Clinical Policy: Bevacizumab (Avastin, Mvasi)
Reference Number: ERX.SPA.86
Effective Date: 03.01.14
Last Review Date: 02.19
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Bevacizumab (Avastin®) and bevacizumab-awwb (Mvasi®) are vascular endothelial growth factor-specific angiogenesis inhibitors.

FDA Approved Indication(s)
Avastin and Mvasi are indicated for the treatment of:
• Metastatic colorectal cancer, in combination with intravenous 5-fluorouracil (5-FU)-based chemotherapy for first- or second-line treatment
• Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab product-containing regimen
• Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer (NSCLC), in combination with carboplatin and paclitaxel for first-line treatment
• Recurrent glioblastoma in adults
• Metastatic renal cell carcinoma (RCC) in combination with interferon alfa
• Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan

Avastin is also indicated for the treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer:
• In combination with carboplatin and paclitaxel, followed by Avastin as a single agent, for stage III or IV disease following initial surgical resection
• In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens
• In combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by Avastin as a single agent, for platinumsensitive recurrent disease

Limitation(s) of use: Bevacizumab-products are not indicated for adjuvant treatment of colon cancer.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Avastin and Mvasi are medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. All FDA-Approved Indications (must meet all):
      1. Diagnosis of one of the following (a-f):
         a. Colorectal cancer:
         b. Non-squamous non-small cell lung cancer:
         c. Glioblastoma;
         d. Metastatic renal cell carcinoma:
         e. Carcinoma of the cervix:
Bevacizumab, Bevacizumab-awwb

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1. Epithelial ovarian, fallopian tube, or primary peritoneal cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a-f):
   a. For colorectal cancer: used in combination with 5-FU based chemotherapy;
   b. For non-squamous non-small cell lung cancer: used in combination with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease;
   c. For glioblastoma: member has progressive disease;
   d. For metastatic renal cell carcinoma: used in combination with interferon alfa;
   e. For cervical cancer: used in combination with paclitaxel and cisplatin or topotecan;
   f. For epithelial ovarian, fallopian tube, or primary peritoneal cancer: disease is persistent, recurrent, or metastatic;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 10 mg/kg every 2 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
Approval duration: 6 months

B. Oncology - Non-FDA Approved Indications (off-label) (must meet all):
1. Diagnosis of one of the following conditions (a-j):
   a. AIDS-related Kaposi sarcoma;
   b. Anaplastic gliomas;
   c. Breast cancer;
   d. Endometrial carcinoma;
   e. Intracranial and spinal ependymoma
   f. Low-grade (WHO Grade II) infiltrative supratentorial astrocytoma/oligodendroglioma;
   g. Malignant pleural mesothelioma;
   h. Medulloblastoma
   i. Primary central nervous system cancers;
   j. Soft tissue sarcoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
Approval duration: 6 months

C. Ophthalmology - Non-FDA Approved Indications (off-label) (must meet all):
1. Diagnosis of one of the following conditions (a-g):
   a. Neovascular (wet) age-related macular degeneration;
   b. Macular edema following retinal vein occlusion;
   c. Diabetic macular edema;
   d. Proliferative diabetic retinopathy;
   e. Neovascular glaucoma;
   f. Choroidal neovascularization associated with: angioid streaks, no known cause, inflammatory conditions, high pathologic myopia, or ocular histoplasmosis syndrome;
   g. Diabetic retinopathy associated with ocular neovascularization (choroidal, retinal, iris);
2. Prescribed by or in consultation with an ophthalmologist;
3. Age ≥ 18 years;
4. Request meets one of the following (a or b):
   a. Dose does not exceed 2.5 mg per dose;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
Approval duration: 6 months
D. Other diagnoses/indications
   1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy
   A. All Indications in Section I (must meet all):
      1. Member meets one of the following (a or b):
         a. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
         b. Documentation supports that member is currently receiving Avastin for a covered oncology indication listed in section I and has received this medication for at least 30 days;
      2. Member is responding positively to therapy;
      3. If request is for a dose increase, request meets one of the following (a or b):
         a. New dose does not exceed 15 mg/kg IV every 3 weeks or 10 mg/kg IV every 2 weeks;
         b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

   Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2):
   1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.  
   
