Drug Monograph

A - Drug Name

bevacizumab

COMMON TRADE NAME(S): Avastin®; Mvasi®; Zirabev®; Bambevi®; Abevmy®; Aybintio®; Vegzelma™

- Different bevacizumab products are **not interchangeable**.
- For additional information on biosimilars, refer to:
  - Position Statements for the Clinical Operational Implementation of Oncology Biosimilars from the pan-Canadian Clinical Operations Working Group
  - Clinician Fact Sheet

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B - Mechanism of Action and Pharmacokinetics

Human vascular endothelial growth factor (VEGF) binding to its receptor initiates angiogenesis (endothelial proliferation and the formation of new blood vessels). Bevacizumab is a recombinant humanized monoclonal antibody that prevents binding of VEGF to its receptors on the surface of endothelial cells and inhibits the biologic activity of VEGF.

Absorption	Oral: Not orally bioavailable	
Distribution	Pharmacokinetics of bevacizumab are linear at doses ranging from 1 to 10 mg/kg. The predicted time to reach steady state is 100 days. Male subjects had a higher volume of distribution (+ 22%) than females.	
	Cross blood brain barrier?	No information found (unlikely)
	PPB	No information found

Metabolism	Bevacizumab is metabolized and eliminated via the reticuloendothelial system.	
	Active metabolites	no
	Inactive metabolites	no
Elimination	Males and patients with low albumin or high alkaline phosphatase have higher clearance (+20-26%).	
	Urine	no
	Half-life	20 days

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C - Indications and Status

Health Canada Approvals:

- Colorectal cancer
- Non-small cell lung cancer (NSCLC)
- Ovarian, fallopian tube, or primary peritoneal cancer
- Glioblastoma

Refer to the product monograph for a full list and details of approved indications.

Other Uses:

- Cervical cancer
- Mesothelioma
- Hepatocellular carcinoma

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

Adverse effects noted below are based on bevacizumab monotherapy from the phase II study, compared to combination with irinotecan in patients with glioblastoma. Severe or life-threatening events are also listed from pooled analyses of multiple indications or post-marketing data.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (<10%)	E
	Arterial thromboembolism (6%)	E
	Cardiotoxicity (13%) (2% severe)	I E
	Hypertension (44%) (up to 18% severe)	I E
	Pulmonary hypertension (rare)	E D L
	Venous thromboembolism (≤17%) (8% severe)	E
Dermatological	Other - Necrotizing fasciitis (rare)	E
	Rash (13%) (may be severe)	E
Gastrointestinal	Abdominal pain (4%)	E
	Anorexia (13%)	E
	Constipation (14%)	E
	Diarrhea (21%)	I E
	GI obstruction (<10%)	E
	GI perforation (3%) (or GI ulceration)	E
	Nausea, vomiting (16%)	I E
	Other (7%) - Pharyngolaryngeal pain	E
General	Delayed wound healing (4%) /dehiscence	E
	Fatigue (45%)	E
	Fistula (GI - 2%; tracheo-esophageal, biliary, urogenital; rare), organ perforation (nasal; rare)	E D L
Hematological	Hemorrhage (≤50%) (includes epistaxis; < 10% severe)	E
	Myelosuppression ± infection (7%) (may be severe)	E
	Thrombotic microangiopathy (rare)	E
Hypersensitivity	Hypersensitivity (≤5%)	I E
Infection	Infection (12%)	E
Musculoskeletal	Musculoskeletal pain (14%)	E
	Osteonecrosis of jaw and other (rare)	E
Nervous System	Dizziness (7%)	E
	Headache (37%)	E
	Insomnia (14%)	E D

	Posterior reversible encephalopathy syndrome (PRES) (rare)	E
	Somnolence (<10%)	E
Renal	Proteinuria (38%) (severe 10%)	E D
Respiratory	Cough, dyspnea (14%)	E D
	Dysphonia (≤10%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for bevacizumab include bleeding, fatigue, hypertension, proteinuria, headache, diarrhea, venous thromboembolism, nausea, vomiting and constipation.

The most serious adverse effects include **gastrointestinal perforation, fistulas, hemorrhage, thromboembolism, severe hypertension (including PRES), cardiac and renal effects**.

Bevacizumab may exacerbate common toxicities of chemotherapy (hand foot syndrome, neurotoxicity, thrombocytopenia) when given in combination.

Hypertension is commonly observed, likely dose-dependent and should be managed with antihypertensives. Avoid diuretics in patients receiving cisplatin chemotherapy. The risk may be greater in platinum-sensitive, recurrent ovarian cancer patients. Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment.

