DRUG NAME: Panitumumab

SYNONYM(S):

COMMON TRADE NAME(S): VECTIBIX®

CLASSIFICATION: miscellaneous

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

MECHANISM OF ACTION:

Panitumumab is a recombinant, fully human monoclonal antibody that binds with high affinity to the human epidermal growth factor receptor (EGFR), thus competitively inhibiting ligand-induced receptor autophosphorylation. Binding results in internalization of the receptor, cell growth inhibition, induction of apoptosis, and decreased production of interleukin 8 and vascular endothelial growth factor.[1] Mutation of the *K-ras* gene, a part of the EGFR signaling cascade, may affect response to panitumumab, in that mutated *K-ras* in the tumour cell may render EGFR inhibitors ineffective.[2]

PHARMACOKINETICS:

Distribution	non-linear pharmacokinetics; distributes to normal and tumour cells where EGFR is expressed	
	cross blood brain barrier?	no information found
	volume of distribution	0.042 L/kg central compartment; 0.026 L/kg peripheral compartment
	plasma protein binding	no information found
Metabolism	no information found	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	saturable elimination mediated via reticuloendothelial system, and internalization and degradation of EGFR	
	urine	no information found
	feces	no information found
	terminal half life[1,3]	7.5 days (range 4-11 days)
	clearance	4.6 mL/day/kg

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:

*Colorectal cancer

*Health Canada approved indication

Other uses:

Developed: 1 August 2009
Revised: 1 January 2020

SPECIAL PRECAUTIONS:

Caution:

- ***Severe infusion reactions***, characterized by anaphylactic reaction, bronchospasm, fever, chills, and hypotension, have been reported in 1% patients. Fatal reactions have not been reported.[1] Routine premedication is not required.[4] Severe or persistent reactions require immediate discontinuation of treatment[1]
- ***Late onset hypersensitivity*** reactions have been reported, including a fatal case of angioedema occurring more than 24 hours after infusion.[1]
- History or evidence of ***interstitial pneumonitis*** or ***pulmonary fibrosis*** require caution. Discontinue treatment in the event of acute onset or worsening of pulmonary symptoms.[1]
- Limit ***sun exposure*** during treatment to prevent exacerbation of dermatologic toxicity.[1]
- ***Concurrent therapy*** with standard cytotoxic chemotherapy has been associated with increased toxicity and decreased overall survival. Exacerbation of severe diarrhea has also been reported in combination with irinotecan, fluorouracil, and leucovorin.[1]

Special populations: Patients ***65 years and older*** may experience an increased incidence of side effects, and side effects are more likely to lead to permanent discontinuation of treatment.[1,5]

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: Animal studies have shown reversible effects on menstrual cycle and reduced female fertility.[1]

Pregnancy: FDA Pregnancy Category C.[3] Animal studies have shown fetal risks, but there are no controlled studies in women. Panitumumab should be given during pregnancy only if the potential benefit justifies the potential risk to the fetus. Appropriate contraception should be used during and for six months following cessation of treatment.[1]

Breastfeeding is not recommended during treatment and for two months following cessation of treatment due to the potential secretion into breast milk.[1]

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.[6]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	***angioedema;*** sometimes fatal; possible late onset (greater than 24 h)
	hypersensitivity, within 24 h (1%)
	infusion reactions, within 24 h (3-4%, severe 1%)[7]; may require dose reduction or treatment cessation[7]; see paragraph following **Side Effects** table
auditory/hearing	vertigo (2%)
blood/bone marrow/ febrile neutropenia	anemia (7%, severe 2%)
cardiovascular (general)	edema (6%, severe 1%)

