Avastin

Description

Avastin (bevacizumab)

Background
Neoplastic tissue originates as host-derived cells that proliferate atypically due to loss of ability to control growth. 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. Anti-VEGF pharmacotherapies have been developed with a goal of inhibiting tumor angiogenesis and thereby inhibiting growth and metastasis. 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 (1-4).

Regulatory Status
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.

8. Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with carboplatin and paclitaxel or in combination with carboplatin and emcitabine, followed by Avastin as a single agent.

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
Alecensa, Cyramza, Erbitux, Eylea, Gilotrif, Herceptin, Iressa, Keytruda, Lonsurf, Lucentis, Lynparza, Mekinist, Opdivo, Perjeta, Portrazza, Stivarga, Tafinlar, Tarceva, Tagrisso, Tecentriq, Tykerb, Vectibix, Xalkori, Zaltrap, 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 cancer, non-squamous non-small cell lung cancer, metastatic
renal cell carcinoma, platinum-resistant or platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, ocular neovascular disease, or persistent, recurrent or late-stage cervical cancer and if the conditions below for each indication are met.

Avastin is considered **investigational** in patients who are less than 18 years of age and for all other indications.

**Prior-Approval Requirements**

**Age**

18 years of age or older

**Diagnoses**

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

1. Metastatic colorectal cancer

   AND **ONE** of the following:
   
   a. 1<sup>st</sup> line treatment
   
   i. Concurrent intravenous 5-Fluorouracil-based chemotherapy

   b. 2<sup>nd</sup> line treatment with **ONE** of the following regimens:
   
   i. Fluoropyrimidine- irinotecan-based chemotherapy
   
   ii. Fluoropyrimidine- oxaliplatin-based chemotherapy
   
   iii. 5-Fluorouracil-based chemotherapy

2. Non-Squamous non-small cell lung cancer

   a. 1<sup>st</sup> line treatment
   
   b. Unresectable, locally advanced, recurrent or metastatic
   
   c. Concurrent therapy with carboplatin and paclitaxel

3. Glioblastoma multiforme (GBM)

   a. Single agent therapy
   
   b. Progressive disease following prior therapy

4. Metastatic renal cell carcinoma

   a. Concurrent therapy with interferon-alfa

5. Platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancers
5.21.04

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a. Concurrent therapy with ONE of the following:
   i. paclitaxel
   ii. pegylated liposomal doxorubicin
   iii. topotecan

6. Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer
   a. Concurrent therapy with ONE of the following
      i. Carboplatin and paclitaxel followed by Avastin as a single agent
      ii. Carboplatin and gemcitabine followed by Avastin as a single agent

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

Age 18 years of age or older

Diagnoses

Patient must have ONE of the following:

1. Metastatic colorectal cancer

   AND ONE of the following:
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Subsection: Antineoplastic Agents
Subject: Avastin

a. 1st line treatment
   i. Concurrent intravenous 5-Fluorouracil-based chemotherapy

b. 2nd line treatment with ONE of the following regimens:
   i. Fluoropyrimidine- irinotecan-based chemotherapy
   ii. Fluoropyrimidine- oxaliplatin-based chemotherapy
   iii. 5-Fluorouracil-based chemotherapy

2. Non-Squamous non-small cell lung cancer
   a. Concurrent therapy with carboplatin and paclitaxel

3. Glioblastoma multiforme (GBM)
   a. Single agent therapy

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

5. 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

6. Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer
   a. Single agent therapy

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

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 first- or second-line metastatic colorectal cancer; first line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer; adults patients with progressive glioblastoma; treatment for metastatic renal cell carcinoma or metastatic colorectal cancer; persistent, recurrent, or metastatic cervical cancer; platinum-resistant or platinum-sensitive recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer. 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 (1-6).

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>Addition to PA</td>
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<tr>
<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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<tr>
<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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| January 2010 | 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, angioid streaks, neovascular glaucoma and ocular histoplasmosis. Practicing ophthalmologists consulted also report general acceptance of 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
<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>December 2015</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
<td>June 2016</td>
<td>Annual editorial review and reference update</td>
</tr>
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<td></td>
<td>Policy number change from 5.04.04 to 5.21.04</td>
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<tr>
<td>January 2017</td>
<td>Addition of the diagnosis of platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with carboplatin and paclitaxel or in combination with carboplatin and emcitabine, followed by Avastin as a single agent to criteria</td>
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<tr>
<td>March 2017</td>
<td>Annual review</td>
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<tr>
<td>June 2017</td>
<td>Annual editorial review</td>
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**Keywords**

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 15, 2017 and is effective on October 1, 2017.