Patients with a history of hypertension may be at increased risk for the development of **proteinuria**. This is likely dose-related and may not completely resolve after discontinuing bevacizumab. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during bevacizumab therapy (see Monitoring section). Grade 4 proteinuria was seen in up to 1.4% of patients and was sometimes fatal.

Infusion and hypersensitivity reactions (including hypertension, respiratory and neurologic symptoms and hypertensive crisis) have been reported and appear to be more common when given in combination with chemotherapy.

Posterior reversible encephalopathy syndrome (PRES) is rare and may occur from 16 hours to 1 year after the start of bevacizumab. Patients present with seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without associated hypertension. It is reversible if treated promptly after diagnosis with brain imaging, particularly MRI. Treatment of specific symptoms, including control of hypertension is recommended along with discontinuation of bevacizumab.

An increased risk of **arterial thromboembolic** events, including cerebrovascular accident, transient ischemic attack and myocardial infarction have been reported, especially in older patients, those with diabetes or prior events. **Venous thromboembolism** is also a risk, especially in patients with

a prior history and patients with glioblastoma or cervical cancer (increased risk reported in clinical trials).

Congestive heart failure has been reported especially in metastatic breast cancer patients as well as patients with risk factors such as prior anthracyclines, radiation treatment, prior cardiovascular disease and in patients with lymphoma treated with R-CHOP. Bevacizumab is not indicated for use in the treatment of metastatic breast cancer.

Gastrointestinal perforation (including gallbladder) has been reported in all tumour types, although it is more common in colorectal and cervical cancer. An increased risk (nearly double) of intestinal perforation has been reported in colorectal cancer patients who have colorectal stents. The use of bevacizumab in these patients should be considered with caution (Health Canada review, Feb 2017).

Fistulas have been reported in all sites, including nasal septal perforation, and more common in colorectal cancer, especially with prior surgery or radiation in the area. Most fistulas were reported within the first 6 months of treatment, but may occur more than a year from treatment initiation. An increased risk (up to 8%) of gastrointestinal-vaginal fistulae was reported in patients with cervical cancer especially those patients who had received pelvic radiation. Use of bevacizumab in cervical cancer is off-label and has not been approved by Health Canada.

Hemorrhagic events may be life-threatening and include tumour-associated hemorrhage in all tumour types as well as CNS bleeding (especially in malignant glioma). The risk of hemoptysis is increased in patients with squamous NSCLC. There does not appear to be an increased risk in patients who are anticoagulated for venous thromboembolism.

Bevacizumab may adversely affect **wound healing** and should not be initiated for at least 28 days following major surgery (and held for 28 days prior to surgery, if elective) or until the surgical wound is fully healed.

Necrotizing fasciitis has been reported rarely, often secondary to wound healing complications, gastrointestinal perforation or fistulas. All patients were receiving additional chemotherapies other than bevacizumab; however, some patients did not have any other risk factors.

There is an increased risk of **myelosuppression** when used in combination with chemotherapy, and of thrombocytopenia when used in combination with gemcitabine/platinum-based treatment, especially in older patients.

Osteonecrosis of the jaw (ONJ) has been reported with prior or concomitant IV bisphosphonate treatment, radiation to the jaw, invasive dental procedures or glucocorticoid treatment.

Increased **ovarian failure** has been reported and appears to be reversible.

Intraocular inflammation or hemorrhage, retinal detachment or tear, increased need for cataract surgery, arterial thromboembolism and hypertension have been reported at increased rates with intraocular use, which is not approved in Canada and for which bevacizumab is not formulated.

Anti-bevacizumab and neutralizing antibodies have been observed rarely (<1%). The clinical significance of these is unknown.

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E - Dosing

Refer to protocol by which patient is being treated.

Bevacizumab should not be initiated in patients with recurrent hemoptysis, uncontrolled hypertension or wounds that require healing.

Prior to treatment, a dental evaluation should be performed and major dental procedures completed.

Routine primary prophylaxis for infusion reactions is not recommended; the use of secondary prophylaxis pre-medications should be based on clinical judgement.

Different bevacizumab products are **not interchangeable.**

Adults:

Combination therapy

Various dosing and schedules are used depending on the indication or chemotherapy regimen; the dosages listed below do not represent a comprehensive list. Refer to the related regimen monographs for details.

