

Bevacizumab: Drug information

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(For additional information [see "Bevacizumab: Patient drug information"](#) and [see "Bevacizumab: Pediatric drug information"](#))

For abbreviations and symbols that may be used in Lexicomp ([show table](#))

Special Alerts

Colorectal Stents with Bevacizumab Safety Alert February 2017

A Health Canada safety review found limited evidence supporting potential increased risk of bowel rupture when colorectal stents and bevacizumab are used concurrently to treat patients with colon cancer. This review was prompted by published studies reporting an increased risk of bowel rupture in these patients. Health Canada will continue monitoring the safety of both colorectal stents and bevacizumab.

Further information can be found at <http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/stents-endoprotheses-eng.php>.

ALERT: US Boxed Warning

GI perforations:

The incidence of GI perforations, some fatal, in bevacizumab-treated patients ranges from 0.3% to 3.2%. Discontinue bevacizumab in patients with GI perforation.

Surgery and wound healing complications:

The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in bevacizumab-treated patients. Discontinue bevacizumab in patients with wound dehiscence. The appropriate interval between termination of bevacizumab and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined. Discontinue at least 28 days prior to elective surgery. Do not initiate bevacizumab for at least 28 days after surgery and until the surgical wound is fully healed.

Hemorrhage:

Severe or fatal hemorrhage, including hemoptysis, GI bleeding, CNS hemorrhage, epistaxis, and vaginal bleeding, occur up to 5-fold more frequently in patients receiving bevacizumab. Do not administer bevacizumab to patients with serious hemorrhage or recent hemoptysis.

Brand Names: US Avastin

Brand Names: Canada Avastin

Pharmacologic Category Antineoplastic Agent, Monoclonal Antibody; Antineoplastic Agent, Vascular Endothelial Growth Factor (VEGF) Inhibitor; Vascular Endothelial Growth Factor (VEGF) Inhibitor

Dosing: Adult

Cervical cancer, persistent/recurrent/metastatic: IV: 15 mg/kg every 3 weeks (in combination with paclitaxel and either cisplatin or topotecan) until disease progression or unacceptable toxicity (Tewari 2014)

Colorectal cancer, metastatic, in combination with fluorouracil-based chemotherapy: IV: 5 mg/kg every 2 weeks (in combination with bolus-IFL) **or** 10 mg/kg every 2 weeks (in combination with FOLFOX4)

Colorectal cancer, metastatic, following first-line therapy containing bevacizumab: IV: 5 mg/kg every 2 weeks **or** 7.5 mg/kg every 3 weeks (in combination with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based regimen)

Glioblastoma: IV: 10 mg/kg every 2 weeks as monotherapy **or** (off-label dosing) 10 mg/kg every 2 weeks (in combination with irinotecan) (Vredenburgh 2007)

Non-small cell lung cancer (nonsquamous cell histology): IV: 15 mg/kg every 3 weeks (in combination with carboplatin and paclitaxel) for 6 cycles followed by maintenance treatment (off-label use) of bevacizumab 15 mg/kg every 3 weeks as monotherapy until disease progression or unacceptable toxicity (Sandler 2006)

Ovarian (epithelial), fallopian tube, or primary peritoneal cancer (platinum-resistant recurrent): IV: 10 mg/kg every 2 weeks (in combination with weekly paclitaxel, every 4 week doxorubicin [liposomal], or days 1, 8, and 15 topotecan) **or** 15 mg/kg every 3 weeks (in combination with every 3 week topotecan) (Pujade-Lauraine 2014)

Ovarian (epithelial), fallopian tube, or primary peritoneal cancer (platinum-sensitive recurrent): IV: 15 mg/kg every 3 weeks (in combination with carboplatin and gemcitabine for 6 to 10 cycles or with carboplatin and paclitaxel for 6 to 8 cycles) then continue with bevacizumab (monotherapy) until disease progression or unacceptable toxicity (Aghajanian 2012; Aghajanian 2015; Coleman 2015).

