

## DRUG NAME: Cetuximab

**SYNONYM(S)**<sup>1</sup>: 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.<sup>1,2</sup> 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.<sup>3</sup> Cetuximab also induces internalization and degradation of EGFR, with resulting downregulation of cell surface receptors and reduced EGFR signaling.<sup>4</sup> 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.<sup>5</sup> Cetuximab may also enhance the cytotoxicity of radiation by blocking EGFR signaling.<sup>6</sup> Cetuximab is cell cycle phase-specific, arresting cells in the G1 phase.<sup>1</sup>

### PHARMACOKINETICS:

Distribution	exhibits non-linear pharmacokinetics; distributes to normal and tumour cells where EGFR is expressed <sup>2,4</sup>	
	cross blood brain barrier?	no information found
	volume of distribution	2-3 L/m <sup>2</sup> ; 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 <sup>4,7,8</sup> ; saturation of elimination pathways occurs at doses between 200-500 mg/m <sup>2</sup> <sup>1,4,8</sup>	
	urine	no information found
	feces	no information found
	terminal half life	112 h (range 63-230 h)
	clearance <sup>2,9</sup>	20 mL/h/m <sup>2</sup>
Sex	females exhibit a lower maximal clearance; clinical significance unknown; dose modification unnecessary	

Adapted from standard reference<sup>2</sup> unless specified otherwise.

### USES:

**Primary uses:**

\*Colorectal cancer

\*Head and neck cancer

\*Health Canada approved indication

**Other uses:**

Lung cancer, non-small cell<sup>3</sup>

Skin cancer, squamous cell<sup>10</sup>

## SPECIAL PRECAUTIONS:

### **Contraindications:**

- History of hypersensitivity reaction to cetuximab or murine proteins.<sup>7</sup>

### **Caution:**

- severe **infusion reactions**, characterized by rapid onset airway obstruction, hypotension, loss of consciousness and/or cardiac arrest have been reported<sup>2</sup>; premedication with an H<sub>1</sub> antagonist (e.g., diphenhydramine)<sup>2,11</sup> and corticosteroid<sup>11</sup> prior to the initial dose is recommended
- **cardiopulmonary arrest** and/or sudden death have been reported<sup>7</sup>; monitor electrolytes and use with caution in patients with a history of coronary artery disease, congestive heart failure, or arrhythmias<sup>2</sup>
- **interstitial lung disease** has been reported; use with caution in patients with pre-existing lung disease<sup>3</sup>
- **limit sun exposure** during treatment and for two months following cessation to prevent exacerbation of dermatologic toxicity<sup>2</sup>

**Carcinogenicity:** No information found.

**Mutagenicity:** Not mutagenic or clastogenic in Ames test or mammalian *in vivo* chromosome test.<sup>2</sup>

**Fertility:** No information found.

**Pregnancy:** Human IgG is known to cross the placental barrier; therefore, it is expected that cetuximab may be transmitted from mother to fetus. Based on animal models, EGFR may play a role in the control of prenatal development and may be essential for normal organogenesis, including proliferation and differentiation in the developing embryo. Animal studies do not suggest a teratogenic effect; however, an increased incidence of abortions was observed in one species at exposures 1.6 to 4 times that of expected human exposure.<sup>12</sup>

**Breastfeeding** is not recommended due to the potential secretion into breast milk. Human IgG is known to be excreted in human milk. The potential for absorption of cetuximab and harm to the infant is unknown. Discontinue breastfeeding during treatment and for 60 days following the last dose.<sup>12</sup>

## 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.<sup>13,14</sup>

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b>bold, italics</b>	
allergy/immunology	<b>infusion reactions</b> (13-21%, severe 2-5%); see paragraph following <b>Side Effects</b> table
auditory/hearing	deafness (1%)
	ear disorder (1%)
	vertigo (1%)
blood/bone marrow/ febrile neutropenia	anemia (9%, severe 3%)
	thrombocytopenia (1%)
cardiovascular (arrhythmia)	atrial fibrillation (1%, severe 1%)
	palpitation (1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b><i>bold, italics</i></b>	
	tachycardia (2%)
cardiovascular (general)	<b><i>cardiopulmonary arrest</i></b> ; see paragraph in <b>Caution</b> 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	<b><i>asthenia/malaise</i></b> (48%, severe 10%)
	cachexia (1%)
	chills/rigors (11-13%) <sup>2,3</sup>
	dehydration (2-10%, severe 3%) <sup>2,3</sup>
	fatigue <sup>3</sup> (89%)
	<b><i>fever</i></b> (27-30%) <sup>2,3</sup>
	weight loss (7-27%) <sup>2,3</sup>
dermatology/skin	<b><i>extravasation hazard: none</i></b> <sup>15</sup>
	<b><i>acneiform rash</i></b> (76-90%, severe 1-17%); see paragraph following <b>Side Effects</b> table
	alopecia (4%); see paragraph following <b>Side Effects</b> table
	cellulitis
	cheilitis
	dry skin <sup>3</sup> (49%)
	hair disorder, unspecified (3-4%); see paragraph following <b>Side Effects</b> table
	hirsutism (3%)
	hypertrichosis <sup>3</sup>
	<b><i>nail changes</i></b> (16-21%) <sup>2,3</sup> ; see paragraph following <b>Side Effects</b> table
	pruritis (11-40%) <sup>2,3</sup>
	radiation dermatitis; see paragraph following <b>Side Effects</b> table
	rash, unspecified <sup>3</sup> (89%)
	skin necrosis (≤1%)
sweating (4%)	

