Avastin

Description

Avastin (bevacizumab)

Background

Neoplastic tissue originates as host-derived cells that proliferate atypically due to loss of ability to control growth. The initial growth is dependent on existing vasculature. An additional supply of nutrients as well as waste removal must be provided in order for tumors to grow beyond 2-3mm\(^3\). In response to tumor-related signaling factors tumor angiogenesis occurs. Vascular endothelial growth factor (VEGF) is an important regulating factor of both normal and abnormal angiogenesis. VEGF interacts with two different receptor tyrosine kinases, VEGFR-1 and VEGFR-2 to alter angiogenesis. Increased levels of VEGF and VEGFR-2 have been observed in multiple cancer types and the levels of expression are related to increased vascularization within tumors. This tumor neovascularization has prognostic significance (1).

Anti-VEGF pharmacotherapies have been developed with a goal of inhibiting tumor angiogenesis and thereby inhibiting growth and metastasis (2-4). Avastin (bevacizumab) is a Vascular Endothelial Growth Factor (VEGF) inhibitor. Avastin (bevacizumab) binds to human vascular endothelial growth factor (VEGF) and prevents interaction of VEGF with its receptors (Flt-1, KDR) on the surface of endothelial cells (2-4).
FDA-approved indications: Avastin (bevacizumab) is an angiogenesis inhibitor indicated for: (5)
1. Metastatic colorectal cancer 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.
2. 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 Avastin-containing regimen.
3. Non-squamous non-small cell lung cancer (NSCLC), with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent, or metastatic disease.
4. Glioblastoma, as a single agent for adult patients with progressive disease following prior therapy.
6. Metastatic carcinoma of the cervix, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease.
7. Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan.

Limitation of Use:
Avastin is not indicated for adjuvant treatment of colon cancer (5).

Off Label Uses:
In comparative trials and uncontrolled case series report improvements in visual acuity and decreased retinal thickness by optical coherence tomography following treatment with intravitreal Avastin for ocular diseases resulting from intravitreal neovascularization (7-8).

Avastin carries a boxed warning for GI perforations including wound-healing complications and hemorrhage. The reported incidence of GI perforations was 2% and hemorrhage was 31%. In both instances, fatalities occurred. The drug is only approved to be started 28 days after surgery and until the surgical wound is fully healed to prevent wound-healing complications (5).

Related policies
Cyramza, Gilotrif, Herceptin, Iressa, Keytruda, Lynparza, Opdivo, Perjeta, Portrazza, Tagrisso, Tykerb, Xalkori, Zykadia

Policy
This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.
Avastin may be considered **medically necessary** for the treatment of patients age 18 years and older with metastatic colorectal carcinoma, when given with 5-FU; 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; non-squamous non-small cell lung cancer, when given with carboplatin and paclitaxel; glioblastoma multiforme if the disease has progressed from prior therapy; metastatic renal cell carcinoma, when given with interferon alfa; platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, when given with paclitaxel or pegylated liposomal doxorubicin or topotecan; ocular neovascular disease; and in the treatment of persistent, recurrent or late-stage cervical cancer, when given with paclitaxel and cisplatin or paclitaxel and topotecan.

Avastin is considered **investigational** in patients less than 18 years of age and in patients who do not meet the criteria for medical necessity.

**Prior-Approval Requirements**

**Age**
18 years of age or older

**Diagnoses**

Patient must have **ONE** of the following:

1. **Metastatic colorectal cancer**
   a. 1\(^{st}\) line or 2\(^{nd}\) line treatment
   b. Concurrent intravenous 5-Fluorouracil-based chemotherapy

2. **Metastatic colorectal cancer**
   a. 2\(^{nd}\) line treatment
   b. Progressed on a first-line Avastin containing regimen
   c. Concurrent therapy with:
      i. Fluoropyrimidine-irinotecan-based chemotherapy, or
      ii. Fluoropyrimidine-oxaliplatin-based chemotherapy

3. **Non-Squamous non-small cell lung cancer**
   a. 1\(^{st}\) line treatment
   b. Unresectable, locally advanced, recurrent or metastatic
   c. Concurrent therapy with carboplatin and paclitaxel

4. **Glioblastoma multiforme (GBM)**
   a. Single agent therapy
b. Progressive disease following prior therapy

5. Metastatic renal cell carcinoma
   a. Concurrent therapy with interferon-alfa

6. Platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancers
   a. Concurrent therapy with ONE of the following:
      i. paclitaxel
      ii. pegylated liposomal doxorubicin
      iii. topotecan

7. Ocular disease resulting from intravitreal neovascularization, including:
   a. Neovascular (Wet) Age-Related Macular Degeneration (AMD)
   b. Diabetic Macular Edema
   c. Macular edema secondary to retinal vascular occlusion
   d. Progressive high myopia
   e. Ocular histoplasmosis
   f. Proliferative diabetic retinopathy
   g. Retinopathy of prematurity
   h. Angioid streaks
   i. Neovascular glaucoma

