

RMHP Formulary Coverage Policy

Avastin (bevacizumab)

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CLASSIFICATION

Bevacizumab is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF).

DESCRIPTION

- Avastin® (bevacizumab), a recombinant humanized monoclonal antibody, is an antineoplastic agent. The drug is an IgG1 antibody that contains human framework regions and murine complementarity-determining regions.
- 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. In vitro models of angiogenesis have shown that interaction of VEGF with its receptors may lead to endothelial cell proliferation and new blood vessel formation. Evidence from animal models has suggested that administration of an anti-VEGF monoclonal antibody (e.g., bevacizumab) may inhibit angiogenesis and thus may reduce microvascular growth of tumors and inhibit metastatic disease progression. Bevacizumab is metabolized and eliminated via the reticuloendothelial system.
- VEGF is the major angiogenic stimulus responsible for the formation of choroidal neovascularization and so represents a new paradigm in the treatment of retinovascular disease. Given intraocularly, it has been investigated to treat a variety of conditions (e.g., age-related macular degeneration (ARMD), proliferative diabetic retinopathy, neovascular glaucoma, and the macular edema of vein occlusions).
- Bevacizumab (Avastin) is closely related to ranibizumab and appears to be a safe and effective treatment in the short term for AMD (Ziemssen et al.). It has been used off-label for many years for these patients. At about 1%-5% of the cost of ranibizumab, many clinicians believe that patients should be informed about this alternative, especially the significant price difference (Ziemssen et al.). The Comparison of the Age-related Macular Degeneration Treatment Trials (sponsored by the US National Eye Institute) is currently in progress. Some authors who have undergone smaller trials and systematic reviews believe that these two modalities will be shown to be equivalent in effect (Schouten et al.).

FORMULARY COVERAGE

Prior authorization: Required

Good Health Formulary: Medical Benefit

Commercial Formulary: Medical Benefit

Medicare Part D coverage: Part B if administered incident to a physician's service. Part D if obtained from any pharmacy.

COVERAGE CRITERIA

Cancer:

RMHP considers bevacizumab (Avastin) medically necessary for the following indications:

1. Metastatic cancer of the colon or rectum (in combination therapy)
2. Metastatic small bowel adenocarcinoma
3. Metastatic renal cell carcinoma (in combination with interferon alfa)
4. Non-squamous, non-small cell lung cancer
5. Metastatic breast cancer, HER-2 negative

6. Metastatic epithelial ovarian cancer (recurrent following platinum-based regimen)
7. Gliomas of the brain including anaplastic astrocytomas (grade 3) and glioblastoma multiforme (grade 4) (salvage therapy)
8. Fallopian tube cancer
9. Primary peritoneal cancer
10. Second-line therapy of cervical cancer

RMHP considers bevacizumab experimental for the treatment of von Hippel Lindau disease, esophageal cancer, pancreatic cancer, prostate cancer, cancer of unknown origin (primary occult), diabetic or radiation retinopathy, radiation necrosis of the brain, endometrial cancer, gallbladder cancer, glaucoma, hepatocellular cancer, melanoma, neuroendocrine tumors, neurofibromatosis, sarcoma (e.g., Kaposi's sarcoma, leiomyosarcoma, liposarcoma, and osteosarcoma), cholangiocarcinoma, desmoid tumor, gastric cancer, mesothelioma, Vogt-Koyanagi-Harada syndrome, radiation necrosis, and all other indications as its effectiveness for these indications has not been established.

Ophthalmic Use:

RMHP considers bevacizumab (Avastin) medically necessary for the following indications:

1. Neovascular (wet) age related macular degeneration. Evaluate adding the following, as per the CMS national coverage policy:
2. diabetic macular edema
3. proliferative diabetic retinopathy
4. Macular edema due to retinal vascular occlusion
5. degeneration of macula and posterior pole
6. peripheral retinal degenerations
7. rubeosis iridis
8. glaucoma associated with vascular disorders

Background:

- Avastin (bevacizumab) is not FDA approved for age related (wet) macular degeneration
- Intravitreal administration of Avastin (bevacizumab) is a CMS Compendia supported use for a variety of ophthalmic disorders
- Avastin (bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that is similar to Lucentis (ranibizumab), a drug developed expressly for intravitreal use
- Avastin (bevacizumab) is widely used by ophthalmologists and the American Academy of Ophthalmology supports treating age-related macular degeneration (AMD) with intravitreal injections of bevacizumab to meet the medical needs of many patients who have not responded to therapy with ocular photodynamic therapy (OPT) with verteporfin or intravitreal pegaptanib
- Intravitreal Avastin (bevacizumab) is prepared by compounding pharmacies and costs under \$100 per eye. Lucentis (ranibizumab) cost is well over \$2,000 per eye
- Avastin (bevacizumab) is formulated for intravenous infusion, not intravitreal injection, thus although Avastin is similar to Lucentis, they differ in some respects:
 - The Avastin molecule is larger than Lucentis (149kD vs. 48kD). This may impact penetration into the layers of the retina, but the clinical implications are unknown
 - Avastin has a longer half-life than Lucentis (20 days compared to 4 hours) that may allow for less frequent administration
 - Lucentis doesn't have Fc portion in this antibody fragment, which may cause less inflammation within the eye.

