MONITORING AND MANAGING SELECTED ADVERSE EVENTS WHEN TREATING WITH AVASTIN-BASED THERAPY

The following information should not be a substitute for your professional medical judgment and should be individualized for the patient.

Indications

Avastin in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan is indicated for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens.

Avastin, either in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by Avastin as a single agent, is indicated for the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Avastin in combination with paclitaxel and cisplatin or paclitaxel and topotecan is indicated for the treatment of persistent, recurrent, or metastatic carcinoma of the cervix.

Avastin is indicated for the treatment of metastatic renal cell carcinoma in combination with interferon alfa.

Avastin is indicated for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer in combination with carboplatin and paclitaxel.

Avastin is indicated for the first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil–based chemotherapy.

Avastin, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line Avastin-containing regimen.

Limitation of Use: Avastin is not indicated for adjuvant treatment of colon cancer.

Boxed WARNINGS

- Gastrointestinal (GI) perforation
  - Serious and sometimes fatal GI perforation occurs at a higher incidence (up to 3.2%) in Avastin-treated patients compared to controls. Discontinue Avastin for GI perforation

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

- Hemorrhage
  - Severe or fatal hemorrhage, hemoptysis, GI bleeding, CNS hemorrhage, epistaxis, and vaginal bleeding are increased in Avastin-treated patients.
  - Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis

Please see accompanying full Prescribing Information, including Boxed WARNINGS, and back cover for additional important safety information.
Angiogenesis is required for tumor growth

- Tumors need a blood supply to grow and to metastasize

As demonstrated in preclinical models:

Avastin may exert certain effects to inhibit tumor growth and development

Proposed effects | Potential effect on vessels | Potential impact on tumor
--- | --- | ---
Anti-vascular | Regression of existing tumor vasculature | Reduction of tumor size
Anti-angiogenesis | Inhibition of new and recurrent tumor vessel growth | Inhibition of tumor growth

Proposed early and later effects of Avastin

ATTAINING VEGF INHIBITION

CONTINUING VEGF INHIBITION

Anti-vascular effects

Anti-angiogenesis

Early effects

Later effects

Please see accompanying full Prescribing Information, including **Boxed WARNINGS**, and back cover for additional important safety information.
Dosing per pivotal Phase III trial protocols

Avastin is administered as a solution for intravenous (IV) infusion at the following doses and schedules:

### Tumor Type Dose/Schedule

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Dose/Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCRC—IFL* (First-line Study 2107)</td>
<td>5 mg/kg IV q2w</td>
</tr>
<tr>
<td>MCRC—FOLFOX4† (Second-line Study E3200)</td>
<td>10 mg/kg IV q2w</td>
</tr>
<tr>
<td>MCRC—fluoropyrimidine-based chemotherapy in patients who had progressed on a first-line Avastin-containing regimen‡ (first- through second-line TML study)</td>
<td>5 mg/kg IV q2w OR 7.5 mg/kg IV q3w</td>
</tr>
<tr>
<td>NSCLC—PC†</td>
<td>15 mg/kg IV q3w</td>
</tr>
<tr>
<td>mRCC—IFN‡</td>
<td>10 mg/kg IV q2w</td>
</tr>
</tbody>
</table>

- q2w=every 2 weeks; q3w=every 3 weeks.
- 5 mg/kg IV dose evaluated in first-line metastatic colorectal cancer (MCRC) in combination with 5-fluourouracil (5-FU)/leucovorin (LV)/irinotecan (IFL).
- 10 mg/kg IV dose evaluated in second-line, Avastin-naive MCRC patients in combination with 5-FU/LV/oxaliplatin (FOLFOX)°.°
- 5 mg/kg IV q2w and 7.5 mg/kg IV q3w doses evaluated, in combination with fluoropyrimidine and either irinotecan- or oxaliplatin-containing chemotherapy, in MCRC patients who had progressed on a first-line Avastin-containing regimen.
- TML=Treatment through Multiple Lines (first and second line).
- 15 mg/kg IV dose evaluated in first-line locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) in combination with paclitaxel/carboplatin (PC). Avastin plus PC was given for up to 6 cycles, after which Avastin was continued alone until disease progression or unacceptable toxicity.°
- 110 mg/kg IV dose evaluated in metastatic renal cell carcinoma (mRCC) in combination with interferon alfa (IFN). AVOREN protocol allowed for IFN dose escalation (attaining a dose of 9 million international units [MIU] within the first 2 weeks), reduction, or discontinuation. IFN was discontinued after 52 weeks or earlier.°
- In the majority of approved indications (NSCLC, second-line MCRC in combination with FOLFOX4 [Study E3200], mRCC, CC, and prOC), Avastin is consistently dosed at the weekly equivalent of 5 mg/kg.
- In first-line MCRC in combination with IFL (Study 2107) and when Avastin is continued in patients who had progressed on a first-line Avastin-containing regimen in combination with fluoropyrimidine-based chemotherapy‡ (the TML study), Avastin is dosed at the weekly equivalent of 2.5 mg/kg.

