Name of Policy: Bevacizumab, Avastin™

Policy #: 377       Latest Review Date: September 2013
Category: Pharmacology       Policy Grade: B

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:
1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**

Bevacizumab (Avastin™; Genentech, San Francisco, CA) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biological activity of human vascular endothelial growth factor (VEGF). It prevents VEGF from stimulating blood vessel growth to the tumor. Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors on the surface of the endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in vitro models of angiogenesis. Administration of bevacizumab results in reduction of microvascular growth and inhibition of metastatic disease progression.

**Other Treatments for AMD**

Other available therapeutic options for AMD not addressed in this policy include antioxidants, thermal laser photocoagulation and vascular endothelial growth factor (VEGF) antagonists or angiostatics. The role for each varies according to location and AMD subclassification. For those whose visual losses impair their ability to perform daily tasks, low-vision rehabilitative services offer resources to compensate for deficits.

Angiostatic agents block some stage in the pathway leading to new blood vessel formation (angiogenesis). In contrast to palliative treatments for CNV (e.g., thermal photocoagulation and photodynamic therapy), they are potentially disease modifying. Drugs currently under study target various parts of the angiogenic pathway: messenger RNA; vascular endothelial growth factors (VEGFs); endothelial cell proliferation, migration, and proteolysis. Pegaptanib (Macugen®, Eyetech and Pfizer) and ranibizumab (Lucentis™, Genentech) are presently the only angiostatic drugs FDA-approved for use in AMD. Pegaptanib and ranibizumab bind extracellular VEGF to inhibit the angiogenesis pathway and are administered by intravitreous injections every four to six weeks.

Please refer to the appropriate BCBSAL medical policy 047 regarding coverage of: Photodynamic Therapy, Ocular; Visudyne (verteporfin).

**Policy:**

**Bevacizumab (Avastin™) meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for treatment of the following conditions:

- Adenocarcinoma of the rectum
- Adenocarcinoma (with mixed subtypes) – Large cell carcinoma of lung.
- Adult intracranial ependymoma (excludes subependymoma and myxopapillary) – Consider single-agent treatment for disease progression after radiation therapy for spine or brain ependymoma recurrence.
- Age related macular degeneration, secondary to choroidal neovascularization.
- Anaplastic gliomas/glioblastoma – Treatment of recurrent disease or salvage therapy as a single agent or in combination with irinotecan, carmustine or temozolomide.
- Angioid streaks (effective 01/01/2012)
- Central serous chorioretinopathy (effective 01/01/2012)
• Cervical cancer, when used as a single agent in second-line therapy, in patients with metastatic disease or with recurrent disease.
• Choroidal neovascularization due to age-related macular degeneration (effective 01/01/2012)
• Choroidal rupture or trauma (effective 01/01/2012)
• Diabetic macular edema.
• Glioblastoma multiforme with recurrent, progressive disease, or salvage therapy following prior therapy.
• High-grade gliomas, such as anaplastic astrocytoma, with recurrent, progressive disease, used as a single agent or in combination with irinotecan or other agents.
• Idiopathic choroidal neovascularization (effective 01/01/2012)
• Macular retinal edema, due to retinal vein occlusion.
• Metastatic breast cancer, HER2-negative, as first-line therapy, recurrent or metastatic disease, in combination with paclitaxel.
• Metastatic breast cancer, in combination with capecitabine, in patients previously treated with an anthracycline and a taxane.
• Metastatic colorectal cancer, first- or second-line therapy, in combination with 5-fluorouracil-based chemotherapy.
• Metastatic colorectal cancer, first-line therapy or after 1st progression of advanced or metastatic disease, in combination with combination chemotherapy (including FOLFOX, FOLFIRI, FU/LV or CapeOX).
• Multifocal choroiditis (effective 01/01/2012)
• Neovascular glaucoma, as an adjunct therapy
• Non-small cell lung cancer (NSCLC), first-line treatment in combination with paclitaxel and carboplatin, for unresectable, locally advanced, recurrent or metastatic non-squamous cell disease or as follow-up maintenance therapy.
• Non-small cell lung cancer (NSCLC), second line therapy in combination with a platinum-based doublet with performance states 0-2 if erlotinib was given first.
• Ovarian cancer-Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer.
• Ovarian cancer, recurrent, following treatment with platinum-based regimens or ovarian stromal tumor in clinical relapse in patients with Stage II-IV granulosa cell tumors.
• Pathologic myopia (effective 01/01/2012)
• Presumed ocular histoplasmosis syndrome (POHS) (effective 03/22/2011)
• Rectal cancer, neoadjuvant therapy for synchronous or met achrromus metastasis, adjuvant therapy for patients with resected synchronous metastasis, or primary therapy for patients’ unresectable synchronous metastasis or who are medically inoperable.
• Rectal cancer, when used as initial therapy for unresectable advanced or metastatic disease or after first progress.
• Renal cell carcinoma (Kidney cancer), recurrent progressive, when used as first-line therapy or subsequent therapy or in combination with interferon alfa as first-line therapy.
• Retinopathy of prematurity, stage 3+ (effective 03/01/2012)
• Ruberosis (neovascularization of the iris) (effective 09/01/2013)
• Soft tissue sarcoma – angiosarcoma
• Soft tissue sarcoma—solitary fibrous tumor/hemangiopericytoma in combination with temozolomide.
• Uveitis (effective 01/01/2012)

**Bevacizumab (Avastin™) does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational when used in combination with **photodynamic therapy** as a treatment of CNV associated with AMD, pathologic myopia, presumed ocular histoplasmosis or for other ophthalmologic disorders, including CNV secondary to central serous chorioretinopathy.

