



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

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Coverage Position Number..... 5025

Subject **Bevacizumab (Avastin®)**

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Hyperlink to Related Coverage Policies

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Position

CIGNA covers bevacizumab (Avastin®) as medically necessary for ANY of the following indications:

- metastatic carcinoma of the colon or rectum
- metastatic or recurrent non-small cell lung cancer (NSCLC)
- metastatic breast cancer that is human epidermal growth factor receptor 2 (HER2) negative
- glioma, astrocytoma, or glioblastoma
- angiosarcoma or solitary fibrous tumor/hemangiopericytoma
- metastatic renal cell carcinoma (RCC)
- metastatic epithelial ovarian cancer
- intravitreal treatment of neovascular (wet) age-related macular degeneration
- intravitreal treatment of branched retinal vein occlusion
- retinopathy of prematurity

CIGNA does not cover bevacizumab (Avastin) for combination therapy with photodynamic therapy (PDT) with verteporfin (Visudyne®) because it is considered experimental, investigational or unproven.

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to bevacizumab (Avastin®).

FDA Approved Indications

NOTE: Effective 12/16/2010 The Food and Drug Administration (FDA) announced that the agency is recommending removing the breast cancer indication from the label for Avastin (bevacizumab) because the drug has not been shown to be safe and effective for that use. Patients currently receiving Avastin for breast cancer should speak with their oncologists (cancer physicians) about whether to continue their treatment or explore other treatment options. Avastin will continue to be an FDA approved treatment option for patients with advanced colon, lung, kidney, and brain (glioblastoma) cancers.

Metastatic Colorectal Cancer

Avastin is indicated 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.

Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Avastin is indicated for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer in combination with carboplatin and paclitaxel.

Metastatic Breast Cancer

Avastin is indicated for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer in combination with paclitaxel. The effectiveness of Avastin in MBC is based on an improvement in progression free survival. Avastin is not indicated for patients with breast cancer that has progressed following anthracycline and taxane chemotherapy administered for metastatic disease.

Glioblastoma

Avastin is indicated for the treatment of glioblastoma with progressive disease following prior therapy as a single agent. The effectiveness of Avastin in glioblastoma is based on an improvement in objective response rate.

Metastatic Renal Cell Carcinoma

Avastin is indicated for the treatment of metastatic renal cell carcinoma in combination with interferon alfa.

FDA Recommended Dosing

First infusion: Administer infusion over 90 minutes. Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated; administer all subsequent infusions over 30 minutes if infusion over 60 minutes is tolerated.

Metastatic Colorectal Cancer

The recommended doses are 5 mg/kg or 10 mg/kg every 2 weeks when used in combination with intravenous 5-FU-based chemotherapy. Administer 5 mg/kg when used in combination with bolus-IFL. Administer 10 mg/kg when used in combination with FOLFOX4.

Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

The recommended dose is 15 mg/kg every 3 weeks in combination with carboplatin and paclitaxel.

Metastatic Breast Cancer

The recommended dose is 10 mg/kg every 2 weeks in combination with paclitaxel.

Glioblastoma

The recommended dose is 10 mg/kg every 2 weeks.

Metastatic Renal Cell Carcinoma

The recommended dose is 10 mg/kg every 2 weeks in combination with interferon alfa.

Drug Availability

Avastin is available as 100 mg per 4 mL single-use vial and 400 mg per 16 mL single-use vial.

General Background

Pharmacology

Bevacizumab is the first member of a class of antineoplastics which inhibit vascular endothelial growth factor (VEGF). The anti-angiogenic therapy of cancer represents a new strategy for destroying tumors because tumor growth is dependent on blood supply. When given with traditional chemotherapy regimens, a synergistic anti-tumor activity can be seen. Bevacizumab is a recombinant monoclonal antibody.

Bevacizumab binds to and inhibits VEGF. Bevacizumab is the first antineoplastic agent to inhibit the development of microvasculature within a solid tumor. Bevacizumab is only available in intravenous (IV) form. The estimated volume of distribution is 46 mL/kg. The clearance of bevacizumab ranges from 2.75 – 5.06 mL/kg/day, and the half life is approximately 20 days (range 11–50 days).

Guidelines

The following are recommendations from the National Comprehensive Cancer Network (NCCN) for bevacizumab:

Breast Cancer

Grade 2A

In combination with paclitaxel for patients with recurrent or metastatic disease that is hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative with visceral crisis or HER2-negative and either hormone receptor-negative or hormone receptor-positive and endocrine therapy refractory or progressive with no clinical benefit after three consecutive endocrine therapy regimens or with symptomatic visceral disease

Primary Central Nervous System Tumors

Grade 2A

Consider as single-agent treatment for disease progression after radiation therapy for spine or brain ependymoma recurrence.