Across all indications, study results were achieved with Avastin given at the approved dose until disease progression or unacceptable toxicity.°,°

**FDA-approved Prescribing Information for the duration of Avastin treatment:**

Patients should continue treatment until disease progression or unacceptable toxicity.

### Tumor Type Dose/Schedule

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<tbody>
<tr>
<td>CC—cisplatin/paclitaxel or topotecan/paclitaxel³</td>
<td>15 mg/kg IV q3w</td>
</tr>
<tr>
<td>prOC**</td>
<td>10 mg/kg IV q2w if used in combination with weekly paclitaxel, PLD, or weekly topotecan or 15 mg/kg IV q3w if used in combination with topotecan q3w</td>
</tr>
<tr>
<td>psOC***</td>
<td>15 mg/kg IV q3w for 6 and up to 8 cycles if used in combination with carboplatin and paclitaxel followed by continued use of Avastin 15 mg/kg IV q3w as a single agent until disease progression or 15 mg/kg IV q3w for 6 and up to 10 cycles if used in combination with carboplatin and gemcitabine followed by continued use of Avastin 15 mg/kg IV q3w as a single agent until disease progression</td>
</tr>
</tbody>
</table>

° 15 mg/kg IV dose evaluated in persistent, recurrent, or metastatic cervical cancer (CC) in combination with either cisplatin/paclitaxel or topotecan/paclitaxel. Treatment was given until disease progression or unacceptable toxicity.

°° 10 mg/kg IV dose evaluated in platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (prOC) in combination with either cisplatin/paclitaxel, pegylated liposomal doxorubicin (PLD), or weekly topotecan; or 15 mg/kg IV dose evaluated in combination with topotecan administered every 3 weeks. Treatment was given until disease progression or unacceptable toxicity.

°°° 15 mg/kg IV dose evaluated in platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (psOC) q3w when administered in combination with carboplatin and paclitaxel for 6 cycles and up to 8 cycles, followed by continued use of Avastin 15 mg/kg IV q3w as a single agent until disease progression. Alternatively, Avastin can be administered as a 15 mg/kg dose q3w when given in combination with carboplatin and gemcitabine for 6 cycles and up to 10 cycles, followed by continued use of Avastin 15 mg/kg IV q3w as a single agent until disease progression or unacceptable toxicity.

Important treatment considerations—Women of childbearing potential

- Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin.

- Long-term effects of Avastin exposure on fertility are unknown.

- Counsel patients about the possible risks, including hazard to the fetus and/or loss of pregnancy, of both continued treatment and prolonged exposure following discontinuation, keeping in mind the approximate half-life of Avastin (20 days; range 11–50 days). Patients should also be counseled to continue adequate contraception for 6 months following the last dose of Avastin.

- Nursing mothers should be advised to discontinue nursing or Avastin, taking into account the half-life of the product and the importance of Avastin to the mother.

Please see accompanying full Prescribing Information, including Boxed WARNINGS, and back cover for additional important safety information.
Preparation for administration

- Avastin should be diluted for infusion using aseptic technique
- Withdraw the necessary amount of Avastin to obtain the required dose and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP
- Inspect visually for particulate matter and discoloration prior to administration. Discard any unused portion left in a vial, as the product contains no preservatives
- Diluted Avastin solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for up to 8 hours
- Avastin infusions should not be administered or mixed with dextrose solution