Renal cell cancer, metastatic: IV: 10 mg/kg every 2 weeks (in combination with interferon alfa) **or** (off-label dosing) 10 mg/kg every 2 weeks as monotherapy (Yang 2003)

Age-related macular degeneration (off-label use/route): Intravitreal: 1.25 mg (0.05 mL) monthly for 3 months, then may be given scheduled (monthly) or as needed based on monthly ophthalmologic assessment (Chakravarthy 2013; Martin 2012)

Breast cancer, metastatic (off-label use): IV: 10 mg/kg every 2 weeks (in combination with paclitaxel) (Miller 2007)

Endometrial cancer, recurrent or persistent (off-label use): IV: 15 mg/kg every 3 weeks (as monotherapy) until disease progression or unacceptable toxicity (Aghajanian 2011)

Hereditary hemorrhagic telangiectasia (off-label use): IV: 5 mg/kg every 2 weeks for 6 doses

(Dupuis-Girod 2012). Additional data may be necessary to further define the role of bevacizumab in this condition.

Malignant pleural mesothelioma, unresectable (off-label use): IV: 15 mg/kg every 3 weeks (in combination with pemetrexed and cisplatin) for up to 6 cycles, followed by bevacizumab maintenance therapy at 15 mg/kg once every 3 weeks until disease progression or unacceptable toxicity (Zalcman 2016)

Soft tissue sarcoma, angiosarcoma, metastatic or locally advanced (off-label use): IV: 15 mg/kg every 3 weeks until disease progression or unacceptable toxicity (Agulnik 2013). Additional data may be necessary to further define the role of bevacizumab in this condition.

Dosing: Geriatric Refer to adult dosing.

Dosing: Renal Impairment There are no dosage adjustments provided in the manufacturer's labeling.

Dosing: Hepatic Impairment There are no dosage adjustments provided in the manufacturer's labeling.

Dosing: Adjustment for Toxicity IV administration (systemic): There are no recommended dosage reductions. Temporary suspension is recommended for severe infusion reactions, at least 4 weeks prior to (and after) elective surgery, in moderate-to-severe proteinuria (in most studies, treatment was withheld for ≥ 2 g proteinuria/24 hours), or in patients with severe hypertension which is not controlled with medical management. Permanent discontinuation is recommended (by the manufacturer) in patients who develop wound dehiscence and wound healing complications requiring intervention, necrotizing fasciitis, fistula (gastrointestinal and nongastrointestinal), gastrointestinal perforation, intra-abdominal abscess, hypertensive crisis, hypertensive encephalopathy, serious bleeding/hemorrhage, severe arterial thromboembolic event, life-threatening (grade 4) venous thromboembolic events (including pulmonary embolism), nephrotic syndrome, or PRES.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, Intravenous [preservative free]:

Avastin: 100 mg/4 mL (4 mL); 400 mg/16 mL (16 mL)

Generic Equivalent Available (US) No

Administration

IV: Infuse the initial dose over 90 minutes. The second infusion may be shortened to 60 minutes if the initial infusion is well tolerated. The third and subsequent infusions may be shortened to 30 minutes if the 60-minute infusion is well tolerated. Monitor closely during the infusion for signs/symptoms of an infusion reaction. After tolerance at the 90-, 60-, and 30-minute infusion rates has been established, some institutions use an off-label 10-minute infusion rate (0.5 mg/kg/minute) for bevacizumab dosed at 5 mg/kg (Reidy 2007). In a study evaluating the safety of the 0.5 mg/kg/minute infusion rate, proteinuria and hypertension incidences were not increased with the shorter infusion time (Shah 2013). Do not administer IV push. Do not administer with dextrose solutions. Temporarily withhold bevacizumab for 4 weeks prior to elective surgery and for at least 4 weeks (and until the surgical incision is fully healed)

after surgery.

Intravitreal injection (off-label use/route): Adequate local anesthesia and a topical broad-spectrum antimicrobial agent should be administered prior to the procedure.

Use

Cervical cancer, persistent/recurrent/metastatic: Treatment of persistent, recurrent, or metastatic cervical cancer (in combination with paclitaxel and either cisplatin or topotecan).