**Bevacizumab (Avastin™) does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational except when used as treatment for the above listed indications.

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

**Key Points:**
This medical criterion for coverage is based on the FDA-labeled indications and/or compendia based accepted off-label indications and/or the National Comprehensive Cancer Network (NCCN) drug compendium.

**Adenocarcinoma of the pancreas**
In 2009, Crane et al assessed the one-year survival in a case series of patients with locally-advanced, unresectable pancreatic cancer. Overexpression of VEGF by pancreatic cancer cells may diminish the effectiveness of radiation therapy. The authors suggest that the action of bevacizumab in reducing VEGF expression may therefore improve radiation therapy outcomes. One-year overall survival in patients with locally-advanced disease receiving radiation and paclitaxel without VEGF inhibition was 43% in a previous study. To examine the effectiveness of the combination of bevacizumab, capecitabine, and radiation, 94 patients were recruited to detect a 15% improvement in the one-year survival rate over the 43% seen in the previous study. Crane et al. reported a 47% survival rate (95% CI, 36% to 57%, not statistically different compared to the previous study). The authors concluded that the addition of bevacizumab does not contribute to an improved one-year survival rate.

Javle et al reported the results of a single-arm study of 50 patients with metastatic pancreatic cancer treated with capecitabine, gemcitabine, and bevacizumab. The primary endpoint was PFS based on radiologic measure or tumor size, and serum CA 19-9 levels, the latter a biomarker associated with pancreatic cancer burden. Secondary endpoints included OS, response rate, and toxicity. In this study, discontinuation of therapy was higher than anticipated, with 46 of 50
(92%) subjects not continuing due to death, disease progression, or adverse events. Although some radiologic response and reduction in CA 19-9 levels did occur, PFS at one year was 19% (95% CI: 9.4-31.6%). Overall survival at one year reached 35.5% (95% CI: 21.7-49.5%). The authors commented that, based on this study and previous results for bevacizumab, they have chosen not to proceed with Phase III studies.

In 2010, Astsaturov et al reported on a comparative trial for patients with metastatic pancreatic cancer. Patients were randomly assigned to receive bevacizumab alone or in combination with docetaxel cytotoxic therapy. There was no blinding. The primary endpoint was PFS. However, at four months, only two and three patients were stable, respectively, and the trial was discontinued on the study-defined grounds of futility of less than 25% PFS at that time.

Ko et al reported partial results of an observational study of gemcitabine refractory metastatic pancreatic cancer patients treated with bevacizumab and erlotinib. Recruitment stalled after publication of the relative ineffectiveness of bevacizumab in the Phase III trials previously described. Of the 36 patients followed in the study, eight reached the primary endpoint of six-month survival (22%). This survival rate is inferior to published rates of cytotoxic regimens.

Martin and colleagues investigated the safety and efficacy of bevacizumab combined with gemcitabine followed by infusional 5-fluorouracil (5-FU) in patients with advanced pancreatic cancer in a Phase 2 trial. The primary endpoint was the proportion of patients with PFS at six months from initiation of therapy. If PFS at six months was equal to or greater than 41%, the regimen would be considered promising. Of the 42 patients enrolled in the study, 39 were evaluable for the primary endpoint. PFS at six months was 49% (95% CI: 34% to 64%). Median PFS was 5.9 months (95% CI: 3.5 to 8.1), and median OS was 7.4 months (95% CI: 4.7 to 11.2). Partial response and stable disease occurred in 30% and 45% of patients, respectively. Grade 3 to 4 toxicities included fatigue (14%), hypertension (5%), and venous thrombosis (5%). The authors concluded that the study met its primary endpoint and that further investigation of anti-VEGF therapy in combination with fluoropyrimidine-based therapy is warranted in advanced pancreatic cancer.

Ko and colleagues conducted a Phase II randomized study of cetuximab and bevacizumab alone or in combination with gemcitabine as first-line therapy for advanced pancreatic adenocarcinoma. Patients with locally advanced or metastatic pancreatic adenocarcinoma, previously untreated, were randomized to bevacizumab plus cetuximab, either with (Arm A; n=30) or without (Arm B; n=31) gemcitabine. Tumor assessments were performed every eight weeks. The primary study endpoint was progression-free survival (PFS). The median treatment duration was nine weeks in Arm A and eight weeks in Arm B (range: 2.0-40.4). Patients in Arm A had median PFS and overall survival (OS) values of 3.55 months and 5.41 months, respectively, compared to 1.91 months and 4.17 months in Arm B. The study closed early due to lack of sufficient efficacy in both treatment arms. The authors concluded that the combination of cetuximab and bevacizumab did not result in promising activity with or without gemcitabine, and suggested that a strategy of dual epidermal growth factor receptor (EGFR)/VEGF inhibition in pancreatic cancer does not warrant further development.
Fogelman and colleagues conducted a Phase II trial of bevacizumab plus gemcitabine and oxaliplatin as first-line therapy for metastatic or locally advanced pancreatic cancer. Eligible patients had Stage III (n=14) or IV (n=36) pancreatic cancer and had received no prior gemcitabine. Treatment cycles were repeated every two weeks, and CT imaging was performed every six weeks. Fifty patients were enrolled: 14 had Stage III disease, the remainder, Stage IV. Median age was 59 years. The overall response rate was 36%; 34% demonstrated stable disease. The median PFS was 4.9 months; median survival was 11.9 months; one year survival was 42%. Patients with locally advanced disease lived 12.8 months; patients with metastatic disease lived 10.2 months. The authors concluded that the regimen did not meet the objective of a 14-month median survival and that the toxicity was significant.

