I. Medication Description

Bevacizumab binds to vascular endothelial growth factor (VEGF) and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in-vitro models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused a reduction of microvascular growth and inhibition of metastatic disease progression.

Vascular targeting therapies are aimed at inhibiting tumor neovascularization and are not directly cytotoxic. Therefore, vascular targeting therapies used in cancer therapy usually need to be given in combination with traditional cytotoxic treatment modalities, except in maintenance regimens.

II. Position Statement

- Requests for use with certain diagnostic codes do not require prior authorization and supporting clinical documentation. See Addendum.
- Coverage is determined through a prior authorization process with supporting clinical documentation for all other requests.

III. Policy

Avastin is covered in adult patients (≥ 18 years of age) for the following indications:

- Metastatic colorectal cancer
  - In combination with intravenous (IV) 5-fluorouracil, capecitabine or irinotecan-based chemotherapy
- Non-squamous non-small cell lung cancer
  - Treatment in combination with a platinum-based treatment regimen for recurrence or metastases for patients with performance status 0-1
  - Continuation-maintenance therapy if given first line with chemotherapy for recurrence or metastases for patients with performance status 0-2
- Breast cancer
  - In combination with paclitaxel for recurrent or metastatic disease in one of the following settings:
    - HER2 negative disease with symptomatic visceral disease or visceral crisis
    - HR negative and HER2 negative disease
    - HR positive and HER2 negative disease refractory to endocrine therapy
• Central nervous system cancers
  o Adult intracranial and spinal ependymoma (excludes subependymoma) – single agent treatment for disease progression
  o Anaplastic gliomas – treatment of recurrent disease or salvage therapy as a single agent or in combination with irinotecan, carmustine, lomustine or temozolomide
  o Glioblastoma – treatment of recurrent disease or salvage therapy as a single agent or in combination with irinotecan, carmustine, lomustine or temozolomide

• Cervical cancer
  o First-line therapy in combination with paclitaxel and cisplatin, carboplatin or topotecan for recurrent or metastatic disease

• Endometrial cancer
  o As a single agent in patients who have progressed on prior cytotoxic chemotherapy

• Malignant pleural mesothelioma
  o Used in combination with pemetrexed and cisplatin followed by single agent maintenance therapy as treatment of
    ▪ Unresectable clinical stage I-III disease and tumors of epithelial or mixed histology OR
    ▪ Clinical stage IV disease, tumors of sarcomatoid histology or medically inoperable tumors in patients with performance status 0-2

• Metastatic renal cell carcinoma
  o For relapsed or stage IV disease
    ▪ As first-line therapy in combination with interferon alfa-2b for patients with predominant clear cell histology OR
    ▪ As a single agent in patients with non-clear cell histology

• Soft Tissue Sarcoma
  o Angiosarcoma- as a single agent
  o Solitary Fibrous Tumor/Hemangiopericytoma- in combination with temozolomide

• Ovarian cancer
  o Persistent disease or recurrence (if platinum-resistant, in combination with liposomal doxorubicin, weekly paclitaxel or topotecan) if bevacizumab not previously received
  o As a single agent for persistent disease or recurrence if bevacizumab not previously received
  o As a single agent for clinical relapse in patients with stage II-IV granulose cell tumors

• Neovascular (wet) Age-related macular degeneration (AMD) and Diabetic Macular Edema (DME)

IV. Quantity Limits

• For oncology indications:
  o No more than 170 billable units (1700mg) in a single administration AND
  o No more than 170 billable units (1700mg) in a 21-day cycle

• For ophthalmic indications:
  o 1 billable unit per eye
V. Coverage Duration

Coverage is available for 6 months and may be renewed.

VI. Coverage Renewal Criteria

- Coverage for the treatment of metastatic colorectal cancer (in combination with fluoropyrimidine and irinotecan or oxaliplatin based chemotherapy) can be renewed when there is an absence of unacceptable toxicity from the drug even after a progression on a first-line bevacizumab-containing regimen.
- Coverage for other oncology indications can be renewed based upon the following criteria:
  - Disease response with stabilization of disease or decrease in size of tumor or tumor spread AND Absence of unacceptable toxicity from the drug
- Coverage for ophthalmic indications can be renewed based upon the following criteria:
  - Disease response with stabilization or regression of disease AND Absence of unacceptable toxicity from the drug