Developed: 1 August 2009
Revised: 1 January 2020

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hypertension (5%)
	peripheral edema (3-12%, severe 1%)[1,3,8,9]
constitutional symptoms	asthenia (14-15%, severe 3-7%)[1,8]
	chills (3%)
	dehydration (1-4%, severe 2%)
	fatigue (24-50%, severe 3-9%)[1,3,8,9]
	fever (4-18%, severe 1%)[1,8,9]
	general physical health deterioration, unspecified (9%; severe 6%)
	lethargy (2%, severe 1%)
	weight loss (6%, severe 1%)
dermatology/skin	*extravasation hazard:* none[10]
	acne (13-17%, severe 1-2%)
	alopecia (2%)
	dermatitis acneiform (16-62%, severe 7-9%)[1,3,8,9]; see paragraph following **Side Effects** table
	dry skin (10-26%)[1,3,9]
	erythema (64-71%, severe 5-8%)[1,3,8]
	exfoliative rash (25%, severe 2-3%)[1,3]
	hair disorder (2%); see paragraph following **Side Effects** table
	hirsutism[11,12] (≤50%); see paragraph following **Side Effects** table
	hyperpigmentation[11,12]; may be aggravated by UV exposure[11]
	intertrigo (2%)
	nail disorder (9-11%)[1,3]; loosening or shedding of nails (2-4%); see paragraph following **Side Effects** table
	palmar-plantar erythrodysesthesia (2%)
	paronychia (10-33%, severe 1-3%)[1,9]; see paragraph following **Side Effects** table
	pruritus (34-69%, severe 1-4%)[1,3,8,9]
	rash (20-78%, severe 1-3%)[1,3,9]; erythematous, papular, or pruritic (7%)
	scab (5%, severe 2%)
	skin exfoliation (11-25%, severe 2%)[1,9]
	skin fissures (20-24%, severe 1-2%)[1,3]
	skin ulcer (7%, severe 1%)
	sweating (2%)
gastrointestinal	*emetogenic potential:* low[13]
	abdominal distension (4%, severe 1%)
	anorexia (12-30%, severe 3-6%)[1,8,9]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	aphthous stomatitis (2%)
	cachexia (3%)
	constipation (3-24%, severe 3-5%)[1,3,8,9]
	diarrhea (13-24%, severe 1-2%)[1,9]; may result in dehydration
	dysgeusia (2%)
	dyspepsia (4%)
	flatulence (3%)
	gastritis (2%)
	intestinal obstruction (7%, severe 3%)
	mucositis (6-8%, severe ≤1%)[3,7]
	nausea (16-23%, severe 1%)[1,3,9]
	stomatitis (7-14%)[1,9]
	vomiting (7-19%, severe 1-3%)[1,3,9]
	xerostomia (5%, severe 1%)
hemorrhage	epistaxis (5%)
	rectal hemorrhage (2%)
hepatobiliary/pancreas	ascites (5%, severe 2%)
	hepatic failure (2%)
	hepatomegaly (6%, severe 2%)
	jaundice (7%, severe 3%)
infection	bronchitis (2%)
	cellulitis (≤1%)
	eye, eyelid infection (5%)
	folliculitis (2%)
	fungal infection (2%)
	impetigo (2%)
	nasopharyngitis, pharyngitis (7%)
	respiratory tract infections (4%)
	sepsis (≤1%)
	urinary tract infection (2%, severe 1%)
metabolic/laboratory	hyperbilirubinemia (1-2%, severe 1-2%)
	hypocalcemia (2%)
	hypokalemia (4-13%, severe 1%)[1,9]; mild, transient[9]
	hypomagnesemia (1-39%, severe 1-5%)[1,14]; see paragraph following **Side Effects** table
musculoskeletal	gout (1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	muscle spasms (4%)
	muscle weakness (2%)
neurology	agitation (1%, severe 1%)
	anxiety (3%)
	confusion (2%, severe 1%)
	depression (5%, severe 1%)
	dizziness (2%)
	headache (4%, severe 1%)
	insomnia (5%, severe 1%)
	neuropathy (2%, severe 1%)
	paresthesias (3%)
ocular/visual	conjunctivitis (3-6%)[1,3,9]
	eye or eyelid irritation (2%)
	eyelash growth abnormalities (2-10%)[1,3]
	lacrimation (1-4%)[1,3]
	ocular hyperemia (1-6%)[1,3]
pain	***abdominal pain*** (6-27%, severe 7%)[1,3,8,9]
	arthralgia (1-6%, severe 2%)[1,9]
	back pain (10-13%, severe 1-2%)[1,8]
	bone pain (3%, severe 1%)
	dysuria (2%, severe 1%)
	musculoskeletal chest pain (4%)
	myalgia (2%)
	pain (4-8%)
	pharyngolaryngeal pain (2%)
	proctalgia (2%, severe 1%)
	renal pain (2%)
pulmonary	cough (2-20%)[1,3,9]
	dysphonia (2%)
	dyspnea (2-19%, severe 1-5%)[1,8,9]
	hemoptysis (2%)
	pleural effusion (2%)
	productive cough (2%)
	pulmonary embolism (≤1%)
	pulmonary fibrosis (≤1%)[7]; sometimes fatal, caution with pre-existing lung disease[1,7]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
renal/genitourinary	hematuria (2-4%, severe 1%)
	oliguria (2%, severe 1%)
	renal failure (2%); see paragraph following **Side Effects** table
	urinary retention (2%)

Adapted from standard reference [1] unless specified otherwise.