   Approval duration: Duration of request or 6 months (whichever is less); or
   2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:
   A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information
   Appendix A: Abbreviation/Acronym Key
   5-FU: fluorouracil
   5-FU/LV: fluorouracil, leucovorin
   CapeOX: capecitabine, oxaliplatin
   FDA: Food and Drug Administration
   FOLFIRI: fluorouracil, leucovorin, irinotecan
   FOLFOX: fluorouracil, leucovorin, oxaliplatin
   FOLFOXIRI: fluorouracil, leucovorin, oxaliplatin, irinotecan
   NCCN: National Comprehensive Cancer Network

   Appendix B: Therapeutic Alternatives
   This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX4 = Infusional 5-FU/leucovorin/oxaliplatin</td>
<td>Oxaliplatin 85 mg/m² IV over 2 hours day 1; leucovorin 200 mg/m² IV over 2 hours days 1 &amp; 2, followed by 5-FU 400 mg/m² IV bolus over 2-4 minutes, followed by 600 mg/m² IV 5-FU continuous infusion over 22 hours on days 1 &amp; 2. Repeat cycle every 14 days.</td>
<td>varies</td>
</tr>
<tr>
<td>FOLFIRI = Camptosar 180 mg/m² IV over 90 minutes day 1; Leucovorin 400 mg/m² IV over 2 hours day 1 followed by 5-FU 400 mg/m² IV</td>
<td>varies</td>
<td></td>
</tr>
<tr>
<td>Drug Name</td>
<td>Dosing Regimen</td>
<td>Dose Limit/Maximum Dose</td>
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<tr>
<td>Infusional 5-FU/leucovorin/Camptosar&lt;sup&gt;®&lt;/sup&gt; (irinotecan)</td>
<td>bolus over 2-4 minutes, followed by 2.4 gm/m² IV 5-FU continuous infusion over 46 hours. Repeat cycle every 14 days.</td>
<td></td>
</tr>
<tr>
<td>capecitabine (Xeloda&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>2500 mg/m² PO BID for 2 weeks; repeat cycles of 2 weeks on and 1 week off. For patients who cannot tolerate intensive therapy.</td>
<td>varies</td>
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<tr>
<td><strong>NSCLC</strong></td>
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<tr>
<td>cisplatin</td>
<td>Various doses</td>
<td>varies</td>
</tr>
<tr>
<td>carboplatin and paclitaxel</td>
<td></td>
<td></td>
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<tr>
<td>docetaxel</td>
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<tr>
<td>vinorelbine</td>
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<tr>
<td>gemcitabine</td>
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<tr>
<td>etoposide</td>
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<tr>
<td>irinotecan</td>
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<td>vinblastine</td>
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<td>mitomycin</td>
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<td>ifosfamide</td>
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<tr>
<td>pemetrexed disodium (Alimta&lt;sup&gt;®&lt;/sup&gt;)(2nd line)</td>
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<tr>
<td><strong>Ovarian Cancer</strong></td>
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<tr>
<td>carboplatin and paclitaxel</td>
<td>Carboplatin dosed at an area under the curve (AUC) of 5-7.5 and paclitaxel 175 mg/m² IV over 3 hours given every 3 weeks for 6 courses.</td>
<td>varies</td>
</tr>
<tr>
<td>docetaxel taxotere and carboplatin</td>
<td>Docetaxel, 60-75 mg/m² IV over 1 hour plus carboplatin dosed at AUC of 5 to 6 every 3 weeks.</td>
<td>varies</td>
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<tr>
<td><strong>Glioblastoma Multiforme</strong></td>
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<td></td>
</tr>
<tr>
<td>temozolomide (Temodar&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Maintenance phase cycles: 150 mg-200 mg/m² PO days 1-5. Repeat every 28 days.</td>
<td>varies</td>
</tr>
<tr>
<td>carmustine (Bincu&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>150 mg to 200 mg/m² IV on day 1. Repeat every 6-8 weeks for one year or tumor progression.</td>
<td>varies</td>
</tr>
<tr>
<td><strong>Cervical Cancer</strong></td>
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<tr>
<td>cisplatin/paclitaxel</td>
<td>Paclitaxel: 135 mg/m² IV as a continuous infusion over 24 hours day 1. Cisplatin: 50 mg/m² IV on day 2. Repeat cycle every 21 days for up to a total of 6 cycles; responders may continue beyond 6 cycles.</td>
<td>varies</td>
</tr>
<tr>
<td>cisplatin/topotecan (Hycamtin&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Topotecan: I0.75 mg/m²/day IV on days 1, 2, and 3. Cisplatin: 50 mg/m² IV on day 1 only. Repeat cycle every 21 days for up to a total of 6 cycles; responders may continue beyond 6 cycles.</td>
<td>varies</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Dosing Regimen</td>
<td>Dose Limit/Maximum Dose</td>
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</tr>
<tr>
<td>topotecan (Hycamtin®)/paclitaxel</td>
<td>Paclitaxel: 135 mg/m² IV continuous infusion over 24 hours day 1</td>
<td>varies</td>
</tr>
<tr>
<td></td>
<td>Topotecan: 0.75 mg/m²/day IV on days 1, 2, and 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Repeat cycle every 21 days for up to a total of 6 cycles; responders may continue beyond 6 cycles</td>
<td></td>
</tr>
</tbody>
</table>