VII. Billing/Coding Information

- Avastin J9035 – 1 billable unit is 10mg
- Avastin C9257- 1 billable unit is 0.25mg
- Pertinent indications:
  - Metastatic colorectal cancer –C17.0-C17.2, C17.8, C17.9, C18.0-C18.9, C19, C20, C21.8, C78.00-C78.02, C78.6, C78.7, Z85.038
  - Non-squamous non-small cell lung cancer - C33, C34.00-C34.02, C34.10-C34.12, C34.2, C34.30-C34.32, C34.80-C34.82, C34.90-C34.92, Z85.118
  - Breast cancer – C50.011, C50.012, C50.019, C50.021, C50.022, C50.029, C50.111, C50.112, C50.119, C50.121, C50.122, C50.129, C50.211, C50.212, C50.219, C50.221, C50.222, C50.229, C50.311, C50.312, C50.319, C50.321, C50.322, C50.329, C50.411, C40.412, C50.419, C50.421, C50.422, C50.429, C50.511, C50.512, C50.519, C50.521, C50.522, C50.529, C50.611, C50.612, C50.619, C50.621, C50.622, C50.629, C50.811, C50.812, C50.819, C50.821, C50.822, C50.829, C50.911, C50.912, C50.919, C50.921, C50.922, C50.929, Z85.3
  - CNS cancer - C71.0-C71.9, C72.9, D43.0-D43.2, D43.4, Z85.841
  - Cervical cancer –C53.0, C53.1, C53.8, C53.9, Z80.49
  - Renal cell carcinoma –C64.1, C64.2, C64.9, C65.1, C65.2, C65.9, Z85.528
  - Ovarian cancer - C48.1, C48.8, C48.2, C56.1, C56.2, C56.9, C57.00-C57.02, C57.10-C57.12, C57.20-C57.22, C57.3, C57.4, C57.7-C57.9, Z85.43
  - Soft Tissue Sarcoma –C48.0-C48.2, C49.0, C49.10-C49.12, C49.20-C49.22, C49.3-C49.6, C49.8, C49.9
  - Endometrial cancer –C54.1-C54.3, C54.9, Z80.49
  - Malignant pleural mesothelioma- C38.4, C45.0

VIII. Summary of Policy Changes

- 3/1/11:
  - Coverage duration changed to 6 months for all indications
  - Indications expanded to include ophthalmic uses (no longer a separate policy)
  - Addition of Coverage renewal criteria
  - Addition of Warnings/Precautions
  - Addition of Billing/Coding information
- 6/15/12: Removal of metastatic breast cancer indication as revoked by FDA
- 3/15/13:
  - Breast cancer coverage added back to policy per NCCN recommendations
  - Addition of covered indications under pertinent diagnoses
  - Addition of coverage for soft tissue sarcoma, cervical cancer, uterine cancer
  - Update coverage criteria for NSCLC, RCC, ovarian cancer, and CNS cancers
  - Updated renewal criteria for mCRC
- 6/2013: updated to include statement regarding investigational administration, cited Eylea as related policy
- 3/15/14: metastatic renal cell carcinoma updated to allow first line therapy of Avastin as single agent for non-clear cell histology; coverage of uterine/endometrial cancers no longer supported
- 4/16/14: updated to cervical cancer and endometrial cancer criteria in accordance with NCCN treatment guidelines
- 6/9/14: criteria in ovarian cancer updated to reflect current NCCN guidelines
- 7/21/14: criteria in central nervous system cancers updated to reflect current NCCN guidelines
- 10/2014: addition of topotecan in combination with Avastin as first line therapy in cervical cancer based on FDA approval
- 3/15/15: no policy changes
- 6/15/15: no policy changes
- 7/1/15: formulary distinctions made
- 10/1/15: ICD9 references omitted
- 6/15/16: included criteria for malignant pleural mesothelioma
- 4/5/17: policy updated to correspond with current NCCN treatment guidelines

IX. References

1. UpToDate Online, retrieved October 2010
2. Clinical Pharmacology Online, retrieved 1/2015
3. Facts and Comparisons Online, retrieved October 2010
7. ECRI. Avastin (Bevacizumab) for the Treatment of Neovascular Age-related Macular Degeneration. Updated 09/21/08.

- **Addendum:**

<table>
<thead>
<tr>
<th>ICD10</th>
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<tr>
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<td>Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy with macular edema</td>
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<tr>
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<td>Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy with macular edema</td>
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<td>Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy with macular edema</td>
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<tr>
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<td>Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema</td>
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<tr>
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The Plan fully expects that only appropriate and medically necessary services will be rendered. The Plan reserves the right to conduct pre-payment and post-payment reviews to assess the medical appropriateness of the above-referenced therapies.
Drug therapy initiated with samples will not be considered as meeting medical necessity for coverage for non-preferred or prior authorized medications.

The preceding policy is a guideline to allow for coverage of the pertinent medication/product, and is not meant to serve as a clinical practice guideline.