Additional serious adverse events

- Additional serious and sometimes fatal adverse events with increased incidence in the Avastin-treated arm vs control included
  - GI fistulae (up to 2% in metastatic colorectal cancer and ovarian cancer patients)
  - Non-GI fistulae (<1% in trials across various indications; 1.8% in a cervical cancer trial)
  - Arterial thromboembolic events (grade ≥3, 2.6%)
  - Proteinuria (nephrotic syndrome, <1%)
- Additional serious adverse events with increased incidence in the Avastin-treated arm vs control included
  - GI-vaginal fistulae occurred in 8.3% of patients in a cervical cancer trial
  - Venous thromboembolism (grade 3–4, up to 10.6%) in patients with persistent, recurrent, or metastatic cervical cancer treated with Avastin
  - Hypertension (grade 3–4, 5%–18%)”
  - Posterior reversible encephalopathy syndrome (PRES) (<0.5%)
- Infusion reactions with the first dose of Avastin were uncommon (<3%), and severe reactions occurred in 0.2% of patients
- Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin
- Avoid use in patients with ovarian cancer who have evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction

Administration and infusion times

- DO NOT ADMINISTER AS AN IV PUSH OR BOLUS
- DO NOT INITIATE AVASTIN UNTIL AT LEAST 28 DAYS FOLLOWING SURGERY AND UNTIL THE SURGICAL WOUND IS FULLY HEALED

- In clinical studies, infusion reactions with the first dose of Avastin were uncommon (<3%), and severe reactions occurred in 0.2% of patients
- Infusion reactions in clinical trials and in postmarketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, NCI-CTC grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis
- Stop infusion if a severe infusion reaction occurs and administer appropriate medical therapy

NCI-CTC=National Cancer Institute Common Toxicity Criteria.

Please see accompanying full Prescribing Information, including Boxed WARNINGS, and back cover for additional important safety information.
Duration of Avastin therapy in pivotal trials

Treat MCRC with Avastin until second disease progression\(^7,26\)

To realize the clinical benefit of Avastin, patients in clinical trials were treated until disease progression or unacceptable toxicity

- **Patient starts with Avastin**
  - Administer as indicated
  - Monitor and manage adverse events
  - Continue Avastin until
    - Cancer grows or spreads
    - Unacceptable adverse events

- **Patient continues with Avastin**
  - Administer Avastin
  - Monitor and manage
  - Continue Avastin

- **Second disease progression or unacceptable toxicity**

Avastin treatment may be continued when chemotherapy is switched

Indications

Avastin is indicated for the first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil–based chemotherapy.

Avastin, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line Avastin-containing regimen.

Limitation of Use: Avastin is not indicated for adjuvant treatment of colon cancer.

Important treatment considerations—Dose modifications

- There are no recommended dose reductions
- Discontinue Avastin in patients with
  - Gastrointestinal (GI) perforations (GI perforations, fistula formation in the GI tract, intra-abdominal abscess)
  - Fistula formation involving an internal organ
  - Wound dehiscence and wound healing complications requiring medical intervention
  - Severe hemorrhage (ie, requiring medical intervention)
  - Severe arterial thromboembolic event (ATE)
  - Life-threatening (grade 4) venous thromboembolic events, including pulmonary embolism
  - Hypertensive crisis or hypertensive encephalopathy
  - Posterior reversible encephalopathy syndrome (PRES)
  - Nephrotic syndrome
- Temporarily suspend Avastin for: at least 4 weeks prior to elective surgery, severe hypertension not controlled with medical management, moderate to severe proteinuria, and severe infusion reactions
- The safety of resumption of Avastin therapy in patients that experienced PRES or ATE is unknown

Across all indications, study results were achieved with Avastin given at the approved dose until disease progression or unacceptable toxicity\(^7,25\)

First-line advanced nsNSCLC\(^7,27^*\)

Duration

Across all studies, Avastin was discontinued in 8.4% to 21% of patients because of adverse reactions

Most common adverse events

- Across indications, the most common adverse reactions observed in Avastin patients at a rate >10% and at least twice the control arm rate were
  - Epistaxis
  - Proteinuria
  - Lacrimation disorder
  - Headache
  - Taste alteration
  - Back pain
  - Hypertension
  - Dry skin
  - Exfoliative dermatitis
  - Rhinitis
  - Rectal hemorrhage

Please see accompanying full Prescribing Information, including Boxed WARNINGS, and back cover for additional important safety information.

AVASTIN®
bevacizumab
Solution for intravenous infusion
Hypertension in VEGF inhibition

Why hypertension may occur

VEGF interacts with nitric oxide to regulate vascular tone

- The exact mechanism of Avastin-related hypertension is not fully understood
- Some studies suggest that VEGF increases nitric oxide production, resulting in vasodilation
- Nitric oxide is a messenger molecule (a molecule that carries signals between cells) that can regulate various physiologic functions, including blood pressure (BP)
- Reducing nitric oxide production results in vasoconstriction; it has been hypothesized that this process could play a role in hypertension

The presence of VEGF is associated with the production of nitric oxide.