Summary
Treatment of advanced adenocarcinoma of the pancreas with bevacizumab is not an FDA-approved indication. The available evidence does not clearly demonstrate that addition of bevacizumab to chemotherapy regimens for advanced adenocarcinoma of the pancreas improves the net health outcome of those patients. Therefore, bevacizumab for patients with advanced adenocarcinoma of the pancreas is considered investigational.

Age Related Macular Degeneration (AMD)
One-year results of the National Eye Institute-sponsored multicenter (44 sites) Comparison of AMD Treatment Trials (CATT) were published in 2011. CATT was a randomized single-blind head-to-head comparison of the safety and effectiveness of ranibizumab and bevacizumab in treating wet AMD. A total of 1,208 patients with previously untreated active CNV due to AMD (neovascularization, fluid, or hemorrhage under the fovea) and visual acuity between 20/25 and 20/320 on electronic visual acuity testing were enrolled in the study.

Patients were randomly assigned to receive intravitreal injections of ranibizumab (0.5 mg) or bevacizumab (1.25 mg) on either a monthly schedule or as needed with monthly evaluation. Every 28 days, patients in the groups that received study drugs as needed underwent time-domain optical coherence tomography (OCT) and were evaluated for treatment. Signs of active neovascularization were defined as fluid on OCT, new or persistent hemorrhage decreased visual acuity as compared with the previous examination, or dye leakage or increased lesion size on fluorescein angiography. The mean number of injections on the as needed schedule was 6.9 for ranibizumab and 7.7 for bevacizumab over the first year of the study (significantly different). Treatment decisions by study ophthalmologists were found to be consistent with the retreatment protocol for 71.5% of examinations in the group assigned to ranibizumab as needed, and 74.3% in the group assigned to bevacizumab as needed. Among the 1,161 patients who were alive 1 year after enrollment, visual-acuity scores were available for 1,105 patients (95.2%).

The primary outcome measure was a change in visual acuity at one year, with a non-inferiority limit of five letters on the eye chart. Secondary outcome measures were the proportion of patients with a decrease or gain of visual acuity, anatomical changes in the retina, number of treatments, adverse events, and cost. When administered according to the same schedule, bevacizumab and ranibizumab had equivalent (not inferior) effects on visual acuity. With bevacizumab and ranibizumab administered monthly, patients gained an average of 8.0 and 8.5 letters, respectively. When administered as needed, the number of letters gained with bevacizumab was similar to that of ranibizumab, with 5.9 and 6.8 letters gained, respectively.
Ranibizumab as needed was also found to be equivalent (not inferior) to monthly ranibizumab. The comparisons of bevacizumab as needed versus monthly bevacizumab (5.9 vs. 8.0 letters, respectively) and bevacizumab as needed versus monthly ranibizumab (5.9 vs. 8.5 letters gained, respectively) were inconclusive. At one-year, there were no significant differences in the proportion of patients who lost or gained >15 letters.

There were significant differences in the anatomy of the retina with the different treatments. At one year, monthly ranibizumab decreased central retinal thickness to a greater extent (196 microns) than the other three groups (152 to 168 microns). The proportion of patients who had complete resolution of fluid ranged from 19.2% among patients who received bevacizumab as needed to 43.7% among those who received ranibizumab monthly. The absolute between-drug difference in the amount of residual fluid was small; at one year, total thickness at the fovea was 266 microns for the ranibizumab monthly group and close to 300 microns for the other three groups. In comparison, the retinal thickness of healthy eyes measured by OCT at the fovea averages 212 microns. Dye leakage was absent on angiography in 58.8% of patients in the ranibizumab-monthly group, 57.7% in the bevacizumab-monthly group, 46.7% in the ranibizumab-as-needed group, and 41% in the bevacizumab-as-needed group.

Rates of death, myocardial infarction (MI), and stroke were similar for patients receiving either bevacizumab or ranibizumab. However, the proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19%, respectively; risk ratio [RR]: 1.29; 95% confidence interval [CI]: 1.01 to 1.66). It was noted that these events were broadly distributed in disease categories not considered to be areas of concern for use of bevacizumab and were not dose-dependent.

An accompanying editorial notes that although the OCT retinal thickness measurements favor ranibizumab, this difference is not reflected in any of the visual-acuity or angiographic outcomes; whether this difference is associated with changes in vision should become clear during the second year of follow-up. Results from the second year of the study will provide more information regarding the relative risk of adverse events, as well as the possible association between anatomical changes in the retina and visual acuity.

In 2010, Tufail et al reported a randomized multicenter study (ABC Trial) of bevacizumab for neovascular AMD in 131 patients (eyes), 65 of whom received bevacizumab. Outcomes at 54 weeks were compared to patients who had received standard care from the United Kingdom’s National Health Service (NHS), which was considered on a case-by-case basis. Patients with classic or predominantly classic choroidal neovascularization were randomized to PDT or bevacizumab with sham PDT. Patients with minimally classic or occult CNV were randomized to bevacizumab or (depending on NHS funding) pegaptanib or placebo. The standard care group included 38 patients treated with pegaptanib, 16 treated with verteporfin, and 12 treated with a sham intravitreal injection. Bevacizumab (1.25 mg in 0.05 mL) was prepared in single use sterile plastic syringes in sealed plastic pouches (shelf life of six weeks) and administered once every six weeks for the first 18 weeks; further injections were provided based on standardized criteria. Patients received a mean of 7.1 (range 3-9) injections of bevacizumab or 7.3 (range 3-9) sham injections. Active verteporfin PDT was administered at a mean of 3.2 times (range 2-5). Independent assessment of outcomes found that 21 patients (32%) in the bevacizumab group gained 15 or more letters compared with two (3%) in the standard care group. More patients receiving bevacizumab lost fewer than 15 letters (91% vs. 67%,
respectively). The mean change in visual acuity at 54 weeks increased by +7.0 letters in the bevacizumab group and decreased by –9.4 letters in the standard care group.

