DRUG NAME: Bevacizumab

SYNONYM(S): NSC704865

COMMON TRADE NAME(S): AVASTIN®, MVASI® (biosimilar), ZIRABEV® (biosimilar)

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Bevacizumab is a recombinant humanized monoclonal antibody that selectively binds to and neutralizes the biologic activity of human VEGF.[1] This reduces the vascularization of tumours, thereby inhibiting tumour growth. It does not appear to be cell-cycle specific.

PHARMACOKINETICS:

Interpatient variability	clearance may vary up to 44%[2]; 30% change in body weight associated with 19% change in clearance[2]; some markers of disease severity (albumin ≤ 29 g/dL, alkaline phosphatase ≥ 484 U/L) associated with 20% increase in clearance[1]	
Distribution	cross blood brain barrier?	no information found
	volume of distribution	2.66 - 3.25 L
	plasma protein binding	no information found
Metabolism	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	urine	no information found
	feces	no information found
	terminal half life	19 - 20 d
	clearance	0.207 - 0.262 L/d
Gender	males have 22% larger volume of distribution and 26% higher clearance, even after correcting for body weight	
Elderly	no difference in bevacizumab clearance	

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:

* Colorectal cancer
* Lung cancer, non-small cell
* Brain tumour
* Ovarian cancer
* Liver cancer

Other uses:

Head and neck cancer[3]
Mesothelioma[3]
Prostate cancer[3]
Renal cell cancer[3,4]

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to bevacizumab or other recombinant human or humanized antibodies, or Chinese hamster ovary cell products
- untreated central nervous system metastases

Caution:
- increased risk of ***post-operative bleeding*** and ***wound healing*** complications; suggest hold bevacizumab for at least 28 days before or after major ***surgery*** and until surgical wound is fully healed[4,5]
- ***osteonecrosis of the jaw*** has been reported, mainly in association with prior or concurrent bisphosphonate therapy***;*** consider appropriate preventive dentistry prior to treatment[6]
- uncontrolled ***hypertension***
- risk factors for ***thromboembolic*** events: history of arterial thromboembolic events or age greater than 65 years
- risk factors for development of ***CHF***: prior anthracycline exposure or chest wall radiation
- congenital ***bleeding*** diatheses, acquired coagulopathy, full dose anticoagulants
- serious ***hypersensitivity reactions***, including anaphylactic and anaphylactoid-type reactions, have been reported[5]
- ***ovarian failure*** has been reported; fertility preservation strategies and hormonal changes associated with ovarian failure should be discussed with premenopausal women prior to treatment.[7,8]

Special populations: Patient age > 65 years is associated with an increased risk of arterial thromboembolic events, including cerebrovascular accidents, transient ischemic attacks, and myocardial infarction. Other reactions seen with a higher frequency include grade 3-4 leukopenia and thrombocytopenia, proteinuria, and all grade neutropenia, diarrhea, nausea, headache, and fatigue.[5]

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: The inhibition of angiogenesis is considered likely to result in an adverse effect on female fertility.[5] New cases of ovarian failure have been observed in premenopausal women treated with bevacizumab.[7,8] Ovarian function recovered in the majority of patients after discontinuation of treatment. Long term effects on fertility are not known.[8] In animals, fertility was impaired by several mechanisms, including endometrial proliferation, number of menstrual cycles, arrested follicular development, decreased ovary weight, or absent corpora lutea[9]; however, results were reversible upon treatment cessation.[5] No effect on male reproductive organs was observed.[5]

Pregnancy: FDA Pregnancy Category C.[9] Animal studies have shown embryotoxicity and teratogenicity. There are no controlled studies in women; however, angiogenesis is critical to fetal development, so inhibition of angiogenesis is likely to result in adverse effects on pregnancy. Bevacizumab should be given only if the potential benefit justifies the potential risk to the fetus. Consider appropriate contraception during and for at least 6 months following bevacizumab therapy.[5]

Breastfeeding is not recommended during therapy and for at least 6 months following the last dose.[1,5]

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.[10,11] When placebo-controlled trials are available, adverse events are generally included if the incidence is $\geq$ 5% higher in the treatment group.[12,13] **Incidence data in the Side Effect table is based on bevacizumab monotherapy data unless indicated with an asterisk (*).**