Colorectal Cancer:
Intravenous: 5 mg/kg Every 2 weeks (refer to FOLFIRI+BEVA or mFOLFOX6+BEVA)
Intravenous: 7.5 mg/kg Every 3 weeks* (refer to XELOX+BEVA or CAPE+BEVA)

Glioblastoma (in combination with lomustine):
Intravenous: 10 mg/kg Every 2 weeks

NSCLC:
Intravenous: 15 mg/kg Every 3 weeks

Recurrent epithelial ovarian, fallopian tube and primary peritoneal cancer in platinum-resistant or platinum-sensitive patients, in combination with

- q3w topotecan (platinum-resistant) or
- carboplatin and gemcitabine (platinum-sensitive)

Intravenous: 15 mg/kg Every 3 weeks

Recurrent epithelial ovarian, fallopian tube and primary peritoneal cancer in platinum-resistant patients, in combination with

- weekly topotecan, or
- weekly paclitaxel, or
- pegylated liposomal doxorubicin

Intravenous: 10 mg/kg Every 2 weeks

High Risk epithelial ovarian, fallopian tube and primary peritoneal cancer (in combination with carboplatin and paclitaxel*)**:**
Intravenous: 7.5 mg/kg Every 3 weeks

*based on NDFP, not Health Canada

Dosage with Toxicity:

Dose reductions are not recommended. Bevacizumab should be held or discontinued based on toxicity.

Bevacizumab action	**Toxicity**		
	Any grade	**Grade 3**	**Grade 4**
Hold:	Uncontrolled hypertension		
	Delayed wound healing		
	Proteinuria ≥ 2g/ 24 hours*		
	Surgery**		
Discontinue:		Hypertension, not controlled with medical management	Hypertension
	Wound dehiscence, poor healing requiring medical intervention; necrotizing fasciitis		
	Nephrotic syndrome; non-recovery of proteinuria ≥ 2g/24 hours		
	Tracheo-esophageal fistula,		

	other non-GI fistulae		Any internal fistula
	GI perforation or fistula		
	PRES, hypertensive encephalopathy		
	Arterial thromboembolism	Pulmonary embolism	Venous thromboembolism (including pulmonary embolism)
	Symptomatic cardiac failure		
	Recurrent hemoptysis > 2.5 mL	Bleeding (any)	Bleeding (any)
	Intracranial bleeding		
* may restart when < 2g/24hrs ** for 28 days PRIOR (if surgery elective) and AFTER major surgery, or until wound healed			

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • Once symptoms resolve, the infusion can be restarted at a slower rate, unless a serious reaction occurred.	• No specific recommendations can be made at this time
3 or 4	• Stop treatment. • Aggressively manage symptoms.	

Dosage with Hepatic Impairment:

Has not been studied. Not a major route of bevacizumab metabolism or excretion.

Dosage with Renal Impairment:

Has not been studied. Not a major route of bevacizumab metabolism or excretion.

Dosage in the elderly:

Use with caution; patients > 65 years old have an increased risk of arterial thrombotic events as well as myelosuppression, fatigue, proteinuria, hypertension, dizziness, dysphonia, anorexia and GI effects (except gastrointestinal perforation).

Dosage based on gender:

Women have increased risk of severe hypertension, fatigue and abdominal pain, and lower bevacizumab clearance than men; however, no dose adjustment is required.

Children:

The safety and efficacy of bevacizumab in patients less than 18 years of age have not been established. The addition of bevacizumab to standard of care did not show clinical benefit in this population in some phase II clinical trials. Osteonecrosis has been observed in clinical trials.

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F - Administration Guidelines

Different bevacizumab products are **not interchangeable.**

- DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.
- Bevacizumab infusions should **NOT** be administered or mixed with dextrose or glucose solutions due to potential for drug degradation.
- Mix in 100 mL bag NS. (Final concentration should be 1.4 -16.5 mg/mL).
- Compatible with PVC or polyolefin bags.
- Do not shake. Should not be mixed or diluted with other drugs.
- Infuse over 90 minutes as loading dose, if well tolerated next infusion can be given over 60 minutes; if well tolerated, can thereafter be given over 30 minutes as maintenance dose.
- Bevacizumab rapid infusion (over 10 minutes) has safely been administered with no significant increase in infusion reactions (for 5mg/kg and 7.5mg/kg doses)[1].
- Refrigerate unopened vials and protect from light; do not freeze.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

[1]Mahfood et al. 2012, Reidy et. al 2007

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G - Special Precautions

Contraindications:

- Patients with known hypersensitivity to bevacizumab or its components
- Patients with known hypersensitivity to Chinese hamster ovary cell product or to other recombinant human or humanized antibodies
- Patients with untreated CNS metastases

Other Warnings/Precautions:

- Elderly patients
- Patients with a history of arterial thromboembolism or significant cardiovascular disease or cardiac failure
- Patients with coagulopathies (congenital, acquired or therapeutic)
- Patients with recurrent hemoptysis (>2.5ml), serious hemorrhage, or with *squamous* NSCLC
- Patients with colorectal cancer and colorectal stents; increased risk of GI perforation has been reported; use with caution.
- Hypertension should be controlled prior to starting treatment
- Bevacizumab should not be initiated for at least 28 days following major surgery or until wound healing has occurred; hold for 28 days prior to major elective surgery
- Use caution if given with bisphosphonates or other anti-angiogenic agents, given increased risk of ONJ
- Do not use with diuretics in patients who are receiving platinum-based chemotherapy
- The safety and efficacy of concurrent radiotherapy and bevacizumab has not been established
- Bevacizumab IV solution is not formulated for, and has not been authorized for intravitreal use

Other Drug Properties:

- Carcinogenicity: Unknown
  Carcinogenicity and mutagenicity have not been studied.