In 2010, Curtis et al reported a retrospective cohort study of 146,942 Medicare beneficiaries 65 years or older with a claim for AMD. On the basis of claims, beneficiaries were assigned to one of four treatment groups (PDT, pegaptanib, bevacizumab, or ranibizumab). Patients were censored if they received a therapy different from the initial therapy. Among patients in the PDT group, 32.6% switched to a different therapy within the year compared with 55.3% in the pegaptanib group, 28.1% in the bevacizumab group, and 24.0% in the ranibizumab group. After adjustment for baseline characteristics and comorbid conditions, there were no significant differences in the hazard of mortality or myocardial infarction (MI) between bevacizumab use and the other therapies. There was no statistically significant relationship between treatment group and bleeding events or stroke. A sub-analysis intended to mitigate potential selection bias found no significant differences in study outcomes between the ranibizumab and bevacizumab groups. In contrast, a recent preliminary report of 77,886 Medicare beneficiaries found an 11% higher risk in overall mortality and a 57% higher risk of hemorrhagic cerebrovascular accident following treatment with bevacizumab in comparison with ranibizumab. The authors note that the study is limited by incomplete information on some important confounding factors, e.g., smoking, lipid and blood pressure levels, which would further clarify the relative safety of these treatments in wet AMD.

The potential for an increased risk of adverse events with bevacizumab remains controversial. A randomized study from 2013 found that a single intravitreal injection of bevacizumab led to significantly reduced levels of VEGF in plasma (from 89.7 pg/mL to 22.8 pg/mL) for up to one month after intravitreal injection. However, this large reduction appears to be driven largely by one outlier with plasma VEGF levels of close to 400 pg/mL. VEGF levels in plasma were not affected by ranibizumab or pegaptanib. In 2012, Schmucker et al reported a meta-analysis of the safety of bevacizumab compared with ranibizumab. Direct comparison (three trials, 1,333 patients) found a significantly higher rate of ocular and systemic adverse effects with bevacizumab compared to ranibizumab. Arterial thromboembolic events were similar between the two conditions. The investigators were unable to evaluate the safety profile of bevacizumab in indirect comparisons (five trials, 4,054 patients) due to the poor quality of adverse event monitoring and reporting.

Central Serous Chorioretinopathy
Literature searches through have identified two small controlled studies from Asia that assessed the efficacy of bevacizumab for central serous chorioretinopathy (CSC). In a 2010 report, 32 eyes with acute CSC (<3 months’ duration) were randomized to a single 1.25 mg intravitreal injection of bevacizumab or to observation. Twelve eyes in each group completed six months of follow-up and were included in the analysis, eight eyes were excluded due to irregular follow-up or lack of post-treatment data. During the six-months of follow-up, there were no significant differences in visual acuity, central retinal thickness, or remission duration between the bevacizumab and control group. All patients had complete resolution of their macular subretinal fluid during the six months of follow-up.
In another prospective study reported in 2010, 15 eyes of 15 patients with persistent CSC treated with a single 2.5 mg intravitreal injection of bevacizumab were compared with 15 eyes with the same characteristics from patients who declined treatment. Inclusion criteria were subfoveal or juxtafoveal persistent CSC >3 months, BCVA of 20/200 or better, clinical findings suggesting idiopathic CSC, and presence of subretinal fluid involving the fovea on OCT. Visual and anatomic responses were measured at baseline and at one, three, and six months after treatment. Baseline characteristics were similar for the two groups. At six-month follow-up, the mean log MAR BCVA was significantly better in the treatment group (0.03) compared with the control group (0.14), and all 15 (100%) treated eyes had stable or improved vision, compared with 10 (66%) eyes in the control group. The presence of subretinal fluid was seen in three (20%) patients treated with bevacizumab and 46.6% of control patients. The baseline mean central foveal thickness was 485 microns for the treatment group and 480 microns for the control group. At six months, the mean central foveal thickness for the bevacizumab-treated group remained significantly lower compared to the control group, 174 microns and 297 microns, respectively. Eleven (73.3%) of 15 eyes in the treatment group showed a complete absence of fluorescein leakage compared with five (33.3%) of 15 eyes in the control group. Ocular or systemic complications were not encountered in the study.

**Diabetic Macular Edema**

A number of smaller RCTs from Asia have been published that assessed the efficacy of bevacizumab for diabetic macular edema.

In 2008, Ahmadieh et al. reported the efficacy of three injections of bevacizumab (1.25 mg every six weeks) either alone or in combination with triamcinolone in 115 eyes (101 patients) with macular edema that was unresponsive to macular laser photoagulation. Patients were randomized to one of three study arms (three injections of bevacizumab, combined triamcinolone and bevacizumab, or sham injection). Improvement in BCVA was observed earlier in the combined group (six weeks) than the bevacizumab-only group (12 weeks). At 24 weeks, BCVA was similar in the two treatment groups, (-0.18 and -0.21 logMAR [logarithm of the minimum angle of resolution]), vs. -0.3 logMAR for the sham group. The change in central macular thickness was -95.7 microns in the bevacizumab arm, -92.1 microns in the combined group, and +34.9 microns in the control group. Elevation of intraocular pressure occurred in three eyes (8.1%) of the combined treatment group.

