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 2-3mm³. 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).

Regulatory Status

FDA-approved indications: Avastin (bevacizumab) is an angiogenesis inhibitor indicated for: (5)
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<td>Antineoplastic Agents</td>
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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, Gilotirif, Herceptin, Iressa, Keytruda, Lonsurf, Lynparza, Opdivo, Perjeta, Portrazza, Stivarga, Tagrisso, Tykerb, 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 carcinoma; 1\textsuperscript{st} line treatment when given with 5-FU; metastatic colorectal cancer; 2\textsuperscript{nd} line treatment with one of the following regimens: fluoropyrimidine-irinotecan, fluoropyrimidine-oxaliplatin based, or 5-fluorouracil-based chemotherapy; 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 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\textsuperscript{st} line treatment
      i. Concurrent intravenous 5-Fluorouracil-based chemotherapy
   b. 2\textsuperscript{nd} 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\textsuperscript{st} 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
   a. Concurrent therapy with ONE of the following:
      i. paclitaxel
      ii. pegylated liposomal doxorubicin
      iii. topotecan

6. 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

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

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**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
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
June 2016 Annual editorial review and reference update
Policy number change from 5.04.04 to 5.21.04

Keywords
This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 24, 2016 and is effective on July 1, 2016.

Deborah M. Smith, MD, MPH