Treatment of recurrent disease or salvage therapy as a single agent or in combination with irinotecan, carmustine, or temozolomide for anaplastic glioma.

Treatment of recurrent disease or salvage therapy as a single agent or in combination with irinotecan, carmustine, or temozolomide for glioblastoma.

Colon Cancer

Grade 2A

Used in combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), FOLFIRI (fluorouracil, leucovorin, and irinotecan), or CapeOX (capecitabine and oxaliplatin) regimen as neoadjuvant therapy for patients with synchronous liver and/or lung metastases or with resectable metachronous metastases; adjuvant therapy for patients with resected synchronous liver and/or lung metastases or with metachronous metastases; primary therapy for patients with unresectable synchronous liver and/or lung metastases, with synchronous abdominal/peritoneal metastases, or with unresectable metachronous metastases.

Initial therapy for patients with unresectable advanced or metastatic disease in combination with capecitabine or with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), FOLFIRI (fluorouracil, leucovorin, and irinotecan), 5-FU/LV (fluorouracil and leucovorin), or CapeOX (capecitabine and oxaliplatin) regimen for patients who can tolerate intensive therapy or in combination with infusional 5-FU/LV for patients who cannot tolerate intensive therapy.

NSCLC

Grade 1

Single-agent continuation maintenance therapy if given first line with chemotherapy for recurrence or metastasis in patients with performance status 0-1, tumors of nonsquamous cell histology, and no history of hemoptysis who achieve tumor response or stable disease following first-line chemotherapy.

Grade 2A

First-line therapy in combination with cisplatin- or carboplatin-based regimens for recurrence or metastasis in patients with performance status 0-1, tumors of nonsquamous cell histology, and no history of hemoptysis.

Ovarian Cancer**Grade 2A**

May be considered as therapy for clinical relapse in patients with stage II-IV granulosa cell tumors.

Preferred recurrence therapy as a single agent for recurrence as evidenced by serially rising CA-125 levels in patients who have received prior chemotherapy; progressive, stable, or persistent disease on primary chemotherapy; relapse after complete remission following primary chemotherapy stage II-IV disease showing partial response to primary treatment.

Rectal Cancer**Grade 2A**

Used in combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), FOLFIRI (fluorouracil, leucovorin, and irinotecan), or CapeOX (capecitabine and oxaliplatin) regimen as neoadjuvant therapy for patients with synchronous or metachronous metastases or adjuvant therapy for patients with resected synchronous metastases who received neoadjuvant chemoradiation or who have pathologic findings of T1-2, N0, M1 disease and have not received neoadjuvant therapy or adjuvant therapy for patients with metachronous metastases primary therapy for patients with unresectable synchronous metastases or who are medically inoperable. Initial therapy for patients with unresectable advanced or metastatic disease in combination with capecitabine or with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), FOLFIRI (fluorouracil, leucovorin, and irinotecan), 5-FU/LV (fluorouracil/leucovorin), or CapeOX (capecitabine and oxaliplatin) regimen for patients who can tolerate intensive therapy or in combination with infusional 5-FU/LV for patients who cannot tolerate intensive therapy.

Soft Tissue Sarcoma**Grade 2A**

Used as a single agent for angiosarcoma. In combination with temozolomide for the treatment of solitary fibrous tumor and hemangiopericytoma.

Clinical Efficacy

The safety and efficacy of Avastin in the treatment of patients with metastatic carcinoma of the colon or rectum was studied in three randomized, controlled clinical trials in combination with intravenous 5-fluorouracil-based chemotherapy. The activity of Avastin in patients with metastatic colorectal cancer that progressed on or after receiving both irinotecan based- and oxaliplatin based-chemotherapy regimens was evaluated in an open-access trial in combination with intravenous 5-fluorouracil-based chemotherapy.

The safety and efficacy of Avastin as first-line treatment of patients with locally advanced, metastatic, or recurrent NSCLC was studied in a single, large, randomized, active-controlled, open-label, multicenter study, supported by a randomized, dose ranging, active controlled Phase II study. Thirty-one percent of the patients in the low dose bevacizumab group and 44% of the patients in the high dose group experienced grade 1 or 2 epistaxis compared with 4% of the control group.