Incidence of hypertension in select Avastin clinical trials

| MCRC* | First-line Study 2107 Grade 3–4 | Avastin + IFL | 12% |
|       | Placebo + IFL | 2% |
| Second-line Avastin-naive Study E3200 Grade 3–5† | Avastin + FOLFOX4 | 9% |
|       | FOLFOX4 alone | 2% |
| NSCLC | First-line Study E4599 Grade 3–5 | Avastin + PC | 8% |
|       | PC alone | 0.7% |

*When continued beyond first progression in MCRC, no new safety signals were observed in the TML study (ML18147) when Avastin was administered in second-line MCRC patients who progressed on an Avastin-containing regimen in first-line MCRC. The safety data was consistent with the known safety profile established in first- and second-line MCRC.

†These data are likely to underestimate the true adverse event rates due to the reporting mechanisms used in this study.

Monitoring BP

- The incidence of severe hypertension is increased in patients receiving Avastin
- BP monitoring should be conducted every 2 to 3 weeks during treatment with Avastin
- Patients with Avastin-induced or -exacerbated hypertension who discontinue Avastin should continue to have their BP monitored at regular intervals

Managing hypertension in patients receiving Avastin

- In clinical trials, appropriate antihypertensives were used to help manage hypertension
- Avastin should be temporarily suspended in patients with severe hypertension that is not controlled with medical management
- If appropriate, restart Avastin after hypertension is well controlled and within normal range
- Discontinue Avastin in patients with hypertensive crisis or hypertensive encephalopathy

Hypertension monitoring and management with Avastin

The following information should not be a substitute for your professional medical judgment and should be individualized for the patient.

<table>
<thead>
<tr>
<th>Monitoring Method</th>
<th>Observations</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure BP every 2 to 3 weeks</td>
<td>Hypertension</td>
<td>Administer appropriate antihypertensive therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Continue to monitor BP regularly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Temporarily suspend Avastin with severe hypertension not controlled with medical management</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If appropriate, restart Avastin after hypertension is well controlled and within normal range</td>
</tr>
</tbody>
</table>

Hypertensive crisis or hypertensive encephalopathy

Discontinue Avastin

Continue to monitor BP regularly

Please see accompanying full Prescribing Information, including Boxed WARNINGS, and back cover for additional important safety information.
Proteinuria in VEGF inhibition

Why proteinuria may occur
- Proteinuria, or an excess of protein in the urine, can occur with cancer and some cancer therapies.\(^{3,35,36}\)
- The exact mechanism of Avastin-related proteinuria is not fully understood.
- In the clinical setting, impairment of the glomeruli that make up the kidneys may be a pathologic cause of persistent proteinuria.\(^{37}\)
- In the preclinical setting, inhibition of VEGF, a key endothelial growth factor, has been shown to impair glomerular endothelial cells.\(^{38}\)

Incidence of proteinuria in select Avastin clinical trials\(^{7,23,25}\)

<table>
<thead>
<tr>
<th>MCRC*</th>
<th>First-line Study 2107</th>
<th>Grade 3</th>
<th>0.8%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Second-line Avastin-naive Study E3200†</td>
<td>Grade 3</td>
<td>0.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade 4</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>NSCLC</td>
<td>First-line Study E4599</td>
<td>Grade 3–5</td>
</tr>
</tbody>
</table>

When continued beyond first progression in MCRC, no new safety signals were observed in the TML study (ML18147) when Avastin was administered in second-line MCRC patients who progressed on an Avastin containing regimen in first-line MCRC. The safety data was consistent with the known safety profile established in first- and second-line MCRC.\(^{7}\)

These data are likely to underestimate the true adverse event rates due to the reporting mechanisms used in this study.\(^{7}\)

- Nephrotic syndrome occurred in <1% of patients receiving Avastin in clinical trials, in some instances with fatal outcome.\(^{7}\)
- Discontinue Avastin in patients with nephrotic syndrome.

Background information
- Nephrotic syndrome involves protein levels in the urine of more than 3.5 g/24 hours, low blood protein levels, high cholesterol levels, high triglyceride levels, and edema.\(^{41}\)
- A urine dipstick is generally reported as negative (<10 mg/dL), trace (10–20 mg/dL), 1+ (30 mg/dL), 2+ (100 mg/dL), 3+ (300 mg/dL), or 4+ (1000 mg/dL).\(^{42}\)

Diagnosing and monitoring proteinuria\(^7\)
- The incidence and severity of proteinuria are increased in patients receiving Avastin.
- Urine dipstick or urinalyses are performed to detect proteinuria in most cases.
- Patients should be monitored for the development or worsening of proteinuria with serial urinalyses.
- Data from a postmarketing safety study showed poor correlation between urine protein/creatinine ratio and 24-hour urine protein.