8. Persistent, recurrent, or metastatic Cervical cancer
   a. Concurrent therapy with ONE of the following:
      i. paclitaxel and cisplatin
      ii. paclitaxel and topotecan

Prior – Approval Renewal Requirements
Same as above

Policy Guidelines

Pre - PA Allowance
None

Prior - Approval Limits
Duration 12 months
Prior – Approval **Renewal** Limits

**Duration**  
12 months

**Rationale**

**Summary**  
Avastin (bevacizumab) is medically necessary for the treatment of angiogenesis-dependent neoplasms as approved by the FDA. These indications are (1) first- or second-line treatment with intravenous 5-FU of metastatic colorectal cancer; (2) first line treatment with carboplatin and paclitaxel of unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, (3) single agent treatment for adults patients with progressive glioblastoma and (4) treatment with interferon alfa of metastatic renal cell carcinoma, and (5) 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; and cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease (5). In addition, there is an evidence base to support the off-label intravitreal use of Avastin (bevacizumab) for the treatment of ocular disease resulting from neovascularization (6).

Prior authorization is required to ensure the safe, clinically appropriate and cost effective use of Avastin (bevacizumab) while maintaining optimal therapeutic outcomes.

**References**


### Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>February 2008</td>
<td>U.S. Food and Drug Administration (FDA) granted accelerated approval for Avastin (bevacizumab), in combination with paclitaxel chemotherapy, for the treatment of patients who have not received chemotherapy for their metastatic HER2-negative breast cancer.</td>
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<td>July 2008</td>
<td>Recent studies for the treatment of glioblastoma with combination bevacizumab/irinotecan have shown promising results. Conclusions of several studies have been that the treatment is well tolerated and active against recurrent malignant gliomas. A 6-month progression-free survival among 35 patients was 46%. The 6-month overall survival was 77%. The National Comprehensive Cancer Network recommends bevacizumab with irinotecan for recurrent/salvage therapy of glioblastoma. Bevacizumab has reportedly become the standard of care at the Duke Brain Tumor Institute</td>
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<td>May 2009</td>
<td>FDA has approved Avastin treatment of glioblastoma, as a single agent for patients with progressive disease following prior therapy. Prior to the FDA approval the studies for the treatment of glioblastoma involved the combination therapy of bevacizumab/irinotecan. Due to the FDA approval of treating glioblastoma without concurrent irinotecan therapy in some cases the criteria is being updated to remove IV irinotecan as a requirement for approval.</td>
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<tr>
<td>August 2009</td>
<td>FDA has approved Avastin treatment of metastatic renal cell carcinoma (mRcc) with concurrent administration of interferon-alfa.</td>
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<td>January 2010</td>
<td>The use of bevacizumab to treat wet AMD has been demonstrated to be safe and effective and is widely accepted in clinical practice. The clinical literature supports the use of bevacizumab in the following ocular conditions characterized by neovascularization: diabetic macular edema, macular edema secondary to retinal vascular occlusion, progressive high myopia, proliferative diabetic retinopathy, retinopathy of prematurity, angiod streaks, neovascular glaucoma and ocular histoplasmosis. Practicing ophthalmologists consulted also report general acceptance of</td>
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the use of bevacizumab for these conditions. Use of bevacizumab as monotherapy for polypoidal choroidal vasculopathy, which is genetically linked to AMD, has been found in some cases to result in a treatment-refractory response. Decreased efficacy is possibly due to bevacizumab being unable to reach the location of the PCV or PCV development resulting from a non-VEGF source.

November 2011
Approved indication of breast cancer deleted, based on loss of FDA approval for breast cancer.

May 2012
The CATT two year study was released in 2012 and showed that Avastin and ranibizumab have similar efficacy in the treatment of neovascular AMD. Monthly dosing results in minimally better visual outcomes than ‘as needed’ dosage. However, the clinical difference is so small that ‘as needed’ dosing may be quite appropriate for some patients in certain social and financial situations. Avastin is associated with a higher rate of non-specific serious systemic adverse events. The significance of this finding is unclear and may be related to the overall advanced age of the study participants.8 (Consultant ophthalmologist assessment.)

September 2012
Annual editorial and reference update

December 2012
Added recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancers to approved indications, to align with NCCN Guidelines.

January 2013
FDA added a new indication 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. Editorial review and reference update.

June 2013
Annual editorial review and reference update

December 2013
Annual editorial review and update

August 2014
Addition of new FDA approved indication to treat patients with persistent, recurrent or late-stage cervical cancer.

September 2014
Annual review and reference update.

November 2014
Change to include the new indication for platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan

March 2015
Annual editorial review and update

December 2015
Annual editorial review and reference update
Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 3, 2015 and is effective on January 1, 2016.

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