb Canada). ERBITUX® product monograph. Branchburg, New Jersey, USA; 20 Dec 2012.
32. Mai-Loan Leha. Manager Medical Services. Personal communication. Bristol-Myers Squibb Canada; 28 February 2013.
33. Jonn Wu MD. Personal communication. BC Cancer Agency Head and Neck Tumour Group; 27 February 2013.
34. Francis Wong MD. Personal communication. BC Cancer Agency Head and Neck Tumour Group; 24 February 2013.