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	***hypersensitivity reaction*** (≤5%*)[5,14]; see paragraph following **Side Effects** table
blood/bone marrow/ febrile neutropenia	anemia (1%)[5]
	leucopenia[15] (21%*)
	neutropenia (2%)[5]
	thrombocytopenia (2%)[5]
	pancytopenia (rare*)[3]
cardiovascular (general)	***hypertension*** (7-34%, severe 3-18%*)[1,5,16,17]; see paragraph following **Side Effects** table
	hypertensive crisis[5] (≤1%*)
	hypotension (7-15%*)[18]
	congestive heart failure (0-3%, severe 1-4%*)[1,18,19]; possible risk factors include prior anthracycline exposure and/or prior chest wall radiation [5]
	tachycardia (3-4%*)
coagulation	***arterial thromboembolism*** (3-11%, severe 2-4%)[5,16,17,19]; includes cerebrovascular accident, transient ischemic attack, and myocardial infarction; see paragraph following **Side Effects** table
	venous thromboembolism[5] (2-18%, severe 4-8%*)[5,16,17,19]; includes deep vein thrombosis and pulmonary embolus
constitutional symptoms	asthenia, muscular weakness (10-11%)[5]
	fatigue (45%)[5,16,17]
	fever (8%)[5]
	weight decrease[5] (6%)
	weight increase[5] (7%)
dermatology/skin	*extravasation hazard: none*[20]
	alopecia[5] (1%)
	erythema (2-15%*)
	nail disorders (2-8%*)[3,18]
	rash[5] (13%)
	wound healing complications (4-20%, severe 2%)[5,16,17,19]; including wound dehiscence; see paragraph following **Side Effects** table
endocrine	Cushingoid[5] (6%)
eye	blurred vision[5] (7%)
gastrointestinal	*emetogenic potential: rare*[21]
	anorexia, decreased appetite (6-13%)[5]
	constipation (14%)[5]
	dehydration[5] (8%)
	diarrhea (21%)[5]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	dyspepsia (1%)[5]
	dysphagia[5] (2%)
	gastrointestinal fistula or perforation (<3%*)[5,17]; 2% in colorectal cancer, less common in other cancers[22]; see paragraph following **Side Effects** table
	gastrointestinal reflux disease (1%)[5]
	hemorrhoids[5] (5%)
	intestinal obstruction (9%*)
	intestinal necrosis (rare*)[3]
	nausea (16%)[5]
	osteonecrosis of the jaw (<1%)[6]
	stomatitis (24-32%*)[18,23]
	transesophageal fistula (reported only in patients with lung or esophageal cancer)[22]
	vomiting[5] (6%)
hemorrhage (see paragraph following **Side Effects** table)	epistaxis[5,17] (19-26%); usually grade 1, lasting less than 5 minutes
	gingival bleeding[5] (6%)
	hemoptysis[5] (2%)
	intracranial hemorrhage[5] (2-3%)[16,19]
	mucocutaneous hemorrhage, including epistaxis, gingival, and vaginal bleeding (20-40%*)
	pulmonary hemorrhage (4-31%* in lung cancer)[24]
	rectal hemorrhage (2%)[5]
	tumour-associated hemorrhage (3-5%*); usually severe, can occur suddenly
hepatobiliary/pancreas	biliary fistula (<1%*)[22]
infection	candidiasis[5] (4%)
	cellulitis[5] (2%)
	nasopharyngitis[5] (7%)
	necrotizing fasciitis[25] (<1%); may be fatal
	pneumonia[5] (1%)
	sepsis (8%*)
	upper respiratory tact [5] (12%)
	urinary tract[5] (12%)
metabolic/laboratory	alkaline phosphatase, increased (severe ≥ 5%*)
	ALT, increased[5] (11%)
	AST, increased[5] (7%)
	hyperglycemia (17%)[5]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hypocalcemia[5] (1-4%)
	hypokalemia (8%)[5]
	hyponatremia (4%)[5]
	hypophosphatemia (severe ≥ 5%*)
neurology	agitation[5] (2%)
	amnesia [5] (7-13%)
	anxiety[5] (6%)
	aphasia [5] (5-13%)
	ataxia [5] (1-11%)
	cognitive disorder, memory impairment[5] (7-13%)
	confusion[5] (14%)
	convulsion[5,16] (6-16%; severe 6%)
	depression[5] (7%)
	dizziness[5] (7%)
	encephalopathy, hypertensive (<1%*)[3,5]
	hemiparesis[5] (11%)
	gait disturbance[5] (8%)
	insomnia[5] (14%)
	paresthesia, hypoesthesia (5-11%)[1,5]
	reversible posterior leukoencephalopathy syndrome (RLPS) (≤1%*); unpredictable onset, reported to occur from 16 hours to 1 year after start of therapy[5]; see paragraph following **Side Effects** table
	somnolence[5] (10%)
	tremor[5] (6%)
ocular/visual	eye disorder (≥10%*)[22]
pain	abdominal pain (4%)[1,5]
	arthralgia[5] (14%)
	back pain[5] (8%)
	extremity pain[5] (14%)
	headache[5] (37-38%)
	musculoskeletal pain[5] (8%)
	pain (34-50%, severe 5-6%*)
	pharyngolaryngeal pain[5] (7%)
pulmonary	bronchopleural fistula (<1%*)[22]
	congestion, nasal or sinus[5] (4-7%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	cough[5] (14%)
	dysphonia[5] (1-11%)
	dyspnea (12%)[5,22]
	nasal septum perforation[5] (1-9%*)[26-28]
	pulmonary hypertension[5]; manifesting as dyspnea on exertion, fatigue, syncope, angina, hemoptysis, and Raynaud's phenomenon
	rhinorrhea[22] (4%)
renal/genitourinary	***proteinuria*** (≤38%,severe <5%*)[5]; see paragraph following **Side Effects** table
	ureteral stricture (rare*)[3]
	urogenital fistula (<1%*)[22]
vascular	flushing[5] (1%*)
	peripheral edema[5] (13%)
	renal thrombotic microangiopathy[5]; clinically manifested as proteinuria