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/BoxedWarnings

- Contraindication(s): none reported
- Boxed warning(s): gastrointestinal perforations, surgery and wound healing complication, and hemorrhage
  - Gastrointestinal perforation: Occurs in up to 3.2% of bevacizumab-treated patients. Discontinue bevacizumab for gastrointestinal perforation.
  - Surgery and wound healing complications: Discontinue in patients with wound dehiscence. 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, hemoptysis, gastrointestinal bleeding, CNS hemorrhage, and vaginal bleeding are increased in bevacizumab-treated patients. Do not administer bevacizumab to patients with serious hemorrhage or recent hemoptysis.

Appendix D: General Information

- The FDA revoked the approval of the breast cancer indication for Avastin (bevacizumab) on November 18, 2011. Avastin used for metastatic breast cancer has not been shown to provide a benefit, in terms of delay in the growth of tumors that would justify its serious and potentially life-threatening risks. Nor is there evidence that use of Avastin will either help women with breast cancer live longer or improve their quality of life. More information at: http://www.fda.gov/NewsEvents/Newsroom/ucm279485.htm
- Fatal pulmonary hemorrhage can occur in patients with NSCLC treated with chemotherapy and bevacizumab. The incidence of severe or fatal hemoptysis was 31% in patients with squamous histology and 2.3% with NSCLC excluding predominant squamous histology. Patients with recent hemoptysis should not receive bevacizumab.
- Bevacizumab has been added to the National Comprehensive Cancer Network (NCCN) practice guidelines as category 2A for recurrent ovarian cancer for patients who have progressed on two consecutive single-agent regimens without evidence of clinical benefit.
- Age-related macular degeneration, secondary to choroidal neovascularization
  - In a prospective time-series trial, bevacizumab 2.5 mg was administered by intravitreal injection every 4 weeks for a total of 3 injections.
  - In one retrospective study, bevacizumab 1.25 mg was administered by intravitreal injection once monthly for a total of three injections.
  - In another retrospective study intravitreal bevacizumab 1.25 mg was administered once monthly until macular edema, subretinal fluid, and/or pigment epithelial detachment resolved (Avery et al, 2006).
- Bevacizumab is effective for the treatment of neovascular glaucoma that is not responsive to maximal doses of antiglaucoma medications. While most studies did not indicate the agents that were tried and failed prior to the use of bevacizumab in neovascular glaucoma, one study did indicate the use of timolol, dorzolamide, and brimonidine before a bevacizumab injection.