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b>bold, italics</b>	
gastrointestinal	<i>emetogenic potential: low-moderate</i> <sup>17</sup>
	anorexia (23%, severe 2%)
	<b>constipation</b> (26-46%, severe 2%) <sup>2,3</sup>
	<b>diarrhea</b> (25-39%, severe 2%)
	dyspepsia (6%, severe 7%) <sup>2,3</sup>
	dysphagia (2%, severe 1%)
	flatulence (3%)
	glossitis (3%)
	hepatomegaly (1%)
	intestinal obstruction (6%)
	jaundice (5%, severe 2%)
	<b>nausea</b> (29%, severe 2%)
	<b>stomatitis</b> (10-25%) <sup>2,3</sup>
	<b>vomiting</b> (25-37%, severe 3%) <sup>2,3</sup>
xerostomia (2-11%) <sup>2,3</sup>	
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 <sup>3</sup> (5-10%)
	bilirubinemia (2%, severe 1%)
	hypocalcemia (1%); clinically significant ( $\leq 1\%$ ) <sup>18</sup>
	<b>hypokalemia</b> (5%, severe 1%)
	<b>hypomagnesemia</b> (3-55%, severe 6-17%); see paragraph following <b>Side Effects</b> table
	hypophosphatemia (1%)
	transaminases, increased <sup>3</sup> (5-10%)
musculoskeletal	joint disorder (1%)
	leg cramps (1%)
	myasthenia (3%)
	weakness <sup>3</sup> (45-48%)
neurology	agitation (1%)
	anxiety (4-14%) <sup>2,3</sup>
	confusion (3-15%, severe 1%) <sup>2,3</sup>

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b>bold, italics</b>	
	convulsion (1%)
	depression (7-13%) <sup>2,3</sup>
	dizziness (5%)
	<b>headache</b> (26-33%, severe 2%) <sup>2,3</sup>
	insomnia (10-30%) <sup>2,3</sup>
	neuralgia (1%)
	neuropathy (3%)
	paresthesia (4%)
	somnolence (3%, severe 1%)
ocular/visual	amblyopia (1%)
	blepharitis (≤1%) <sup>3</sup>
	conjunctivitis (7%)
	dry eyes, lacrimation disorder (2%)
	keratitis <sup>3</sup>
pain	<b>abdominal pain</b> (26-59%, severe 9%) <sup>2,3</sup>
	arthralgia (4%)
	back pain (10%, severe 2%) <sup>2,3</sup>
	bone pain (1-15%) <sup>2,3</sup>
	chest pain (4%) <sup>2</sup>
	dysuria (3%)
	myalgia (4%)
	pain, unspecified (17-51%, severe 5%) <sup>2,3</sup>
pulmonary	asthma (1%)
	bronchospasm <sup>3</sup> (≤1%)
	cough (11-29%, severe 1%) <sup>2,3</sup>
	<b>dyspnea</b> (17-48%, severe 7%) <sup>2,3</sup>
	<b>interstitial lung disease</b> (<0.5%), sometimes fatal; see paragraph following <b>Side Effects</b> table
	interstitial pneumonitis, sometimes fatal <sup>7</sup>
	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 <b>bold, italics</b>	
	renal failure (1%)
	urinary retention (1%)
syndromes	flu syndrome (4%)

Adapted from standard reference<sup>2</sup> unless specified otherwise.