Managing proteinuria in patients receiving Avastin\(^7\)
- Patients with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection.
- Suspend Avastin administration for ≥2 grams of proteinuria/24 hours and resume when proteinuria is <2 g/24 hours.
- Avastin should be temporarily suspended in patients with moderate to severe proteinuria.
- Patients with moderate to severe proteinuria based on 24-hour collections should be monitored regularly until improvement and/or resolution is observed.
- Discontinue Avastin in patients with nephrotic syndrome.

Proteinuria monitoring and management with Avastin\(^7\)
The following information should not be a substitute for your professional medical judgment and should be individualized for the patient.

### Monitoring Method

<table>
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<tbody>
<tr>
<td>&lt;2+ urine dipstick</td>
<td>Continue to monitor</td>
</tr>
<tr>
<td>≥2+ urine dipstick</td>
<td>Undergo further assessment with 24-hour urine collection</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Discontinue Avastin</td>
</tr>
</tbody>
</table>

### Observations

- <2+ urine dipstick
- ≥2+ urine dipstick
- Nephrotic syndrome

### Actions

- Continue to monitor
- Undergo further assessment with 24-hour urine collection
- Discontinue Avastin
- Suspend Avastin if ≥2 g of protein/24 hours and monitor regularly
- Continue to monitor nephrotic syndrome as appropriate
- Restart Avastin when protein level is <2 g/24 hours

Please see accompanying full Prescribing Information, including Boxed WARNINGS, and back cover for additional important safety information.
Incidence of GI perforation in Avastin-treated patients
Serious, and sometimes fatal, GI perforation occurs at a higher incidence in Avastin-treated patients compared to controls. The incidences of GI perforation, some fatal, in Avastin-treated patients range from 0.3% to 3.2% across clinical trials.

What to look for during treatment with Avastin
The typical presentation may include:
- Abdominal pain
- Nausea
- Emesis
- Constipation
- Fever
Perforation can be complicated by intra-abdominal abscess, fistula formation, and the need for diverting ostomies. The majority of cases occurred within the first 50 days of initiation of Avastin.

Management
Discontinue Avastin in patients with GI perforations (GI perforation, fistula formation in the GI tract, intra-abdominal abscess).

Non-GI fistulae: Incidence and management of Avastin
Incidence of non-GI fistulae in Avastin-treated patients
Serious and sometimes fatal fistula formation involving tracheo-esophageal, bronchopleural, biliary, vaginal, renal, and bladder sites occurs at a higher incidence in Avastin-treated patients compared to controls. Uncommon (<1%) reports of fistulae that involve areas of the body other than the gastrointestinal tract were observed in clinical trials across various indications and have also been reported in postmarketing experience. Most events occurred within the first 6 months of Avastin therapy.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer, 1.8% of Avastin-treated patients and 1.4% of control patients were reported to have had non-gastrointestinal vaginal, vesical, or female genital tract fistulae.

Management
Permanently discontinue Avastin in patients with tracheo-esophageal (TE) fistula or any grade 4 fistula. Discontinue Avastin in patients with fistula formation involving an internal organ.

Wound healing and/or surgical complications: Incidence and management of Avastin
Incidence of wound healing and/or surgical complications in Avastin-treated patients
The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients. In a controlled clinical trial, the incidence of wound healing complications, including serious and fatal complications, in patients with MCRC who underwent surgery during the course of Avastin treatment was 19%; in patients who did not receive Avastin, the incidence was 4%.

Necrotizing fasciitis, including fatal cases, has been reported in patients treated with Avastin; usually secondary to wound healing complications, GI perforation, or fistula formulation.

Management
In clinical trials, administration of Avastin was not allowed until at least 28 days after surgery. Do not administer Avastin until the wound is fully healed. Discontinue Avastin in patients with wound healing complications requiring medical intervention.

The appropriate interval between the last dose of Avastin and elective surgery is unknown; however, the half-life of Avastin is estimated to be 20 days (range 11–50 days). Suspend Avastin for at least 28 days prior to elective surgery.