In 2009 and 2012, Soheilian et al reported an RCT of intravitreal bevacizumab (1.25 mg alone or combined with triamcinolone) versus macular photocoagulation in 150 treatment-naïve eyes (129 patients). Sham laser and sham injections were performed, and evaluators were blinded to the treatment condition. Evaluations were performed through nine months in the 2009 report and through 24 months in the follow-up study. At nine months, BCVA changes were -0.28 for bevacizumab alone, -0.04 for bevacizumab and triamcinolone, and +0.01 logMAR for photocoagulation. BCVA improvement greater than 2 Snellen lines was detected in 37%, 25%, and 14.8% of patients in the bevacizumab alone, bevacizumab and triamcinolone, and photocoagulation groups, respectively. Central macular thickness changes were not different between the groups. Throughout the follow-up, eyes with significant macular edema were retreated with the assigned intervention at 12-week intervals. The mean number of treatments for each arm of the study was 3.1 for bevacizumab, 2.6 for bevacizumab/triamcinolone, and 1.0 for
photocoagulation. At 24-month follow-up, there was no significant difference in visual or anatomic outcomes between the three groups, suggesting that the superiority of bevacizumab may diminish over time when administered at this interval.

Michaelides and colleagues reported 12-month results from the BOLT study, an RCT that compared multiple intravitreal injections of bevacizumab (1.25 mg) with photocoagulation in 2010. A total of 80 eyes of 80 patients who had diabetic macular edema and at least one prior macular laser therapy were randomized to bevacizumab every six weeks as needed (minimum of three and maximum of nine) or macular laser therapy (minimum of one and maximum of four). The baseline BCVA was 55.7 in the bevacizumab group and 54.6 in the laser arm. With a median of nine injections over the 12-month study, the bevacizumab group had gained a median of eight letters while the laser group lost a median of 0.5 letters (61.3 vs. 50.1). The odds of gaining >10 letters was 5.1 times greater with bevacizumab. There was a trend toward a greater decrease in central macular thickness (from 507 to 378 microns in the bevacizumab group and from 481 to 413 microns in the laser group, p=0.06).

The results from these lower quality randomized controlled trials suggest that bevacizumab is effective for the treatment of diabetic macular edema, similar to results found for ranibizumab.

**Multifocal Choroiditis**

In 2010, Parodi et al reported a pilot randomized clinical trial that compared intravitreal bevacizumab and PDT in 27 patients with CNV associated with multifocal choroiditis. Retreatments (2.8 for bevacizumab and 0.7 for PDT) were performed if any leakage from CNV was noted on fluorescein angiography. At the 12-month follow-up, five of 14 eyes (36%) in the bevacizumab group and 0 of 13 eyes (0%) in the PDT group had a gain of >3 lines of vision. Twelve eyes (86%) in the bevacizumab group and six eyes (46%) in the PDT group gained more than one line. There was a significant difference in BCVA favoring the bevacizumab group at the end of follow-up. The two groups showed a similar improvement in central macular thickness.

**Pathologic Myopia**

Parodi et al compared intravitreal bevacizumab with laser photocoagulation and PDT in a randomized trial of 54 patients with juxtafoveal CNV secondary to pathologic myopia in 2010. Additional intravitreal bevacizumab injections were administered when OCT revealed persistent or recurrent fluid, or when the fluorescein angiography examination revealed CNV activity or progression. Eyes in the laser therapy or PDT groups that developed recurrent CNV with subfoveal location during follow-up could be retreated using PDT. At 24 months, the bevacizumab group had gained 1.8 lines from baseline with a mean of 3.8 intravitreal bevacizumab injections; four of 19 eyes (21%) required intravitreal bevacizumab injections during the second year. The laser photocoagulation group lost 1.1 lines with a mean of 1.17 PDT treatments and the PDT group lost two lines with 2.55 re-treatments.

Another small randomized trial from 2010 compared ranibizumab and bevacizumab in 32 eyes (32 patients) with pathologic myopia. Follow-up was performed at one, three, and six months. BCVA at baseline was 26.44 letters in the ranibizumab group and 29.50 letters in the bevacizumab group. At six months, ranibizumab-treated eyes had gained 17.31 letters and
bevacizumab-treated eyes had gained 15.87 letters. Twelve eyes in the ranibizumab group (75%) and 13 in the bevacizumab group (81.2%) gained >10 letters. Foveal center thickness improved from 251 to 206 microns with ranibizumab and from 237 to 185 microns with bevacizumab. No significant differences in BCVA improvement or foveal center thickness reduction were found between the groups. Complete resolution of fluorescein leakage was observed in all 16 bevacizumab-treated eyes and in 15 of 16 (93.7%) of ranibizumab-treated eyes.

**Presumed Ocular Histoplasmosis Syndrome (POHS)**

Schadie et al (2008) conducted a retrospective chart review study to define the role of intravitreal bevacizumab in individuals with choroidal neovascularization (CNV) resulting from Ocular Histoplasmosis Syndrome (OHS). The course of 28 eyes of 28 patients who underwent intravitreal injection of bevacizumab for treatment of CNV secondary to OHS were reviewed. Outcomes were measured by pretreatment and posttreatment visual acuity (VA). The average pretreatment logarithm of the minimum angle of resolution (logMAR) VA was 0.65 (Snellen equivalent of 20/88). Mean follow-up was 22.43 weeks with an average of 1.8 intravitreal injections. Average final logMAR VA was 0.43 (Snellen equivalent of 20/54). Twenty eyes (71%) experienced an increase in central VA, whereas four eyes (14%) were unchanged and four eyes (14%) experienced a decrease in vision. The authors concluded that intravitreal bevacizumab may improve or stabilize VA in a significant majority of patients with neovascular complications of OHS (24 eyes [85.7%] in our study population).