Dermatologic toxicities, including dermatitis acneiform, pruritus, erythema, exfoliative rash, and paronychia, are reported in 91-95% of patients.[1,9] Reactions are usually mild to moderate in severity, but 5-16% are reported as grade 3 or 4.[1,3,7,9] Skin rash, characterized by multiple pustular, macular, or papular-appearing lesions, most commonly occurs on the face, upper back and chest, but can extend to the extremities.[1] Dry, flaking skin, pruritis, and fissures are commonly reported. Perioral fissures and cracks on the lips may be extremely painful.[11] Typical time to onset is 9-14 days, with resolution occurring between 20-84 days after treatment.[1,3,7,9] Sunlight exposure is known to exacerbate skin reactions and hyperpigmentation, and should be limited.[1,11] Dose reduction may be required and treatment should be withheld until recovery for severe skin reactions. Monitor for inflammatory and infectious complications with severe dermatologic toxicity. Local abscesses may require incision and drainage; and sepsis, in rare cases, has lead to death.[1] Treatment with topical or oral antibiotics (metronidazole, clindamycin, tetracyclines) may be required. Topical steroids may have a limited role in treatment, but systemic steroids should be avoided. Emollients are suggested for dry skin. Retinoids and benzoyl peroxide may worsen the condition and are not recommended. Oral antihistamines may be useful for itching.[15-17] Pre-emptive management of dermatologic toxicity may be beneficial.[16]

Characteristic ***hair changes*** are reported. Alopecia is infrequently reported with EGFR inhibitors, but curly, more brittle hair, with a dry pruritic scalp is also noted. Increased or thickening hair growth on the extremities and new hair growth circumferentially around the eyes are reported. Up to 50% of women receiving panitumumab for longer than six weeks in one study reported hirsutism. Trichomegaly and increased eyelash growth, as well as thickened, rigid eyebrow hairs are observed.[11,15]

Nail changes are a late manifestation with EGFR inhibitors, usually starting 4-8 weeks after therapy initiation. Nails are reportedly more brittle and may crack, and tend to grow more slowly. Initially, paronychia may mimic an ingrown toenail, with gradual progression to periungual granulation-type changes, associated with erythema, swelling and fissuring of the lateral folds and distal tufts of the digits. Pyogenic granuloma of the nail folds may develop in severe cases. Secondary infections with bacteria or fungi commonly develop.[11,15]

Hypomagnesemia (any grade) is observed in up to 39%,[1] and may result from magnesium wasting through urinary excretion.[14] Symptoms include severe weakness, cramps, and fatigue. Serious cases of hypomagnesemia, however, may be subclinical, and have been reported greater than 6 weeks after initiation of treatment.[1,5,14] Elderly patients may be more susceptible.[5] Oral magnesium replacement may be ineffective and poorly tolerated.[5,14] Most grade 3 or higher hypomagnesemia require intravenous electrolyte repletion. Electrolytes should be monitored before, during, and for 8 weeks after cessation of treatment and replenished as necessary.[1,14]

Infusion reactions include chills, fever, or dyspnea, and are usually mild in intensity. Most mild reactions resolve without treatment, and do not require interruption of administration.[1] Mild to moderate reactions can be managed by reducing infusion rate.[7] Severe infusion reactions occur in approximately 1%, and require permanent discontinuation of treatment.[1] Fatal infusion reactions have not been reported. Routine premedication is not required.[4,7]

Acute ***renal failure*** has been reported in patients developing severe diarrhea and dehydration, primarily with combination chemotherapy. Monitor for decreased urine output, dizziness, hypotension, and rapid heartbeat and treat as appropriate. Withhold panitumumab until recovery.[1]

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INTERACTIONS: no information found

SUPPLY AND STORAGE:

***Injection*:** Amgen Canada Inc. supplies panitumumab as 100, 200, and 400 mg ready-to-use, single-use, preservative free vials at a concentration of 20 mg/mL. Refrigerate.[1]

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 particulates in the vials will not affect the quality of the product. Do not use if solution is discoloured. Administer using a 0.2 or 0.22 micron low protein binding in-line filter.[1]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous[1]	do NOT use
Intermittent infusion[18-23]	• ***doses ≤1000 mg: infuse over 60 minutes***; if first infusion is tolerated, subsequent infusions may be administered over 30-60 minutes • doses >1000 mg: infuse over 90 minutes
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.

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***Adults*:**

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

Intravenous:	Cycle Length: ***2 weeks***[1,24]: ***6 mg/kg IV for one dose on day 1***
Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"
Dosage in renal failure:	renal function appears to have no impact on the pharmacokinetics of panitumumab[18]; panitumumab has been used in chronic kidney disease without dose adjustment[25]
Dosage in hepatic failure:	hepatic function appears to have no impact on the pharmacokinetics of panitumumab[18]; panitumumab has been used in hepatic dysfunction without dose adjustment[26]
Dosage in dialysis:	physicochemical properties of panitumumab suggest that significant drug removal is unlikely during dialysis[27]

Children: no information found

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