V. Dosage and Administration
<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic colorectal cancer</td>
<td>5 mg/kg IV every 2 weeks with bolus-IFL Or 10 mg/kg IV every 2 weeks with FOLFOX4 Or 5 mg/kg IV every 2 weeks or 7.5 mg/kg IV every 3 weeks with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy after progression on a first-line Avastin containing regimen</td>
<td>15 mg/kg IV every 3 weeks Or 10 mg/kg IV every 2 weeks Doses up to 20 mg/kg IV have been administered in clinical trials</td>
</tr>
<tr>
<td>Non–squamous NSCLC</td>
<td>15 mg/kg IV every 3 weeks with carboplatin/paclitaxel</td>
<td></td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>10 mg/kg IV every 2 weeks</td>
<td></td>
</tr>
<tr>
<td>Metastatic renal cell carcinoma</td>
<td>10 mg/kg IV every 2 weeks with interferon alfa</td>
<td></td>
</tr>
<tr>
<td>Persistent, recurrent, or metastatic carcinoma of the cervix</td>
<td>15 mg/kg IV every 3 weeks with paclitaxel/cisplatin or paclitaxel/topotecan</td>
<td></td>
</tr>
<tr>
<td>Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer</td>
<td>10 mg/kg IV every 2 weeks with paclitaxel, pegylated liposomal doxorubicin or weekly topotecan Or 15 mg/kg IV every 3 weeks with topotecan given every 3 weeks</td>
<td></td>
</tr>
<tr>
<td>Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer</td>
<td>15 mg/kg IV every 3 weeks in combination with carboplatin/paclitaxel for 6-8 cycles, followed by 15 mg/kg IV every 3 weeks as a single agent Or 15 mg/kg IV every 3 weeks in combination with carboplatin/gemcitabine for 6-10 cycles, followed by 15 mg/kg IV every 3 weeks as a single agent</td>
<td></td>
</tr>
<tr>
<td>Neovascular (wet) macular degeneration</td>
<td>1.25 to 2.5 mg administered by intravitreal injection every 4 weeks</td>
<td>2.5 mg/dose</td>
</tr>
<tr>
<td>Neovascular glaucoma</td>
<td>1.25 mg administered by intravitreal injection every 4 weeks</td>
<td>2.5 mg/dose</td>
</tr>
<tr>
<td>Macular edema secondary to retinal vein occlusion</td>
<td>1 mg to 2.5 mg administered by intravitreal injection every 4 weeks</td>
<td>2.5 mg/dose</td>
</tr>
<tr>
<td>Proliferative diabetic retinopathy</td>
<td>1.25 mg administer by intravitreal injection 5 to 20 days before vitrectomy</td>
<td>2.5 mg/dose</td>
</tr>
<tr>
<td>Diabetic macular edema</td>
<td>1.25 mg administered by intravitreal injection</td>
<td>2.5 mg/dose</td>
</tr>
</tbody>
</table>

VI. Product Availability
Single use vial: 100 mg/4 mL, 400 mg/16 mL

VII. References


<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy created.</td>
<td>02.14</td>
<td></td>
</tr>
<tr>
<td>Policy converted to new template.</td>
<td>07.16</td>
<td>09.16</td>
</tr>
<tr>
<td>Added FDA-labeled ovarian and cervical cancer indications. Added compendial indications, including ocular uses. Updated criteria per NCCN guidelines for monotherapy or combination therapy and first line or maintenance therapy. Added HCPCS and ICD-10 codes. Criteria: added age and max dose; removed requests for documentation, safety criteria, and prescriber restrictions. References: removed 2008 Genentech letter regarding infections correlating with Avastin intravitreal use as it is no longer available.</td>
<td>07.01.17</td>
<td>08.17</td>
</tr>
<tr>
<td>Converted to new template. All off-label uses are referred to the off-label use policy. HCPCS codes, ICD-10-CM Code tablets removed. Updated approval durations from 3/6 months to 6/12 months. Added BBW criteria regarding serious hemorrhage or recent hemoptysis; and surgery within the last 28 days and unhealed surgical wounds. Added appendix B. BBW info Removed Avastin is NOT being used as adjuvant treatment for colon cancer. Diagnosis must be colorectal cancer in this section. For ovarian, FT and peritoneal cancer removed Member has received no more than 2 prior chemotherapy regimens. It is not stated in the PI.</td>
<td>11.20.17</td>
<td>02.18</td>
</tr>
<tr>
<td>1Q 2018 annual review: Simplified criteria based on PA criteria streamline approach Added specific criteria for off-label uses for opthalmic indications Added allowable off-label oncology indications as reflected in the NCCN compendium.</td>
<td>12.11.18</td>
<td>02.19</td>
</tr>
</tbody>
</table>

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional
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