Ehrlich et al (2009) conducted a chart review of retrospective consecutive case series in which intravitreal bevacizumab (1.25 mg) was injected into 24 eyes with choroidal neovascularization resulting from presumed ocular histoplasmosis syndrome. Visual acuity was measured in all patients. Optical coherence tomography and/or fluorescein angiography was performed before and after treatment. The minimum follow-up time was three months. Retreatment criteria included failure to improve visual acuity and/or persistent leakage as determined by optical coherence tomography or fluorescein angiography. Patients' mean age was 43.08 years (standard deviation, 13.58 years) and mean follow-up was 31.8 weeks (standard deviation, 20.79 weeks). The average number of bevacizumab injections was 6.8 injections/year. After three months, visual acuity improved from mean logMAR 0.76 +/- 0.48 (Snellen equivalent of 20/114) to mean logMAR 0.45 +/- 0.47 (Snellen equivalent of 20/55) (P < 0.001, paired t test; n = 24). After 12 months, visual acuity improved from mean logMAR 0.86 +/- 0.35 (Snellen equivalent of 20/150) to mean logMAR 0.34 +/- 0.33 (Snellen equivalent of 20/45) (P = 0.006, paired t test; n = 9). Fourteen (58.3%) eyes had final visual acuity of 20/40 or better compared with five (20.8%) eyes at baseline (P = 0.003, McNemar test). Ten patients (41.6%) had visual acuity of 20/200 or worse at baseline compared with five (20.8%) eyes at the final visit (P = 0.059, McNemar test). The authors concluded that intravitreal injection of bevacizumab seems to be an effective treatment for choroidal neovascularization resulting from presumed ocular histoplasmosis syndrome.

**Retinal Vein Occlusion**

Three RCTs from outside of the U.S. have been published on the use of bevacizumab for macular edema following retinal vein occlusion. Two of the trials were sham-controlled (one central retinal vein occlusion (CRVO) and one branch retinal vein occlusion (BRVO)); the third compared bevacizumab with triamcinolone in patients with BRVO.
In 2012, Epstein et al reported a randomized, sham-controlled, double-masked trial in 60 patients with CRVO. Intraocular bevacizumab or sham injections were administered every six weeks for six months. For the next six months, all patients received bevacizumab every six weeks. Mean BCVA at baseline was 44.1 letters (Snellen equivalent of 20/125). At six-month follow-up, mean BCVA improved by 14.1 letters in the bevacizumab group compared with a decrease of 2.0 letters in the control group. Sixty percent of patients in the bevacizumab group had gained 15 letters or more compared to 20% in the control group, and 6.7% of patients in the bevacizumab group lost more than 15 letters compared to 23.3% in the control group. The mean decrease in central retinal thickness was greater in the bevacizumab group (426 microns) compared to controls (102 microns), and 86.7% of patients in the bevacizumab group had no residual edema (defined as central retinal thickness <300 microns) compared to 20% in the control group. At 12-month follow-up, central retinal thickness decreased to a similar extent in the continued bevacizumab vs. delayed bevacizumab groups (435 microns vs. 404 microns). The percentage of patients who had gained 15 letters or more remained at 60% in the bevacizumab/bevacizumab group, while 33% of patients who received sham/bevacizumab gained 15 letters or more, suggesting that patients receiving delayed treatment may have limited visual improvement.

A 2011 publication reported a double-masked sham-controlled RCT in 81 eyes (81 patients) with branch retinal vein occlusion (BRVO). Bevacizumab or sham injection was administered after baseline and week six. The mean duration of symptoms was 7.5 weeks in the bevacizumab group and 4.9 weeks in the sham group. In the sham group, BCVA was 0.8 logMAR at baseline, 0.75 logMAR at week six, and 0.66 logMAR at week 12. In the bevacizumab group, BCVA improved from 0.74 logMAR at baseline to 0.49 logMAR at week six and 0.42 logMAR at week 12. The difference between groups was statistically significant at week six and approached significance (p=0.064) at week 12. Central macular thickness at baseline was 471 microns for the control group and 575 microns for the bevacizumab group. At week six, the central macular thickness was 462 microns for sham and 325 microns for bevacizumab. Central macular thickness at week 12 was 393 microns for sham versus 309 microns for bevacizumab. The difference in macular thickness was statistically different at both six and 12 weeks’ follow-up.

