Clinical Policy: Bevacizumab (Avastin)
Reference Number: ERX.SPA.86
Effective Date: 03.01.14
Last Review Date: 08.17

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

Description
Bevacizumab (Avastin®) is a vascular endothelial growth factor-specific angiogenesis inhibitor.

FDA approved indication
Avastin is indicated:
- For the treatment of metastatic colorectal cancer, with intravenous 5-fluorouracil (5-FU)-based chemotherapy for first- or second-line treatment
- For the treatment of metastatic colorectal cancer, with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin containing regimen
- For the treatment of non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent, or metastatic disease
- For the treatment of glioblastoma, as a single agent for adult patients with progressive disease following prior therapy
  - Effectiveness is based on improvement in objective response rate. There are no data available demonstrating improvement in disease-related symptoms or survival with Avastin.
- For the treatment of metastatic renal cell carcinoma in combination with interferon alfa
- For the treatment of cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease.
- For the treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that is
  - Platinum-resistant in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan,
  - Platinum-sensitive in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by Avastin as a single agent

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

Policy/Criteria
Provider must submit documentation (which may include office chart notes and lab results) supporting that member has met all approval criteria

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

I. Initial Approval Criteria
   A. Colorectal Cancer (must meet all):
      1. Diagnosis of colorectal cancer;
      2. Age ≥ 18 years;
      3. Meets a or b:
         a. FDA approved use:
            i. Colorectal cancer (a or b):
               a) Primary or subsequent therapy for metastatic disease:
                  1) In combination with 5-FU-based therapy*;
               b) Subsequent therapy for metastatic disease:
                  1) In combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based therapy* after disease progression on a first-line Avastin-containing regimen;
b. Off-label NCCN approved use (i or ii):
   i. Colorectal cancer (a or b):
      a) Primary or subsequent therapy for unresectable, metastatic, or medically
         inoperable disease (1, 2, or 3):
         1) In combination with capecitabine, FOLFOX, FOLFIRI, CapeOX, FOLFOXIRI,
            or 5-FU/LV*;
         2) In combination with irinotecan;
         3) In combination with irinotecan and oxaliplatin;
      b) Adjuvant therapy for resectable metastases:
         1) In combination with capecitabine, FOLFOX, FOLFIRI, CapeOX, FOLFOXIRI,
            or 5-FU/LV*;
   ii. Rectal cancer:
      a) Primary therapy for resectable disease classified as either (T3/N0/M0 [stage IIA])
         or (anyT/N1-2/M0 [stage III]**:
         1) In combination with capecitabine, FOLFOX, FOLFIRI, FOLFOXIRI, CapeOX,
            or 5-FU/LV*;
4. Member’s history is negative for both of the following:
   a. Serious hemorrhage or recent hemoptysis;
   b. Surgery within the last 28 days and unhealed surgical wounds;
5. Request meets any of the following (a or b):
   a. Dose does not exceed 10 mg/kg IV 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).

*Examples of fluoropyrimidines: capecitabine, floxuridine, 5-FU; examples of fluoropyrimidine-based regimens: 5-FU/LV
   (fluorouracil, leucovorin); FOLFOX (5-FU, leucovorin, oxaliplatin); FOLFIRI (5-FU, leucovorin, irinotecan); FOLFOXIRI
   (5-FU, leucovorin, oxaliplatin, irinotecan); CapeOX (capecitabine, oxaliplatin).
**American Joint Committee on Cancer (TNM staging classification (7th ed., 2010) as reported in NCCN Colon and Rectal
   Cancer: T (primary tumor characteristics), N (regional lymph node status), M (metastasis status).

Approval duration: 6 months

B. Non-squamous Non-small Cell Lung Cancer:
   1. Diagnosis of non-squamous non-small cell lung cancer;
   2. Age ≥ 18 years;
   3. Meets a or b:
      a. FDA approved use:
         i. Primary therapy for unresectable, locally advanced, recurrent, or metastatic disease:
            a) In combination with carboplatin and paclitaxel;
      b. Off-label NCCN recommended use (i or ii):
         i. Primary or subsequent therapy for unresectable, locally advanced, recurrent, or
            metastatic disease (a, b, c, or d):
            a) In combination with carboplatin and paclitaxel;
            b) In combination with carboplatin and pemetrexed;
            c) In combination with pemetrexed;
            d) In combination with cisplatin and pemetrexed;
         ii. Continuation maintenance therapy (if prior Avastin use associated with achievement
            of tumor response or stable disease) (a or b):
            a) As single agent;
            b) In combination with pemetrexed;
6. Member’s history is negative for both of the following:
   a. Serious hemorrhage or recent hemoptysis;
   b. Surgery within the last 28 days and unhealed surgical wounds;
7. Request meets any of the following (a or b):
   a. Dose does not exceed 15 mg/kg IV every 3 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
C. **Glioblastoma** (must meet all):
   1. Diagnosis of glioblastoma;
   2. Age ≥ 18 years;
   3. Meets a or b:
      a. FDA approved use:
         i. Subsequent therapy for recurrent or progressive disease;
            a) As single agent;
      b. Off-label NCCN recommended use:
         i. Subsequent therapy for recurrent or progressive disease:
            a) In combination with irinotecan, carmustine, lomustine, temozolomide, or carboplatin;
   4. Member’s history is negative for both of the following:
      a. Serious hemorrhage or recent hemoptysis;
      b. Surgery within the last 28 days and unhealed surgical wounds;
   5. Request meets any of the following (a or b):
      a. Dose does not exceed 10 mg/kg IV 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*