Colorectal cancer, metastatic: First- or second-line treatment of metastatic colorectal cancer (CRC) (in combination with fluorouracil-based chemotherapy); second-line treatment of metastatic CRC (in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy) after progression on a first-line treatment containing bevacizumab.

Limitations of use: Not indicated for the adjuvant treatment of colon cancer.

Glioblastoma: Treatment of progressive glioblastoma (as a single agent).

Non-small cell lung cancer, nonsquamous: First-line treatment of unresectable, locally advanced, recurrent or metastatic nonsquamous non-small cell lung cancer (NSCLC) (in combination with carboplatin and paclitaxel).

Ovarian (epithelial), fallopian tube, or primary peritoneal cancer (platinum-resistant recurrent): Treatment of platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (in combination with paclitaxel, doxorubicin [liposomal], or topotecan) in patients who received no more than 2 prior chemotherapy regimens.

Ovarian (epithelial), fallopian tube, or primary peritoneal cancer (platinum-sensitive recurrent): Treatment of platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (in combination with carboplatin and paclitaxel or with carboplatin and gemcitabine and then followed by single-agent bevacizumab).

Renal cell carcinoma, metastatic: Treatment of metastatic renal cell carcinoma (RCC) (in combination with interferon alfa).

Use: Off-Label

Age-related macular degeneration; Breast cancer, metastatic; Endometrial cancer, recurrent or persistent; Hereditary hemorrhagic telangiectasia; Malignant pleural mesothelioma (unresectable); Soft tissue sarcoma, angiosarcoma; Soft tissue sarcoma, hemangiopericytoma

Medication Safety Issues

Sound-alike/look-alike issues:

Avastin may be confused with Astelin

Bevacizumab may be confused with bezlotoxumab, brentuximab, cetuximab, ranibizumab, riTUXimab

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

International issues:

Avastin [US, Canada, and multiple international markets] may be confused with Avaxim, a brand name for hepatitis A vaccine [Canada and multiple international markets]

Adverse Reactions Percentages reported as monotherapy and as part of combination chemotherapy regimens. Some studies only reported hematologic toxicities grades ≥ 4 and nonhematologic toxicities grades ≥ 3 .

>10%:

Cardiovascular: Hypertension (12% to 34%; grades 3/4: 5% to 18%), venous thromboembolism (secondary: 21%; with oral anticoagulants), peripheral edema (15%), hypotension (7% to 15%), venous thromboembolism (8% to 14%; grades 3/4: 5% to 15%), arterial thrombosis (6%; grades 3/4: 3%)

Central nervous system: Fatigue (33% to 80%; grades 3/4: 4% to 19%), pain (8% to 62%; grades 3/4: 8%), headache (22% to 37%; grades 3/4: 3% to 4%), dizziness (19% to 26%), taste disorder (14% to 21%), peripheral sensory neuropathy (17% to 18%), anxiety (17%)

Dermatologic: Alopecia (6% to 32%), palmar-plantar erythrodysesthesia (11%), exfoliative dermatitis (>10%), xeroderma (>10%)

Endocrine & metabolic: Ovarian failure (34%), hyperglycemia (26%), hypomagnesemia (24%), weight loss (15% to 21%), hyponatremia (19%; grades 3/4: 4%), hypoalbuminemia (16%)

Gastrointestinal: Abdominal pain (50% to 61%; grades 3/4: 8%), vomiting (47% to 52%; grades 3/4: 11%), anorexia (35% to 43%), constipation (40%; grades 3/4: 4%), decreased appetite (34%), diarrhea (21%; grades 3/4: 1% to 34%), stomatitis (15% to 32%), gastrointestinal hemorrhage (19% to 24%), dyspepsia (17% to 24%), mucosal inflammation (13%), nausea (grades 3/4: 12%)

Genitourinary: Proteinuria (4% to 36%; grades >2 : grades 3/4: ≤ 7 %; median onset: 5.6 months; median time to resolution: 6.1 months), urinary tract infection (22%; grades 3/4: 8%), pelvic pain (14%; grades 3/4: 6%)