Discontinue Avastin in patients who develop necrotizing fasciitis.

*Hold Avastin for ≥28 days and until incision is fully healed.
Hemorrhage: Incidence and management of Avastin

Incidence of hemorrhage in Avastin-treated patients

Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system (CNS) hemorrhage, epistaxis, and vaginal bleeding occurred up to 5-fold more frequently in patients receiving Avastin compared to patients receiving only chemotherapy. Across indications, the incidence of grade ≥3 hemorrhagic events among patients receiving Avastin ranged from 0.4% to 6.9%.

Serious or fatal pulmonary hemorrhage occurred in 4 of 13 (31%) patients with squamous cell histology and 2 of 53 (4%) patients with non-squamous NSCLC receiving Avastin and chemotherapy compared to none of the 32 (0%) patients receiving chemotherapy alone.

In clinical studies in NSCLC where patients with CNS metastases who completed radiation and surgery more than 4 weeks prior to the start of Avastin were evaluated with serial CNS imaging, symptomatic grade 2 CNS hemorrhage was documented in 1 of 83 Avastin-treated patients (rate 1.2%, 95% confidence interval, 0.06%–5.93%).

What to look for during treatment with Avastin

Avastin can cause 2 different types of bleeding:

- **Minor bleeding:** Episodes lasting less than 10 minutes not requiring medical intervention; most commonly mild nosebleeds
- **Serious and potentially fatal bleeding:** Including coughing up blood, GI bleeding, vomiting blood, bleeding in the brain, nosebleeds, and vaginal bleeding
  - These events occurred up to 5 times more often in people who received Avastin compared with people who received chemotherapy alone

Management

Patients who have recently coughed up blood (greater than or equal to a half-teaspoon of red blood) or with serious bleeding should not receive Avastin. Avastin should be permanently discontinued if severe bleeding occurs.

Arterial thromboembolic events (ATEs): Incidence and management of Avastin

Incidence of ATEs in Avastin-treated patients

Serious, and sometimes fatal, ATEs occurred at a higher incidence in patients receiving Avastin compared with those in the control arm.

Across indications, the incidence of grade ≥3 ATEs (including cerebral infarction, transient ischemic attacks, myocardial infarction, and angina) in Avastin-treated patients was 2.6% compared with 0.8% in the control arms.

Among patients receiving Avastin in combination with chemotherapy, the risk of developing an ATE during therapy was increased in patients with a history of ATEs or diabetes, or age greater than 65 years.

Management

Permanently discontinue Avastin in patients who experience a severe ATE. The safety of resumption of Avastin therapy after resolution of an ATE has not been studied.

Venous thromboembolic events (VTEs): Incidence and management of Avastin

Incidence of VTEs in Avastin-treated patients

Patients treated for persistent, recurrent, or metastatic cervical cancer with Avastin may be at increased risk of VTEs.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer, grade ≥3 VTEs were reported in 10.6% of patients treated with chemotherapy and Avastin compared to 5.4% in patients receiving chemotherapy alone.

Management

Permanently discontinue Avastin in patients who experience a life-threatening (grade 4) VTE, including pulmonary embolism.

Please see accompanying full Prescribing Information, including Boxed WARNINGS, and back cover for additional important safety information.
Posterior reversible encephalopathy syndrome (PRES): Incidence and management of Avastin

Incidence of PRES in Avastin-treated patients
PRES has been reported with an incidence of <0.5% in clinical studies.

What to look for during treatment with Avastin
PRES is a neurologic disorder that may present with
- Headache
- Seizure
- Lethargy
- Confusion
- Blindness
- Other visual and neurologic disturbances
- Mild to severe hypertension
The onset of symptoms occurred from 16 hours to 1 year after initiation of Avastin.

Management
Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. Discontinue Avastin in patients developing PRES. Symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae. The safety of reinitiating Avastin therapy in patients previously experiencing PRES is not known.

Infusion reactions: Incidence and management of Avastin

Incidence of infusion reactions in Avastin-treated patients
Avastin is a humanized monoclonal antibody. In clinical studies, infusion reactions with the first dose of Avastin were uncommon (<3%), and severe reactions occurred in 0.2% of patients.