Pregnancy and Lactation:

- Embryotoxicity: Yes

- Teratogenicity: Yes
  Bevacizumab is not recommended for use in pregnancy. Cases of fetal abnormalities have been reported. Adequate contraception (including at least 2 contraceptive methods) should be used by both sexes during treatment, and for at least **6 months** after the last dose.
- Excretion into breast milk: Probable
  Breastfeeding is not recommended during treatment and for at least **6 months** following the last dose.
- Fertility effects: Yes
  Long-term effects unknown. Discuss fertility preservation with women of reproductive potential prior to starting treatment.

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H - Interactions

No formal drug interaction studies have been performed. Combinations with EGFR monoclonal antibodies (e.g. cetuximab) and bevacizumab have not been studied and should not be administered for metastatic colorectal cancer. The safety and efficacy of concurrent radiotherapy has not been established.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Anthracycline, thoracic radiation	↑ cardiotoxicity	Unknown	Caution
Irinotecan	Potential ↑ toxicity of Irinotecan	↑ SN38 (irinotecan metabolite) concentrations	Caution
sunitinib	Microangiopathic hemolytic anemia reported when used in combination	Unknown	Avoid this combination
Bisphosphonates, anti-angiogenic drugs	↑ risk of ONJ	Additive	Caution
Platinum or taxane-based chemotherapy	Increased risk of myelosuppression +/- infection, bleeding	Additive	Caution and closely monitor CBC

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and at each visit
Urine dipstick, 24 hour urine collection is recommended for patients with a 2+ or greater urine dipstick	Baseline and at each visit
Blood pressure	Baseline and every 2-3 weeks during therapy; more frequently in patients who develop hypertension
Dental evaluation	Baseline
Clinical assessment of hypersensitivity, perforation, fistula, GI symptoms, ONJ, hemorrhage, infection, myelosuppression, thromboembolism, delayed wound healing, hypertension, neurologic and cardiac effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Liver and renal function tests	Baseline and at each visit
Cardiac function tests (Echo, RNA and/or MUGA scans) especially in patients who are close to the lifetime cumulative dose of anthracyclines/anthracenediones	Baseline and as clinically indicated
INR for patients receiving warfarin	Baseline and as clinically indicated

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Bevacizumab (Biosimilar) - Metastatic (Stage IVB), Persistent, or Recurrent Carcinoma of the Cervix
- Bevacizumab (Biosimilar) with Paclitaxel and Carboplatin - Front-line Treatment (Previously Untreated) Ovarian, Fallopian Tube, and Primary Peritoneal Cancer
- Bevacizumab (Biosimilar) for Platinum-Resistant Recurrent Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
- Bevacizumab (Biosimilar) - Metastatic Colorectal, Small Bowel, or Appendiceal Cancer
- Atezolizumab with Bevacizumab (Biosimilar) - Previously Untreated Unresectable or Metastatic Hepatocellular Carcinoma
- Bevacizumab (Biosimilar) - Metastatic (Stage IVB), Persistent, or Recurrent Carcinoma of the Cervix

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K - References

Colorectal stents and bevacizumab: increased risk of intestinal perforation. Review. Health Canada Product InfoWatch. February 2017.

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Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.

Mahfoud T, Tanz R, Mesmoudi M, et al. Bevacizumab 5 or 7.5 mg/kg in metastatic colorectal cancer can be infused safely over 10 minutes. J Gastrointest Cancer. 2012 Jun;43(2):244-8.

Perren TJ, Swart AM, Pfisterer J, et al; ICON7 Investigators. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med. 2011 Dec 29;365(26):2484-96.

Product Monograph: Avastin® (bevacizumab). Roche Canada. February 2017.

Product Monograph: Avastin® (bevacizumab). Roche Canada. January 2021.

Reidy DL, Chung KY, Timoney JP, et al. Bevacizumab 5 mg/kg can be infused safely over 10 minutes. Journal of Clinical Oncology 2007; 25: 2691-5.

August 2023 Modified Common trade names section

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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