Hematologic & oncologic: Hemorrhage (40%; grades 3/4: ≤ 7 %), leukopenia (grades 3/4: 37%), pulmonary hemorrhage (4% to 31%), neutropenia (12%; grades ≥ 3 : 8% to 27%, grade 4: 27%), lymphocytopenia (12%; grades 3/4: 6%)

Infection: Infection (55%; serious: 7% to 14%; pneumonia, catheter infection, or wound infection)

Neuromuscular & skeletal: Myalgia (19%), back pain (12%; grades 3/4: 6%)

Renal: Increased serum creatinine (16%)

Respiratory: Upper respiratory tract infection (40% to 47%), epistaxis (17% to 35%), dyspnea (25% to 26%), rhinitis (3% to >10%)

Miscellaneous: Postoperative wound complication (including dehiscence, 1% to 15%)

1% to 10%:

Cardiovascular: Thrombosis (8% to 10%), deep vein thrombosis (6% to 9%; grades 3/4: 9%), syncope (grades 3/4: 3%), intra-abdominal thrombosis (venous, grades 3/4: 3%), left ventricular dysfunction (grades 3/4: 1%), pulmonary embolism (1%)

Central nervous system: Voice disorder (5% to 9%)

Dermatologic: Dermal ulcer (6%), cellulitis (grades 3/4: 3%), acne vulgaris (1%)

Endocrine & metabolic: Dehydration (grades 3/4: 4% to 10%), hypokalemia (grades 3/4: 7%)

Gastrointestinal: Xerostomia (4% to 7%), rectal pain (6%), colitis (1% to 6%), intestinal obstruction (grades 3/4: 4%), gingival hemorrhage (minor, 2% to 4%), gastrointestinal perforation ($\leq 3\%$), gastroesophageal reflux disease (2%), gastrointestinal fistula ($\leq 2\%$), gingivitis (2%), oral mucosa ulcer (2%), gastritis (1%), gingival pain (1%)

Genitourinary: Vaginal hemorrhage (4%)

Hematologic & oncologic: Febrile neutropenia (5%), neutropenic infection (grades 3/4: 5%), thrombocytopenia (5%), hemorrhage (CNS; 5%; grades 3/4: 1%)

Infection: Abscess (tooth, 2%)

Neuromuscular & skeletal: Weakness (grades 3/4: 10%), dysarthria (8%)

Ophthalmic: Blurred vision (2%)

Otic: Tinnitus (2%), deafness (1%)

Respiratory: Pneumonitis (grades 3/4: 5%),

Miscellaneous: Fistula (gastrointestinal-vaginal; 8%), fistula (anal; 6%; grades 3/4: 4%), infusion related reaction ($<3\%$), fistula ($\leq 2\%$)

$<1\%$, postmarketing, and/or case reports: Anaphylaxis, anastomotic ulcer, angina pectoris, antibody development (anti-bevacizumab and neutralizing), bladder fistula, bronchopleural fistula, cerebral infarction, conjunctival hemorrhage, endophthalmitis (infectious and sterile), eye discomfort, eye pain, fistula of bile duct, fulminant necrotizing fasciitis, gallbladder perforation, gastrointestinal ulcer, hemolytic anemia (microangiopathic; when used in combination with sunitinib), hemoptysis, hemorrhagic stroke, hypersensitivity, hypertensive crisis, hypertensive encephalopathy, increased intraocular pressure, inflammation of anterior segment of eye (toxic anterior segment syndrome) (Sato 2010), intestinal necrosis, intraocular inflammation (iritis, vitritis), mesenteric thrombosis, myocardial infarction, nasal septum perforation, nephrotic syndrome, ocular hyperemia, osteonecrosis of the jaw, pancytopenia, permanent vision loss, polyserositis, pulmonary hypertension, rectal fistula, renal failure, renal fistula, renal thrombotic microangiopathy, retinal detachment, retinal hemorrhage, reversible posterior leukoencephalopathy syndrome, sepsis, tracheoesophageal fistula, transient ischemic attacks, vaginal fistula, visual disturbance, vitreous hemorrhage, vitreous opacity

Contraindications

There are no contraindications listed in the manufacturer's labeling.