What to look for during treatment with Avastin
Infusion reactions reported in the clinical trials and postmarketing experience include
- Hypertension
- Hypertensive crises associated with neurologic signs and symptoms
- Wheezing
- Oxygen desaturation
- Grade 3 hypersensitivity
- Chest pain
- Headaches
- Rigors
- Diaphoresis

Management
Avastin infusion should be interrupted in all patients with severe infusion reactions and appropriate medical therapy administered.
Embryo-fetal toxicity: Incidence and management of Avastin

Incidence of embryo-fetal toxicity in Avastin-treated patients

Avastin may cause fetal harm based on the drug's mechanism of action and findings from animal studies. Limited postmarketing reports describe cases of fetal malformations with use of Avastin in pregnancy; however, these reports are insufficient to determine drug associated risks.

Congenital malformations were observed with the administration of bevacizumab to pregnant rabbits during organogenesis every 3 days at a dose as low as a clinical dose of 10 mg/kg. Furthermore, animal models link angiogenesis and VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryo-fetal development, and postnatal development.

Management

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with and for 6 months after the last dose of Avastin.

Ovarian failure: Incidence and management of Avastin

Incidence of ovarian failure in Avastin-treated patients

Avastin increases the risk of ovarian failure and may impair fertility.

The incidence of ovarian failure was higher (34% vs 2%) in premenopausal women receiving Avastin in combination with mFOLFOX chemotherapy as compared to those receiving mFOLFOX chemotherapy alone as adjuvant treatment for colorectal cancer, a use for which Avastin is not approved.

Management

Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin. Long-term effects of Avastin exposure on fertility are unknown.

Because of the potential for serious adverse reactions in breastfed infants from bevacizumab, advise a nursing woman that breastfeeding is not recommended during treatment with Avastin.

When to interrupt Avastin

Temporarily suspend Avastin for:
- At least 4 weeks prior to elective surgery
- Severe hypertension not controlled with medical management
- Moderate to severe proteinuria
- Severe infusion reactions

When to discontinue or suspend Avastin

Avastin should be discontinued if patients experience any of the following:
- GI perforations (GI perforations, fistula formation in the GI tract, intra-abdominal abscess)
- Fistula formation involving an internal organ
- Wound dehiscence and wound healing complications requiring medical intervention
- Serious hemorrhage (ie, requiring medical intervention)
- Severe arterial thromboembolic event (ATE)
- Life-threatening (grade 4) venous thromboembolic events, including pulmonary embolism
- Hypertensive crisis or hypertensive encephalopathy
- Posterior reversible encephalopathy syndrome (PRES)
- Nephrotic syndrome

The safety of resumption of Avastin therapy in patients that experienced PRES or ATE is unknown.

Please see accompanying full Prescribing Information, including Boxed WARNINGS, and back cover for additional important safety information.
Most common adverse events (AEs)\(^7\)

Incidence of AEs during treatment with Avastin

- Across all studies, Avastin was discontinued in 8.4% to 21% of patients because of adverse reactions

Across indications, the most common adverse reactions observed in Avastin patients at a rate >10% and at least twice the control arm rate were

- Epistaxis
- Headache
- Hypertension
- Rhinitis
- Proteinuria
- Taste alteration
- Proteinuria
- Rhinitis
- Hypertension
- Headache
- Epistaxis
- Back pain
- Exfoliative dermatitis

NCI-CTCAE V4.03 recommendations for adverse events management

NCI-CTCAE definition of grade

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated</td>
<td>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*</td>
<td>Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL†</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
</tbody>
</table>

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
†Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

Hypertension

<table>
<thead>
<tr>
<th>Grade</th>
<th>AE</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prehypertension</td>
<td>Systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg</td>
<td>Stage 1 hypertension</td>
<td>Systolic BP 140–159 mm Hg or diastolic BP 90–99 mm Hg</td>
<td>Medical intervention indicated</td>
<td>Recurrent or persistent (≥24 hrs)</td>
</tr>
</tbody>
</table>

Treatment with Avastin

<table>
<thead>
<tr>
<th>AE</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Prehypertension</td>
<td>Stage 1 hypertension</td>
<td>Stage 2 hypertension</td>
<td>Life-threatening consequences</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Urgent intervention indicated</td>
</tr>
<tr>
<td>Treatment with Avastin</td>
<td>Continue Avastin treatment</td>
<td>Continue Avastin treatment</td>
<td>Temporarily suspend Avastin treatment if not controlled with medical management</td>
<td>Discontinue Avastin treatment</td>
</tr>
</tbody>
</table>

Proteinuria

<table>
<thead>
<tr>
<th>Grade</th>
<th>AE</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
<td>1+ proteinuria; urinary protein &lt;1.0 g/24 hrs</td>
<td>Adults: 2+ proteinuria; urinary protein 1.0–3.4 g/24 hrs</td>
<td>Adults: urinary protein ≥3.5 g/24 hrs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment with Avastin