Adapted from standard reference[1] unless specified otherwise.

Arterial thromboembolic events (ATE), including stroke, transient ischemic attacks, and myocardial infarction, can occur more commonly in patients receiving bevacizumab (2-fold increased risk) and can be fatal in some cases.[11,18] History of ATE or age greater than 65 years may increase risk.[18]

Gastrointestinal perforation, fistula, and intra-abdominal abscess can occur, and have been fatal in some cases. Gastrointestinal perforation may occur at any time during treatment (i.e., it has not been correlated with duration of exposure) although most cases occur within 50 days of treatment initiation. Patients generally present with fever, abdominal pain, constipation, and/or nausea/vomiting.[1,18] Bevacizumab should be permanently discontinued in patients with tracheoesophageal fistula or any grade 4 fistula.[18]

Hemorrhage, especially tumour-associated hemorrhage, has been reported. These events can occur suddenly and can be fatal. Patients should be monitored for bleeding events and treatment permanently discontinued for grade 3 or 4 bleeding. NSCLC patients with recent ***pulmonary hemorrhage/ hemoptysis*** (>2.5 mL red blood) should not be treated with bevacizumab. Minor mucocutaneous hemorrhages were also reported in 20-40% in clinical trials. Of these, grade 1 epistaxis (possibly dose dependent), was reported most commonly; gingival and vaginal bleeding less commonly.[5]

Hypertension is likely to be dose-dependent,[1] and is generally adequately controlled with oral antihypertensives.[5] It rarely requires discontinuation of bevacizumab or hospitalization. However, very rare cases of hypertensive encephalopathy have been reported, some of which were fatal. Symptoms of hypertensive encephalopathy may include severe hypertension associated with headache, nausea, vomiting, convulsions, or confusion. Hypertensive encephalopathy may be reversible if blood pressure is progressively reduced to near normal range within several hours.[5] Blood pressure should be monitored before each treatment cycle.[29-32]

Infusion and hypersensitivity reactions have been reported in up to 5% of patients and may manifest as dyspnea/difficulty breathing, flushing/redness, rash, hypo- or hypertension, oxygen desaturation, chest pain, rigors, and nausea/vomiting. Infusions should be interrupted in the event of a reaction. In general, routine premedication is not warranted, however use should be dictated by clinical judgement.[5]

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Non-GI fistula may occur throughout treatment, but typically occur within the first 6 months. Fistula formation, sometimes fatal, may occur in tracheo-esophageal, bronchopleural, biliary, vaginal, and bladder areas. Bevacizumab should be discontinued if fistula formation involves an internal organ.[33]

Proteinuria, reported in up to 38% of patients, may range in severity from clinically asymptomatic, transient trace proteinuria to nephrotic syndrome[5] and may be dose-dependent.[1] Although bevacizumab induced proteinuria is rarely associated with renal impairment (nephrotic syndrome, glomerulonephritis), some patients require permanent discontinuation.[5] Animal studies suggest that the mechanism may be a reduction in glomerular endothelial cell proliferation.[34] Patients with a history of hypertension may be at increased risk.[1] Dipstick urinalysis is recommended for all patients, at baseline and throughout treatment.