Canadian labeling: Hypersensitivity to bevacizumab, any component of the formulation, Chinese hamster ovary cell products or other recombinant human or humanized antibodies; untreated CNS metastases

Warnings/Precautions

Concerns related to adverse effects:

- **Fistula/abscess formation:** Gastrointestinal (GI) fistula (including enterocutaneous, esophageal, duodenal, and rectal fistulas), and intra-abdominal abscess have been reported in patients receiving bevacizumab for colorectal cancer, ovarian cancer, and other cancers (not related to treatment duration). Non-GI fistula formation (including tracheoesophageal, bronchopleural, biliary, vaginal, vesical, renal, bladder, and female tract fistulas) has been observed (rarely fatal), most commonly within the first 6 months of treatment. GI-vaginal fistulas have been reported in cervical cancer patients, all of whom had received prior pelvic radiation; patients may also have bowel obstructions requiring surgical intervention and diverting ostomies. Permanently discontinue in patients who develop internal organ fistulas, tracheoesophageal (TE) fistula, or any grade 4 fistula.
- **Gastrointestinal perforation: [US Boxed Warning]: GI perforation, (sometimes fatal) has occurred in 0.3% to 3.2% of clinical study patients receiving bevacizumab; discontinue (permanently) if GI perforation occurs.** All cervical cancer patients with GI perforation had a history of prior pelvic radiation. GI perforation was observed in patients with platinum-resistant ovarian cancer, although patients with evidence of recto-sigmoid involvement (by pelvic exam), bowel involvement (on CT scan), or clinical symptoms of bowel obstruction were excluded from the study; avoid bevacizumab use in these ovarian cancer patient populations. Most cases occur within 50 days of treatment initiation; monitor patients for signs/symptoms (eg, fever, abdominal pain with constipation and/or nausea/vomiting).
- **Heart failure:** Among approved and nonapproved uses evaluated thus far, the incidence of heart failure (HF) and/or left ventricular dysfunction (including LVEF decline) is higher in patients receiving bevacizumab plus chemotherapy when compared to chemotherapy alone. Use with caution in patients with cardiovascular disease. The safety of therapy resumption or continuation in patients with cardiac dysfunction has not been studied. In studies of patients with metastatic breast cancer (an off-label use), the incidence of grades 3 or 4 HF was increased in patients receiving bevacizumab plus paclitaxel when compared to the control arm. Patients with metastatic breast cancer who received prior anthracycline therapy had a higher rate of HF compared to those receiving paclitaxel alone (3.8% vs 0.6% respectively). A meta-analysis of 5 studies which enrolled patients with metastatic breast cancer who received bevacizumab suggested an association with an increased risk of heart failure; all trials included in the analysis enrolled patients who either received prior or were receiving concurrent anthracycline therapy (Choueiri 2011). In a scientific statement from the American Heart Association, bevacizumab has been determined to be an agent that may either cause reversible direct myocardial toxicity or exacerbate underlying myocardial dysfunction (magnitude: moderate/major) (AHA [Page 2016]).
- **Hemorrhage: [US Boxed Warning]: Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, central nervous system hemorrhage, epistaxis, and vaginal bleeding have been reported (up to 5 times more frequently if receiving bevacizumab). Avoid use in patients with serious hemorrhage or recent hemoptysis (≥2.5 mL blood).** Serious or fatal pulmonary hemorrhage has been reported in patients receiving bevacizumab (primarily in patients with non-small cell lung cancer with squamous cell histology [not an FDA-approved indication]). Intracranial hemorrhage, including cases of grade 3 or 4 hemorrhage, has occurred in

patients with previously treated glioblastoma. Treatment discontinuation is recommended in all patients with intracranial bleeding or other serious hemorrhage. Use with caution in patients at risk for thrombocytopenia.