Another study with 52 patients compared triamcinolone (4 mg) or bevacizumab (1.25 mg) monotherapy versus combined therapy (2-mg triamcinolone and 1.25-mg bevacizumab) for macular edema due to BRVO. Fifty-two eyes with BRVO, visual acuity of 20/40 or worse, and central macular thickness of 250 microns or greater were enrolled in the study. Nearly 90% of eyes received intravitreal injections as the primary treatment; the remainder had received grid laser photoagulation at least four months before enrollment. Re-injections of triamcinolone or bevacizumab were done when macular edema recurred that was at least one month apart for bevacizumab monotherapy, two months for bevacizumab plus triamcinolone, and three months for triamcinolone monotherapy, and the mean number of injections within six months ranged from 1.4 to 1.6. Otherwise, grid laser photocoagulation was performed. Macular grid laser photocoagulation was applied within three months of injections in 47% of the triamcinolone monotherapy group, 50% of bevacizumab monotherapy, and 43% of the combined treatment group. All three groups showed significant reductions of central macular thickness and improvement in visual acuity one month after injection, but by six months, only the bevacizumab monotherapy group demonstrated significant improvement in visual acuity (from 0.9 to 0.4.
logMAR). At six months, there was a significant reduction in central macular thickness for all three groups (follow-up was completed in 86-88% of patients in the monotherapy groups but only 48% of the combined therapy group). The average intraocular pressure change from baseline (+1.4) was significantly higher in the triamcinolone monotherapy group. Cataract progression was noted in 36% of phakic eyes in the triamcinolone monotherapy group, 8% of the bevacizumab monotherapy group, and 10% of eyes in the combined treatment group.

Yasuda et al reported rebound of macular edema (>110% of baseline thickness) in seven of 65 eyes (10.8%) after treatment of BRVO with bevacizumab. This retrospective study examined the records of all patients who had received an intravitreal injection of bevacizumab, had received no other treatment for BRVO, and had at least six months of follow-up. Patients were evaluated monthly for BCVA and foveal thickness by OCT. The mean interval between the onset of symptoms and intravitreal bevacizumab was 10 weeks (range, 2 to 52 weeks). Bevacizumab was found to be not effective in three eyes (4.6%), effective without recurrence in 21 eyes (32.3%), effective with a recurrence ≤110% of baseline thickness in 34 eyes (52.3%), and effective with a recurrence >110% of baseline thickness in seven eyes (10.8%). Retreatment was performed as needed. Multivariate logistic regression and subgroup analyses showed that a thinner pretreatment fovea and a shorter interval between symptom onset to the initiation of the intravitreal bevacizumab were significantly associated with a rebound of macular edema. The interval from symptom onset to the initiation of treatment was less than eight weeks in all seven eyes with a rebound macular edema.

Another retrospective study from 2011 evaluated factors predictive for improvement of visual acuity and central retinal thickness following treatment with bevacizumab. A total of 205 eyes (204 patients) with macular edema secondary to BRVO from six sites were included. Measurement of BCVA and retinal thickness was measured every 12 weeks with results at 24 weeks used for analysis of predictive factors. The mean follow-up was 36.8 weeks (range, 18 to 54 weeks). During the follow-up period, retreatments were performed in 85% of eyes, with a median of three injections (range, 1 to 10). Although both non-ischemic and ischemic eyes showed a median two-line improvement of BCVA, the final median BCVA was significantly worse in eyes with ischemic macular edema compared to non-ischemic macular edema (0.6 logMAR vs. 0.3 logMAR). Eyes with a duration of macular edema less than three months had a median 2.5-line increase of BCVA, while eyes with a duration of macular edema between three and 12 months had a median two-line increase in BCVA, and eyes with a duration >12 months had a 0.5-line increase in median BCVA. Other factors identified were absence of previous treatments of macular edema, age younger than 60 years, and low baseline BCVA.

Additional studies are needed to determine the appropriate candidates and timing of bevacizumab and to evaluate durability of treatment over longer periods of follow-up. Comparison with grid photocoagulation for BRVO is also needed.

**Retinopathy of Prematurity**
Retinopathy of prematurity is a neovascular retinal disorder that primarily affects premature infants of low birth weight. It is one of the most common causes of childhood blindness in the United States. Typically, retinal vascularization begins at the optic nerve when the eye begins to develop (16 weeks’ gestation) and reaches the edge of the retina at 40 weeks’ gestation. If an
infant is born prematurely, normal vessel growth may stop, followed by neovascularization at the interface between the vascular and avascular retinal areas. Stages of retinopathy of prematurity are defined by vessel appearance and the level of retinal detachment, ranging from mild (Stage 1) to severe (Stage 5). Stage I or Stage II retinopathy of prematurity may resolve on its own. The optimal time for treatment is Stage III, when a ridge with neovascularization extends into the vitreous gel. The neovascularization may progress and form fibrous scar tissue that causes partial (Stage 4) or total retinal detachment (Stage 5), accompanied by loss of vision. Both cryotherapy and laser therapy have been used to slow or reverse the abnormal growth of blood vessels in the peripheral areas of the retina. While successful in about 50% of cases, these treatments can cause myopia and permanent loss of the peripheral visual field. Vitrectomy may be needed when cryotherapy or laser therapy fail to induce regression.

The BEAT-ROP cooperative study group reported a multicenter randomized trial of a single injection of bevacizumab versus conventional laser therapy in 2011. One hundred and fifty infants (300 eyes with Stage 3+ diseases in Zone I or Zone II) were randomized to receive intravitreal bevacizumab or conventional laser therapy. (Zone I is a circle whose radius extends from the optic disk and is twice the distance between the center of the disk and the center of the macula, while Zone II encircles Zone I with a radius that is three times the distance between the center of the disk and the center of the macula.) The study was not masked, due to the marks made by laser therapy. However, photographs taken at 54 weeks were assessed post hoc by six independent experts at the reading center who were masked to treatment by cropping the photographs. The primary outcome was recurrence of retinopathy of prematurity in one or both eyes requiring retreatment before 54 weeks’ postmenstrual age. Retinopathy of prematurity was found to recur in four infants (4%) in the bevacizumab group compared to 19 infants (22%) in the laser-therapy group. The mean time for recurrence was 16.0 weeks for six eyes after bevacizumab compared with 6.2 weeks for 32 eyes after laser therapy. When divided by zone, a significant treatment effect was found for Zone I disease but not for Zone II. For Zone I disease, recurrences were observed in 6% of infants treated with bevacizumab compared to 42% of infants treated with laser therapy. For Zone II disease, the rate of recurrence was 5% in infants treated with bevacizumab and 12% in infants treated with laser therapy. The study appears to have been underpowered to detect the smaller difference between the groups in zone II, since there is less recurrence following laser therapy in Zone II (12%) than zone I (42%), and the study did not achieve the target enrollment of 50 infants per group with Zone II disease. Notably, intravitreal bevacizumab was found to allow vessel growth into the peripheral retina while conventional laser therapy resulted in permanent destruction of vessels in the peripheral retina. Thus, bevacizumab was more effective than laser for Zone I disease and at least as effective as laser for Zone II disease without the ocular adverse effects of laser therapy, which can include significant loss of visual field.