In a phase III randomized trial the addition of bevacizumab to capecitabine increased response rates but did not affect progression-free or overall survival in patients with previously treated metastatic breast cancer. Interim analysis of data from a phase III randomized trial shows prolonged progression-free survival (11 versus 6 months) and higher response rates (28 versus 14%) for patients receiving bevacizumab and paclitaxel for previously untreated locally recurrent or metastatic breast cancer compared with those receiving paclitaxel alone.

The efficacy and safety of Avastin was evaluated in an open-label, multicenter, randomized, non-comparative study of patients with previously treated glioblastoma. Patients received Avastin (10 mg/kg IV) alone or Avastin plus irinotecan every 2 weeks until disease progression or until unacceptable toxicity. All patients received prior radiotherapy (completed at least 8 weeks prior to receiving Avastin) and temozolomide. Patients with active brain hemorrhage were excluded. Of the 85 patients randomized to the Avastin arm, the median age was 54 years, 32% were female, 81% were in first relapse, Karnofsky performance status was 90–100 for 45% and 70–80 for 55%. The efficacy of Avastin was demonstrated using response assessment based on both WHO

radiographic criteria and by stable or decreasing corticosteroid use, which occurred in 25.9% (95% CI 17.0%, 36.1%) of the patients. Median duration of response was 4.2 months (95% CI 3.0, 5.7). Radiologic assessment was based on MRI imaging. MRI does not necessarily distinguish between tumor, edema, and radiation necrosis.

Another study, a single-arm, single institution trial with 56 patients with glioblastoma was performed. All patients had documented disease progression after receiving temozolomide and radiation therapy. Patients received Avastin 10 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity. The median age was 54, 54% were male, 98% Caucasian, and 68% had a Karnofsky Performance Status of 90–100. The efficacy of Avastin was supported by an objective response rate of 19.6% (95% CI 10.9%, 31.3%) using the same response criteria as in Study 7. Median duration of response was 3.9 months (95% CI 2.4, 17.4).

In a randomized, double-blinded, phase II trial involving 116 patients with metastatic clear-cell renal cancer, those receiving high-dose bevacizumab had longer progression-free survival than those receiving placebo. No difference in progression-free survival was observed in patients receiving low-dose bevacizumab compared with those receiving placebo, and no difference in overall survival was noted between the 3 groups. A phase III randomized trial comparing bevacizumab and interferon alfa-2b versus interferon alfa-2b alone for advanced renal cell cancer is under way.

Off-Label Uses

The National Eye Institute (NEI) of the National Institutes of Health (NIH) announced the start of a multicenter clinical trial to compare the relative safety and effectiveness of two drugs currently used to treat advanced age-related macular degeneration (AMD). The two drugs are Lucentis (ranibizumab) and Avastin (bevacizumab). AMD is a disease that damages the macula. The macula is the area of the retina responsible for central vision. AMD is a leading cause of blindness among older Americans. Lucentis was approved by the FDA in June of 2006 for the treatment of advanced, or wet, AMD. Avastin is a drug closely related to Lucentis. It has been widely used off-label to treat wet AMD. Avastin is thought to remain in the eye longer than Lucentis and therefore possibly allow for less frequent injections. Wet AMD occurs when abnormal blood vessels behind the retina start to grow under the macula. These new blood vessels leak blood and fluid, damaging the macula and causing a rapid loss of vision. The Lucentis- Avastin trial will determine the relative safety and effectiveness of treating wet AMD in 1,200 patients. The primary outcome measure will be change in visual acuity. Secondary outcome measures will include number of treatments, anatomical changes in the retina, adverse events, and cost.

The American Academy of Ophthalmology (AAO) supports reimbursement for 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. A letter from AAO reported that intravitreal bevacizumab, sold under the brand Avastin, is being used by “a large number of retinal specialists (who) believe that it is reasonable and medically necessary for treatment of some patients with neovascular AMD.” AAO’s support for coverage is limited to patients who are deemed by their treating physician to have failed FDA- approved therapies, or in the judgment of their treating physician, based on his/her experience, are likely to have greater benefit from the use of intravitreal bevacizumab. The Academy will continue to monitor new information regarding the safety and efficacy of these treatments and will release new position statements as appropriate. It also encourages physicians to provide appropriate informed consent with respect to the off-label use of bevacizumab.