<table>
<thead>
<tr>
<th>AE</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
<td>Continue Avastin treatment</td>
<td>Suspend Avastin treatment</td>
<td>Discontinue Avastin treatment</td>
<td></td>
</tr>
</tbody>
</table>

ATE/VTE

<table>
<thead>
<tr>
<th>Grade</th>
<th>AE</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic event</td>
<td>Venous thrombosis (e.g., superficial thrombosis)</td>
<td>Venous thrombosis (e.g., uncomplicated deep vein thrombosis)</td>
<td>Medical intervention indicated</td>
<td>Venous thrombosis (e.g., uncomplicated pulmonary embolism [venous]; non-embolic cardiac mural [arterial] thrombus)</td>
<td>Medical intervention indicated</td>
</tr>
</tbody>
</table>

Treatment with Avastin: ATE

<table>
<thead>
<tr>
<th>AE</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic event</td>
<td>Continue Avastin treatment</td>
<td>Continue Avastin treatment</td>
<td>Discontinue Avastin treatment</td>
<td></td>
</tr>
</tbody>
</table>

Treatment with Avastin: VTE

<table>
<thead>
<tr>
<th>AE</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic event</td>
<td>Continue Avastin treatment</td>
<td>Continue Avastin treatment</td>
<td>Continue Avastin treatment</td>
<td>Permanently discontinue Avastin treatment</td>
</tr>
</tbody>
</table>

This information should not be a substitute for your professional medical judgment and should be individualized for the patient.

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Boxed WARNINGS

- **Gastrointestinal (GI) perforation**
  - Serious and sometimes fatal GI perforation occurs at a higher incidence in Avastin-treated patients compared to controls
  - The incidences of GI perforation ranged from 0.3% to 3.2% across clinical studies
  - Discontinue Avastin 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 Avastin-treated patients
  - Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined
  - Discontinue Avastin at least 28 days prior to elective surgery and in patients with wound healing complications requiring medical intervention

- **Hemorrhage**
  - Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin. Across indications, the incidence of grade ≥3 hemorrhagic events among patients receiving Avastin ranged from 0.4% to 6.9%
  - Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis (≥1/2 tsp of red blood)
  - Discontinue Avastin in patients with serious hemorrhage (ie, requiring medical intervention)

Additional serious adverse events

- Additional serious and sometimes fatal adverse events with increased incidence in the Avastin-treated arm vs control included
  - GI fistulae (up to 2% in metastatic colorectal cancer and ovarian cancer patients)
  - Non-GI fistulae (<1% in trials across various indications; 1.8% in a cervical cancer trial)
  - Arterial thromboembolic events (grade ≥3, 2.6%)
  - Proteinuria (nephrotic syndrome, <1%)

- Additional serious adverse events with increased incidence in the Avastin-treated arm vs control included
  - GI-vaginal fistulae occurred in 8.3% of patients in a cervical cancer trial
  - Venous thromboembolism (grade 3–4, up to 10.6%) in patients with persistent, recurrent, or metastatic cervical cancer treated with Avastin
  - Hypertension (grade 3–4, 5%–18%)
  - Posterior reversible encephalopathy syndrome (PRES) (<0.5%)

- Infusion reactions with the first dose of Avastin were uncommon (<3%), and severe reactions occurred in 0.2% of patients

- Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin

- Avoid use in patients with ovarian cancer who have evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction

Pregnancy warning

- Based on the mechanism of action and animal studies, Avastin may cause fetal harm
- Advise female patients that Avastin may cause fetal harm, and to inform their healthcare provider of a known or suspected pregnancy
- Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose of Avastin
- Advise nursing women that breastfeeding is not recommended during treatment with Avastin
- Avastin may impair fertility

Most common adverse events

- Across indications, the most common adverse reactions observed in Avastin patients at a rate >10% and at least twice the control arm rate were
  - Epistaxis
  - Headache
  - Hypertension
  - Rhinitis
  - Proteinuria
  - Taste alteration
  - Dry skin
  - Rectal hemorrhage
  - Lacrimation disorder
  - Back pain
  - Exfoliative dermatitis

- Across all studies, Avastin was discontinued in 8.4% to 21% of patients because of adverse reactions

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555. Please see accompanying full Prescribing Information, including **Boxed WARNINGS**, for additional important safety information.