An **acneiform rash** consisting of a diffuse, erythematous, follicular-based reaction with or without comedones<sup>19</sup> usually develops within the first two weeks of therapy.<sup>2</sup> Rash occurs most frequently on face, upper chest, and back.<sup>7</sup> 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.<sup>16,20,21</sup> Topical retinoids or benzoyl peroxide may worsen the condition and should be avoided.<sup>16</sup> Very rare cases of skin necrosis have been reported. Limit sun exposure during treatment and for 2 months following cessation of treatment.<sup>2</sup>

**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,<sup>2</sup> with fatal events reported 1-43 days following the last treatment.<sup>7</sup> 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.<sup>2</sup>

**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.<sup>16</sup>

Onset of **hypomagnesemia** and accompanying hypocalcemia and hypokalemia may occur days to months after initiation of treatment,<sup>2,7,18</sup> and may result from magnesium wasting through urinary excretion.<sup>18,22</sup> Increasing age associated with increased severity.<sup>18</sup> Hypomagnesemia can manifest as severe fatigue, irritability, paresthesias, cramps, and hypocalcemia.<sup>7,18,22</sup> Monitor electrolytes during treatment and continue for at least 8 weeks following completion of treatment. Replenish electrolytes as necessary.<sup>2,18,22</sup>

**Infusion reactions** may include pyrexia, chills, rigors, dyspnea, bronchospasm, angioedema, urticaria, hypertension, and hypotension. Severe 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).<sup>2</sup> Pre-medication with an H<sub>1</sub> antagonist (e.g., diphenhydramine)<sup>2,11</sup> and corticosteroid<sup>11</sup> 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.<sup>2</sup> Test doses have not been shown to reliably predict risk of reaction and are not recommended.<sup>3</sup> Severe reactions may also occur with subsequent infusions, therefore, caution must be exercised with every infusion.<sup>7</sup> 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. Severe reactions require immediate discontinuation of treatment.<sup>2</sup>

**Nail changes**, particularly affecting the great toes and thumbs,<sup>7</sup> 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.<sup>16</sup>

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.<sup>7</sup> Acute onset or worsening pulmonary symptoms should be investigated, and cetuximab discontinued, if interstitial lung disease is confirmed.<sup>2</sup> Caution is suggested with pre-existing lung disease.<sup>3</sup>

Severe cases of **radiation dermatitis** have been reported, with early erythema, followed by epidermolysis, progressing to dermatitis with necrosis.<sup>24</sup> The likelihood of severe radiation dermatitis increases with radiation dose.<sup>14,25</sup> Severe radiation dermatitis reactions appear to completely resolve with little or no persistent scarring.<sup>25</sup> 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).<sup>2,6,26</sup>

#### INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
cisplatin <sup>2</sup>	no interaction		
doxorubicin <sup>2</sup>	no interaction		
gemcitabine <sup>2</sup>	no interaction		
irinotecan <sup>2</sup>	no interaction		
paclitaxel <sup>2</sup>	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.<sup>2</sup>

**For basic information on the current brand used at BC Cancer, see [Chemotherapy Preparation and Stability Chart in Appendix](#).**

#### SOLUTION PREPARATION AND COMPATIBILITY:

**For basic information on the current brand used at BC Cancer, 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.<sup>2</sup>

**Compatibility:** consult detailed reference

#### PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in **bold, italics**

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous <sup>2</sup>	do NOT use
Intermittent infusion	<b>weekly dosing<sup>12,27,28</sup>:</b> <b>loading dose over 2 h;</b> <b>maintenance doses over 1 h;</b> (maximum rate = 10 mg/min)
	<b>2- weekly dosing<sup>29-31</sup>:</b> <b>first infusion over 2 h;</b> <b>subsequent infusions over 1 h</b>

BC Cancer administration guideline noted in ***bold, italics***

Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
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:

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
<i>Intravenous:</i>	<b>2 weeks</b> <sup>9,29-32</sup> :	<b>500 mg/m<sup>2</sup> IV for one dose starting on day 1</b>
	<b>1 week</b> <sup>12,28</sup> :	<b>400 mg/m<sup>2</sup> IV loading dose</b> for one dose starting on day 1, <b>followed by 250 mg/m<sup>2</sup> IV</b> starting on day 1 of each subsequent cycle
<i>Concurrent radiation:</i>	<b>5-7 weeks</b> <sup>12,27</sup> :	<b>400 mg/m<sup>2</sup> IV loading dose for one dose starting on day minus 7 from radiation start date, followed by 250 mg/m<sup>2</sup> IV weekly starting on day 1.</b>

\* For maintenance doses, the ideal timing of cetuximab relative to radiation is not clear. Although the manufacturer<sup>33,34</sup> recommends to complete cetuximab infusion 1 h 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.<sup>35,36</sup> Refer to protocol by which patient is being treated.

<i>Dosage in myelosuppression:</i>	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"
<i>Dosage in renal failure:</i>	no adjustment required <sup>2</sup>
<i>Dosage in hepatic failure:</i>	no adjustment required <sup>2</sup>
<i>Dosage in dialysis:</i>	no information found



**Children:** no information found

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