- Hypertension: May cause and/or worsen hypertension; the incidence of severe hypertension increased with bevacizumab. Use caution in patients with preexisting hypertension and monitor BP closely (every 2 to 3 weeks during treatment; regularly after discontinuation if bevacizumab-induced hypertension occurs or worsens). Permanent discontinuation is recommended in patients who experience a hypertensive crisis or hypertensive encephalopathy. Temporarily discontinue in patients who develop uncontrolled hypertension.

- Infusion reactions and hypersensitivity: Infusion reactions (eg, hypertension, hypertensive crisis, wheezing, oxygen desaturation, hypersensitivity [including anaphylactic/anaphylactoid reactions], chest pain, rigors, headache, diaphoresis) may occur with the first infusion (uncommon). Interrupt therapy in patients experiencing severe infusion reactions and administer appropriate therapy; there are no data to address routine premedication use or reinstatement of therapy in patients who experience severe infusion reactions.

- Mortality: Bevacizumab, in combination with chemotherapy (or biologic therapy), is associated with an increased risk of treatment-related mortality; a higher risk of fatal adverse events was identified in a meta-analysis of 16 trials in which bevacizumab was used for the treatment of various cancers (breast cancer, colorectal cancer, non-small cell lung cancer, pancreatic cancer, prostate cancer, and renal cell cancer) and compared to chemotherapy alone (Ranpura 2011).

- Necrotizing fasciitis: Cases of necrotizing fasciitis, including fatalities, have been reported (rarely); usually secondary to wound healing complications, GI perforation or fistula formation. Discontinue in patients who develop necrotizing fasciitis.

- Ocular adverse events: Serious eye infections and vision loss due to endophthalmitis have been reported from intravitreal administration (off-label use/route).

- Osteonecrosis of the jaw (ONJ): According to a position paper by the American Association of Maxillofacial Surgeons (AAOMS), medication-related osteonecrosis of the jaw (MRONJ) has been associated with bisphosphonates and other antiresorptive agents (denosumab), and antiangiogenic agents (eg, bevacizumab, sunitinib) used for the treatment of osteoporosis or malignancy. Antiangiogenic agents, when given concomitantly with antiresorptive agents, are associated with an increased risk of ONJ. Other risk factors for MRONJ include dentoalveolar surgery (eg, tooth extraction, dental implants), pre-existing inflammatory dental disease, and concomitant corticosteroid use. The AAOMS suggests that if medically permissible, initiation of antiangiogenic agents for cancer therapy should be delayed until optimal dental health is attained (if extractions are required, antiangiogenesis therapy should be delayed until the extraction site has mucosalized or until after adequate osseous healing). Once antiangiogenic therapy for oncologic disease is initiated, procedures that involve direct osseous injury and placement of dental implants should be avoided. Patients developing ONJ during therapy should receive care by an oral surgeon (AAOMS [Ruggiero 2014]). Cases of non-mandibular ONJ has also been reported in pediatric patients who have received bevacizumab (bevacizumab is not approved for use in pediatric patients).

- Ovarian failure: In premenopausal women receiving bevacizumab in combination with mFOLFOX (fluorouracil/oxaliplatin based chemotherapy) the incidence of ovarian failure (amenorrhea ≥ 3 months) was higher (34%) compared to women who received mFOLFOX alone (2%). Ovarian function recovered in some patients after treatment was discontinued. Premenopausal women

should be informed of the potential risk of ovarian failure.