D. **Renal Cell Carcinoma** (must meet all):
   1. Diagnosis of renal cell carcinoma;
   2. Age ≥ 18 years;
   3. Meets a or b:
      a. FDA approved use:
         i. Metastatic disease:
            1. In combination with interferon alfa-2a/2b;
      b. Off-label NCCN recommended use:
         i. Relapsed or stage IV (advanced or metastatic) disease (a, b, or c):
            a) Clear cell histology - primary therapy:
               1) In combination with interferon alfa-2b;
            b) Clear cell histology - subsequent therapy:
               1) As single agent;
            c) Non-clear cell histology:
               1) As single agent;
   4. Member’s history is negative for both of the following:
      a. Serious hemorrhage or recent hemoptysis;
      b. Surgery within the last 28 days and unhealed surgical wounds;
   5. Request meets any of the following (a or b):
      a. Dose does not exceed 10 mg/kg IV 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*

E. **Cervical Carcinoma** (must meet all):
   1. Diagnosis of cervical carcinoma;
   2. Age ≥ 18 years;
   3. Meets a or b:
      a. FDA approved use:
         i. Persistent, recurrent or metastatic disease (a or b):
            a) In combination with paclitaxel and cisplatin;
            b) In combination with paclitaxel and topotecan;
      b. Off-label NCCN recommended use:
         i. Persistent, recurrent, or metastatic disease (a or b):
            a) Primary therapy (1 or 2):
1) In combination with carboplatin;
2) In combination with topotecan;

b) Subsequent therapy:
   1) As single agent;

4. Member’s history is negative for both of the following:
   a. Serious hemorrhage or recent hemoptysis;
   b. Surgery within the last 28 days and unhealed surgical wounds;

5. Request meets any of the following (a or b):
   a. Dose does not exceed 15 mg/kg IV every 3 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

F. Epithelial Ovarian/Fallopian Tube/Primary Peritoneal Cancer (must meet all):
   1. Diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal cancer;
   2. Age ≥ 18 years;
   3. Meets a or b:
      a. FDA approved use:
         i. Epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (a or b):
            a) Persistent/recurrent platinum-resistant disease (1, 2, or 3):
               1) In combination with paclitaxel;
               2) In combination with pegylated liposomal doxorubicin;
               3) In combination with topotecan;
            b) Persistent/recurrent platinum-sensitive disease (1, 2, or 3):
               1) In combination with carboplatin and paclitaxel;
               2) In combination with carboplatin and gemcitabine;
               3) As single agent;
       b. Off-label NCCN recommended use (i, ii, iii, or iv):
          i. Epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (a, b, or c):
             a) Persistent/recurrent disease:
                1) As single-agent;
             b) Unresectable disease – primary therapy:
                1) In combination with carboplatin and paclitaxel;
             c) Stage II-IV disease post completion surgery* - adjuvant therapy:
                1) In combination with carboplatin and paclitaxel;
          ii. Granulosa cell tumor** (relapsed stage II-IV disease) - subsequent therapy:
             a) As single-agent;
          iii. Serous/endometrioid epithelial carcinoma (stage II-IV low-grade [grade 1]) - adjuvant therapy:
             a) In combination with carboplatin and paclitaxel;
          iv. Mucinous carcinoma of the ovary (stage II-IV) - adjuvant therapy:
             a) In combination with carboplatin and paclitaxel;
   4. Member’s history is negative for both of the following:
      a. Serious hemorrhage or recent hemoptysis;
      b. Surgery within the last 28 days and unhealed surgical wounds;
   5. Request meets any of the following (a or b):
      a. Dose does not exceed 15 mg/kg IV every 3 weeks or 10 mg/kg IV 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).

*Follow-up surgery performed if fertility-conserving strategies are no longer desired.
**A type of malignant sex cord-stromal tumor.

Approval duration: 6 months

G. Other diagnoses/indications
I. 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. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
      2. Member is responding positively to therapy (e.g., no disease progression or unacceptable toxicity);
      3. If request is for a dose increase, request meets any 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, 2, or 3):
      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. If use is intravitreal, currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, and documentation supports positive response to therapy as evidenced by one of the following (a, b, or c):
         a. Detained neovascularization;
         b. Improvement in visual acuity;
      Approval duration: 12 months; or
      3. 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: Black Box Warning – Gastrointestinal Perforations, Surgery and Wound Healing Complication, and Hemorrhage
   - Gastrointestinal perforation: Occurs in up to 3.2% of Avastin-treated patients. Discontinue Avastin 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 Avastin 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 Avastin- treated patients. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis.

   Appendix C: Therapeutic Alternatives
   N/A
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 non–small cell lung cancer</td>
<td>15 mg/kg IV every 3 weeks with carboplatin/paclitaxel</td>
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<tr>
<td>Glioblastoma</td>
<td>10 mg/kg IV every 2 weeks</td>
<td></td>
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<tr>
<td>Metastatic renal cell carcinoma</td>
<td>10 mg/kg IV every 2 weeks with interferon alfa</td>
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<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>
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<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>
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<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>
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VI. Product Availability

Single use vial: 100 mg/4 mL, 400 mg/16 mL

VII. References


### Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
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<tbody>
<tr>
<td>Policy created.</td>
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<tr>
<td>Policy converted to new template. 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>02.14</td>
<td>03.14</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>07.01.17</td>
<td>08.17</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 medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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