RMHP considers the use of Avastin (bevacizumab) to be **experimental** for the treatment of sub-foveal neovascularization due to ocular histoplasmosis, central retinal vein occlusion, macular edema (cystoid or)

Required Provider Specialty:

- Approval is limited to Ophthalmology and Oncology

DOSAGE/ADMINISTRATION:

Intravenous route

- **Glioblastoma multiforme of brain:** Recurrent, progressive disease following prior therapy, 10 mg/kg IV every 2 weeks
- **Metastatic breast cancer, HER2-negative:** First-line therapy in combination with paclitaxel, 10 mg/kg given as a IV infusion once every 14 days
- **Metastatic colorectal cancer:**
 - First-line therapy, in combination with oxaliplatin and capecitabine (XELOX), 7.5 mg/kg IV over 30 to 90 min every 3 weeks was used in a clinical trial
 - First- or second-line therapy, in combination with 5-fluorouracil-based chemotherapy (ie. bolus-IFL [irinotecan, fluorouracil, leucovorin]), 5 mg/kg IV over 90 min every 2 weeks; if tolerated, the infusion may be given over 60 min for the second infusion and 30 min for subsequent infusions
 - First- or second-line therapy, in combination with 5-fluorouracil-based chemotherapy (ie. FOLFOX-4 [oxaliplatin plus leucovorin followed by a bolus and infusional 5-fluorouracil]), 5 mg/kg IV over 30 to 90 min every 2 weeks was used in a clinical trial as first line therapy or 10 mg/kg IV over 90 min every 2 weeks as second line therapy; if tolerated, the infusion may be given over 60 min for the second infusion and 30 min for subsequent infusions
- **Metastatic renal cell carcinoma:** In combination with interferon alfa, 10 mg/kg IV infusion every 2 weeks
- **Non-small cell lung cancer:** First-line treatment in combination with paclitaxel and carboplatin for unresectable, locally advanced, recurrent or metastatic non-squamous cell disease, 15 mg/kg IV infusion, once every 3 weeks

Intravitreal route

- **Age related macular degeneration, secondary to choroidal neovascularization:** 2.5 mg every 4 weeks for a total of 3 injections was used in a prospective time-series trial

PRECAUTIONS:

- Do not administer bevacizumab to patients with recent hemoptysis
- Permanently discontinue bevacizumab in the following conditions: gastrointestinal (GI) perforation, fistula formation in the GI tract, and/or intra-abdominal abscess; fistula formation involving an internal organ; wound dehiscence requiring medical intervention; serious bleeding; severe arterial thromboembolic event; nephrotic syndrome; hypertensive crisis or hypertensive encephalopathy; and reversible posterior leukoencephalopathy syndrome (safety of reinitiating therapy unknown)
- Temporarily suspend bevacizumab in the following conditions: moderate to severe proteinuria, hypertension (severe, not controlled), and surgery

Billing/Coding information

HCPCS Code:

J9035	Injection, bevacizumab, 10mg
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Associated CPT Coding:

67028	Intravitreal injection of a pharmacologic agent
96401 & 96417	Chemotherapy administration, subcutaneous or intramuscular; non-hormonal anti-neoplastic

Associated ICD-9 Coding:

153.0 – 153.9	Malignant neoplasm of colon
154.0 – 154.1	Malignant neoplasm of rectosigmoid junction, rectum
154.8	Malignant neoplasm of rectum, rectosigmoid junction, other
162.3 – 162.9	Malignant neoplasm of bronchus or lung
174.0 – 174.9	Malignant neoplasm of female breast
175.0 – 175.9	Malignant neoplasm of male breast
180	Malignant neoplasm of endocervix
180.1	Malignant neoplasm of exocervix
180.8	Malignant neoplasm of other specified sites of cervix
180.9	Malignant neoplasm of cervix uteri, unspecified
180	Malignant neoplasm of endocervix
180.1	Malignant neoplasm of exocervix
180.8	Malignant neoplasm of other specified sites of cervix
180.9	Malignant neoplasm of cervix uteri, unspecified
183	Malignant neoplasm of the ovary
183.2 – 183.5	Malignant neoplasm of the fallopian tube, broad ligament, parametrium or round ligament
183.8	Malignant neoplasm of other specified sites of uterine adnexa
183.9	Malignant neoplasm of unspecified sites of uterine adnexa
189	Malignant neoplasm of the kidney, except pelvis
189.1	Malignant neoplasm of the renal pelvis
191.0 – 191.9	Malignant neoplasm of the brain
197	Secondary malignant neoplasm of lung
197.5	Secondary malignant neoplasm of large intestine and rectum
V10.05 – V10.06	Personal history of malignant neoplasm, large intestine, rectum
V10.11	Personal history of malignant neoplasm, bronchus and lung
V10.3	Personal history of malignant neoplasm, breast
V10.52	Personal history of malignant neoplasm, kidney
V16.49	Family history of malignant neoplasm of genital organs (other)
V58.11 – V58.12	Encounter for antineoplastic chemotherapy and immunotherapy
362.02	Proliferative diabetic retinopathy
362.07	Diabetic macular edema
362.5	Macular degeneration (senile), unspecified
362.52	Exudative senile macular degeneration
362.53	Cystoid macular degeneration
362.83	Macular retinal edema

COST

AWP (March 2010)

- 100 mg / 4 ml: \$669.90
- 400 mg / 16 ml: \$2,679.60
- Preparation for intravitreal injection (non-licensed): <\$100 per treated eye per month
 - Lucentis (AWP, April 2010): 0.5mg/0.05ml injection: \$2,437.50 per treated eye per month

COMMITTEE APPROVAL:

GUIDELINE UPDATE INFORMATION:

3/25/2010	Initial policy creation

REFERENCES:

- DRUGDEX®, accessed 03/29/2010
- Product Information: AVASTIN(R) IV infusion, bevacizumab IV infusion. Genentech, Inc, South San Francisco, CA, 2009.
- Schouten et al. A systematic review on the effect of bevacizumab in exudative age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2009; 247: 1-11.
- Ziemssen et al. Off-Label Use of Bevacizumab for the Treatment of Age-Related Macular Degeneration- What is the Evidence? Drugs Aging. 2009; 26(4): 295-314.