- Posterior reversible encephalopathy syndrome: Cases of posterior reversible encephalopathy syndrome (PRES) have been reported. Symptoms (which include headache, seizure, confusion, lethargy, blindness and/or other vision, or neurologic disturbances) may occur from 16 hours to 1 year after treatment initiation. Resolution of symptoms usually occurs within days after discontinuation; however, neurologic sequelae may remain. PRES may be associated with hypertension; discontinue therapy and begin management of hypertension, if present. The safety of treatment reinitiation after PRES is not known.
- Proteinuria/nephrotic syndrome: Proteinuria and/or nephrotic syndrome have been associated with use; risks may be increased in patients with history of hypertension. Thrombotic microangiopathy has been associated with bevacizumab-induced proteinuria. Withhold treatment for ≥ 2 g proteinuria/24 hours and resume when proteinuria is < 2 g/24 hours; discontinue in patients with nephrotic syndrome.
- Thromboembolism: Bevacizumab is associated with an increased risk for arterial thromboembolic events (ATE), including cerebral infarction, stroke, MI, TIA, angina, and other ATEs, when used in combination with chemotherapy. History of ATE, diabetes, or ≥ 65 years of age may present an even greater risk. Although patients with cancer are already at risk for venous thromboembolism (VTE), a meta-analysis of 15 controlled trials has demonstrated an increased risk for VTE in patients who received bevacizumab (Nalluri 2008). Cervical cancer patients receiving bevacizumab plus chemotherapy may be at increased risk of grade 3 or higher VTE compared to those patients who received chemotherapy alone. Permanently discontinue therapy in patients with severe ATE or life-threatening (grade 4) VTE, including pulmonary embolism; the safety of treatment reinitiation after ATE has not been studied.
- Wound dehiscence: **[US Boxed Warning]: The incidence of wound healing and surgical complications, including serious and fatal events, is increased in patients who have received bevacizumab; discontinue with wound dehiscence. Although the appropriate interval between withholding bevacizumab and elective surgery has not been defined, bevacizumab should be discontinued at least 28 days prior to surgery and should not be reinitiated for at least 28 days after surgery and until wound is fully healed.** In a retrospective review of central venous access device placements (a minor procedure), a greater risk of wound dehiscence was observed when port placement and bevacizumab administration were separated by < 14 days (Erinjeri 2011). If possible, it may be more appropriate to wait until at least 6 to 8 weeks after bevacizumab discontinuation for major surgical procedures (Cortes 2012; Gordon 2009).

Disease-related concerns:

- CNS metastases: Use with caution in patients with CNS metastases; one case of CNS hemorrhage was observed in a study of NSCLC patients with CNS metastases.
- Renal impairment: An increase in diastolic and systolic blood pressures were noted in a retrospective review of patients with renal insufficiency ($\text{CrCl} \leq 60$ mL/minute) who received bevacizumab for renal cell cancer (Gupta 2011).

Concurrent drug therapy issues:

- Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

- Anthracyclines: May potentiate cardiotoxic effects of anthracyclines. HF is more common with prior anthracycline exposure and/or left chest wall irradiation.
- Myelosuppressive chemotherapy: When used in combination with myelosuppressive chemotherapy, increased rates of severe or febrile neutropenia and neutropenic infection were reported.
- Sorafenib: The incidence of hand-foot syndrome is increased in patients treated with bevacizumab plus sorafenib in comparison to those treated with sorafenib monotherapy.
- Sunitinib: Microangiopathic hemolytic anemia (MAHA) has been reported when bevacizumab has been used in combination with sunitinib. Concurrent therapy with sunitinib and bevacizumab is also associated with dose-limiting hypertension in patients with metastatic renal cell cancer.

Special populations:

- Elderly: Use with caution in patients ≥ 65 years of age; greater risk for adverse events, including arterial thrombotic events and proteinuria. Serious adverse events occurring more frequently in the elderly also include weakness, deep thrombophlebitis, sepsis, hyper-/hypotension, MI, CHF, diarrhea, constipation, anorexia, leukopenia, anemia, dehydration, hypokalemia, and hyponatremia.

Metabolism/Transport Effects None known.