**Key Words:**
Metastatic colorectal cancer, non-small cell lung cancer (NSCLC), metastatic breast cancer, glioblastoma multiforme, glioma, anaplastic astrocytoma, ovarian cancer, kidney cancer, metastatic cervical cancer, macular degeneration, diabetic macular edema, macular retinal edema, neovascular glaucoma, vascular endothelial growth factor (VEGF), angiogenesis, presumed ocular histoplasmosis syndrome (POHS), Angioid streaks, Central serous
chorioretinopathy, Choroidal neovascularization due to age-related macular degeneration, Choroidal rupture or trauma, Idiopathic choroidal neovascularization, Multifocal choroiditis, Pathologic myopia, Uveitis, Retinopathy of prematurity

Approved by Governing Bodies:
On February 26, 2004, the FDA approved bevacizumab as a first-line treatment for patients with metastatic colorectal cancer.
On June 20, 2006, the FDA granted approval for a labeling extension for bevacizumab, administered in combination with intravenous 5-fluorouracil-based chemotherapy, for the second-line treatment of metastatic carcinoma of the colon or rectum.
On October 11, 2006, the FDA granted approval for a labeling extension for bevacizumab, administered in combination with carboplatin and paclitaxel, for the initial systemic treatment of patients with unresectable, locally advanced, recurrent, or metastatic, non-squamous, non-small cell lung cancer.
On February 22, 2008, the FDA granted accelerated approval for bevacizumab, to be used in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer.
On May 5, 2009, the FDA granted accelerated approval to bevacizumab as a single agent for patients with glioblastoma, with progressive disease following prior therapy.
On January 23, 2013, the FDA granted approval for use in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin based chemotherapy, for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line Avastin-containing regimen.

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member’s benefit plan.

Lowe’s Precertification Requirement—Effective for dates of service on or after February 1, 2010, please contact Care Continuum at 866-240-4734 or fax the prescription with accompanying clinical information to 877-540-6223 for precertification. (This Blue Cross and Blue Shield of Alabama’s medical policy does not apply for Lowe’s members for dates of service on or after February 1, 2010. This policy was in effect for Lowe’s prior to February 1, 2010). Effective March 16, 2012, Care Continuum (an independent utilization management company for Lowe’s members) will follow Blue Cross and Blue Shield of Alabama Medical Policy #377, Avastin® (bevacizumab), for ophthalmic indications only. They will utilize the Care Continuum medical policy for all other indications for Avastin.

Pre-certification requirements: Not applicable
Current Coding:
CPT Codes:

**J9035** Injection, bevacizumab, 10 mg

References:


Policy History:
Medical Policy Group, August 2009 (3)
Medical Policy Administration Committee, August 2009
Available for comment August 21-October 5, 2009
Medical Policy Group August 2010
Medical Policy Administration Committee, November 2010
Available for comment November 4 – December 20, 2010
Medical Policy Group November 2010: Updates and References only
Medical Policy Group, March 2011 (1) Updates to Policy (new coverage for POHS), Key Points, Key Words and References
Medical Policy Administration Committee, March 2011
Available for comment April 4 – May 18, 2011
Medical Policy Group, May 2011: Updates to Policy conditions for coverage
Medical Policy Administration Committee May 2011
Available for comment May 11 – June 27, 2011
Medical Policy Group, January 2012 (1) Update to Policy, Key Points, Key Words and References r/t Angioid streaks, Central serous chorioretinopathy, CNV due to AMD, Choroidal rupture or trauma, Idiopathic CNV, Multifocal choroiditis, Pathologic myopia, Uveitis; Update to References r/t adenocarcinoma of the pancreas
Medical Policy Administration Committee, January 2012
Available for comment February 9 – March 26, 2012
Medical Policy Group, March 2012: Updated Lowe’s Benefit Application for Avastin
Medical Policy Group, March 2012 (1): Update to Policy, Key Points and References related to
coverage for retinopathy of prematurity, stage 3+ per MPP update
Medical Policy Administration Committee, April 2012
Available for comment April 25 through June 11, 2012
Medical Policy Panel, September 2012
Medical Policy Group, January 2013 (3): Update to Approved by Governing Bodies for FDA
Supplement Approval 01/23/13
Medical Policy Group, February 2013 (1) Update to Key Points and References related to
pancreatic cancer; no change to policy statement
Medical Policy Panel, March 2013
Medical Policy Group, September 2013 (1) Addition of coverage for rubeosis and removal of
“stage 3+” from ROP; Update to Key Points and References related to ophthalmic disorder
treatment
Medical Policy Administration Committee, September 2013
Available for comment September 12 through October 28, 2013

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.