Reversible posterior leukoencephalopathy syndrome (RPLS), a rare neurologic disorder, has been reported. Symptoms may include seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension, and may be difficult to differentiate from those of uncontrolled hypertension. Brain imaging confirms the diagnosis. Onset of symptoms may occur from 16 hours to 1 year after initiation of bevacizumab. RPLS may be reversible if promptly treated. Symptoms usually resolve within days, although neurologic sequelae may remain.[5]

Wound healing may be impaired. VEGF has been associated with wound healing, and some VEGF inhibitors may inhibit dermal-wound angiogenesis.[12] Complications can occur, and have been fatal in some cases.[1,5] The appropriate interval between bevacizumab and elective surgery is unknown, however it is suggested that bevacizumab should be held for at least 28 days prior to elective surgery,[4] and should not be initiated for at least 28 days following major surgery and until surgical wound is fully healed to prevent complications.[4,5]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
anthracyclines[3]	anthracycline-induced cardiotoxicity may be increased	unknown	monitor cardiac function as per doxorubicin monograph
CARBOplatin[5]	no effect on CARBOplatin pharmacokinetics		
DOXOrubicin[5]	no effect on DOXOrubicin pharmacokinetics		
fluorouracil[5]	no effect on fluorouracil pharmacokinetics		
irinotecan[5,35,36]	toxicity of irinotecan may be increased	unknown; plasma levels of irinotecan active metabolite (SN-38) may increase 33%	consider irinotecan dose reduction for patients developing severe diarrhea or neutropenia.[5]
PACLitaxel[5]	no effect on PACLitaxel pharmacokinetics		
SUNItinib[5,37]	microangiopathic hemolytic anemia (MAHA)	thrombotic lesions in microvessels	combination not recommended; monitor for red cell fragmentation, anemia, thrombocytopenia, and for signs of MAHA[5,37]

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SUPPLY AND STORAGE:

Biosimilar formulations of bevacizumab are available.

Injection:

Hoffmann-La Roche supplies bevacizumab (AVASTIN®) as 100 mg and 400 mg single-use, preservative-free vials in a concentration of 25 mg/mL. Refrigerate. Protect from light. Do not shake.[5]

Amgen Canada Inc. supplies bevacizumab (MVASI®) as 100 mg and 400 mg single-use, preservative-free vials in a concentration of 25 mg/mL. Refrigerate. Protect from light. Do not shake.[38]

Pfizer Canada ULC supplies bevacizumab (ZIRABEV®) as 100 mg and 400 mg single-use, preservative-free vials in a concentration of 25 mg/mL. Refrigerate. Protect from light. Do not shake.[39]

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: Do not mix with dextrose or glucose solutions (e.g., D5W), as a concentration-dependent degradation of bevacizumab has been observed.[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	do NOT use[5]
Intermittent infusion	***over 10-60 minutes***[40-42] alternatively, first dose may be given over 90 minutes; if well tolerated, second dose over 60 minutes; if well tolerated, subsequent infusions over 30 minutes.[43]
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
Intravitreal	has been used for macular degeneration[44]

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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***

Intravenous:	Cycle Length:	
	2 weeks[31,32,38,39,45]:	***5 mg/kg IV for one dose on day 1*** (total dose per cycle 5 mg/kg)
	3 weeks[29,30,46-49]:	***7.5 mg/kg IV for one dose on day 1*** (total dose per cycle 7.5 mg/kg)
	2 weeks[38,39,42,45]:	***10 mg/kg IV for one dose on day 1*** (total dose per cycle 10 mg/kg)
	3 weeks[38,39,42,45,50]:	***15 mg/kg IV for one dose on day 1*** (total dose per cycle 15 mg/kg)
	Dose reduction for adverse events is not recommended. Bevacizumab should be either discontinued or temporarily suspended.[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:	no information found; however, altered pharmacokinetics are not expected due to renal impairment as the kidney is not a major organ for bevacizumab metabolism or excretion[45]	
Dosage in hepatic failure:	no information found; however, altered pharmacokinetics are not expected due to hepatic impairment as the liver is not a major organ for bevacizumab metabolism or excretion[45]	
Dosage in dialysis:	no information found	

Children: safety and efficacy in pediatric patients have not been established[1]

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