Drug Interactions

(For additional information: [Launch drug interactions program](#)) Lexicomp[®]

Antineoplastic Agents (Anthracycline, Systemic): Bevacizumab may enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline, Systemic). *Risk C: Monitor therapy*

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

Belimumab: Monoclonal Antibodies may enhance the adverse/toxic effect of Belimumab. *Risk X: Avoid combination*

Bisphosphonate Derivatives: Systemic Angiogenesis Inhibitors may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Specifically, the risk for osteonecrosis of the jaw may be increased. *Risk C: Monitor therapy*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Dipyrrone: May enhance the adverse/toxic effect of Myelosuppressive Agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased *Risk X: Avoid combination*

Promazine: May enhance the myelosuppressive effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

SORAFenib: Bevacizumab may enhance the adverse/toxic effect of SORAFenib. Specifically, the risk for

hand-foot skin reaction may be increased. *Risk C: Monitor therapy*

SUNItinib: May enhance the adverse/toxic effect of Bevacizumab. Specifically, the risk for a specific form of anemia, microangiopathic hemolytic anemia (MAHA), may be increased. Bevacizumab may enhance the hypertensive effect of SUNItinib. *Risk X: Avoid combination*

Pregnancy Implications Based on its mechanism of action, bevacizumab would be expected to cause fetal harm if administered to a pregnant woman. Information from postmarketing reports following exposure in pregnancy is limited. Women of reproductive potential should use effective contraception during therapy and for 6 months following the last dose (due to the long half-life of bevacizumab). Bevacizumab treatment may also increase the risk of ovarian failure and impair fertility; long term effects on fertility are not known.

Breast-Feeding Considerations It is not known if bevacizumab is excreted in breast milk. Immunoglobulins are excreted in breast milk, and it is assumed that bevacizumab may appear in breast milk. Because of the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended. The half-life of bevacizumab is up to 50 days (average 20 days), and this should be considered when decisions are made concerning breast-feeding resumption.

Monitoring Parameters Monitor closely during the infusion for signs/symptoms of an infusion reaction. Monitor CBC with differential; signs/symptoms of gastrointestinal perforation, fistula, or abscess (including abdominal pain, constipation, vomiting, and fever); signs/symptoms of bleeding, including hemoptysis, gastrointestinal, and/or CNS bleeding, and/or epistaxis. Monitor blood pressure every 2 to 3 weeks; more frequently if hypertension develops during therapy. Continue to monitor blood pressure after discontinuing due to bevacizumab-induced hypertension. Monitor for proteinuria/nephrotic syndrome with urine dipstick; collect 24-hour urine in patients with $\geq 2+$ reading. Monitor for signs/symptoms of thromboembolism (arterial and venous).

AMD (off-label use): Monitor intraocular pressure and retinal artery perfusion

Hereditary hemorrhagic telangiectasia (off-label use): Cardiac output measurements and liver radiologic response (via ultrasound and hepatic CT exams) prior to initial treatment and at 3 and 6 months following the first dose.

Mechanism of Action Bevacizumab is a recombinant, humanized monoclonal antibody which binds to, and neutralizes, vascular endothelial growth factor (VEGF), preventing its association with endothelial receptors, Flt-1 and KDR. VEGF binding initiates angiogenesis (endothelial proliferation and the formation of new blood vessels). The inhibition of microvascular growth is believed to retard the growth of all tissues (including metastatic tissue).

Pharmacodynamics/Kinetics

Distribution: V_d : 46 mL/kg

Half-life elimination:

IV:

Pediatric patients (age: 1 to 21 years): Median: 11.8 days (range: 4.4 to 14.6 days) (Glade

Bender 2008)

Adults: ~20 days (range: 11 to 50 days)

Intravitreal: ~5 to 10 days (Bakri 2007; Krohne 2008)

Pricing: US

Solution (Avastin Intravenous)

100 mg/4 mL (4 mL): \$890.22

400 mg/16 mL (16 mL): \$3560.88

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names Avastin (AE, AR, AT, AU, BE, BG, BH, BR, CH, CL, CN, CO, CR, CU, CY, CZ, DE, DK, DO, EC, EE, ES, FI, FR, GB, GR, GT, HK, HN, HR, HU, ID, IE, IL, IS, IT, JO, JP, KR, KW, LB, LK, LT, LU, LV, MT, MX, MY, NI, NL, NO, NZ, PA, PE, PH, PL, PT, PY, QA, RO, RU, SA, SE, SG, SI, SK, SV, TH, TR, TW, UY, VN); Avastyn (UA); Bevastim (BD); Bivastin (BD)

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