Branch retinal vein occlusion is a frequent cause of visual loss with currently insufficient treatment options. The effect of bevacizumab (Avastin) treatment in patients with macular edema induced by branch retinal vein occlusion was evaluated. A retrospective analysis of 32 eyes in 32 patients with fluorescein angiography proven branch retinal vein occlusion, macular edema and bevacizumab treatment was performed. Outcome measures were best corrected visual acuity in logMAR and central retinal thickness in OCT. Visual acuity was significantly better 4 to 6 weeks after bevacizumab treatment compared to visual acuity prior to treatment. Gain in visual acuity was accompanied by a significant decrease in retinal thickness. Follow up shows that improvement for both visual acuity and retinal thickness last for several months after bevacizumab use. Intravitreal bevacizumab is an effective and lasting treatment for macular edema after branch retinal vein occlusion.

Retinopathy of prematurity is a leading cause of childhood blindness worldwide. Peripheral retinal ablation with conventional (confluent) laser therapy is destructive, causes complications, and does not prevent all vision loss,

especially in cases of retinopathy of prematurity affecting zone I of the eye. Case series in which patients were treated with vascular endothelial growth factor inhibitors suggest that these agents may be useful in treating retinopathy of prematurity. A prospective, controlled, randomized, stratified, multicenter trial to assess intravitreal bevacizumab monotherapy for zone I or zone II posterior stage 3+ (i.e., stage 3 with plus disease) retinopathy of prematurity was performed. Infants were randomly assigned to receive intravitreal bevacizumab (0.625 mg in 0.025 ml of solution) or conventional laser therapy, bilaterally. The primary ocular outcome was recurrence of retinopathy of prematurity in one or both eyes requiring retreatment before 54 weeks' postmenstrual age. 150 infants (total sample of 300 eyes) were enrolled; 143 infants survived to 54 weeks' postmenstrual age, and the 7 infants who died were not included in the primary outcome analyses. Retinopathy of prematurity recurred in 4 infants in the bevacizumab group (6 of 140 eyes [4%]) and 19 infants in the laser-therapy group (32 of 146 eyes [22%], $P = 0.002$). A significant treatment effect was found for zone I retinopathy of prematurity ($P = 0.003$) but not for zone II disease ($P = 0.27$). Intravitreal bevacizumab monotherapy, as compared with conventional laser therapy, in infants with stage 3+ retinopathy of prematurity showed a significant benefit for zone I but not zone II disease. Development of peripheral retinal vessels continued after treatment with intravitreal bevacizumab, but conventional laser therapy led to permanent destruction of the peripheral retina. This trial was too small to assess safety (Mintz-Hittner, H. et.al., 2011).

Ongoing Clinical Studies

Vascular endothelial growth factor (VEGF) seems to be a promoter of tumor progression for epithelial ovarian cancer (EOC) and primary peritoneal cancer (PPC). A phase II trial to assess the efficacy and tolerability of single-agent bevacizumab, an anti-VEGF monoclonal antibody was conducted. Eligible patients had persistent or recurrent EOC/PPC after one to two prior cytotoxic regimens, measurable disease, and Gynecologic Oncology Group performance status of at least 2. Treatment consisted of bevacizumab 15 mg/kg intravenously every 21 days until disease progression or prohibitive toxicity. Primary end points were progression-free survival (PFS) at 6 months and clinical response. The study consisted of 62 eligible and assessable patients, median age 57 years, 41 (66.1%) having received two prior regimens and 26 (41.9%) considered platinum resistant. Grade 3 adverse events at least possibly related to bevacizumab were hematologic (1), GI (3), hypertension (6), thromboembolism (1), allergy (2), hepatic (1), pain (3), coagulation (1), constitutional (1), and dyspnea (1). Grade 4 adverse events included pulmonary embolus (1), vomiting and constipation (1), and proteinuria (1). Thirteen patients (21.0%) experienced clinical responses (two complete, 11 partial; median response duration, 10 months), and 25 (40.3%) survived progression free for at least 6 months. Median PFS and overall survival were 4.7 and 17 months, respectively. There was no significant association of prior platinum sensitivity, age, number of prior chemotherapeutic regimens, or performance status with the hazard of progression or death. Bevacizumab seems to be well tolerated and active in the second- and third-line treatment of patients with EOC/PPC and merits phase III investigation.

Regimens of bevacizumab in combination with chemotherapy are being investigated for use in the treatment of prostate cancer. A phase III randomized trial comparing docetaxel and prednisone, with or without bevacizumab, for the treatment of hormone-refractory metastatic adenocarcinoma of the prostate is under way.

Avastin is currently being studied in a Phase II trial for active malignant melanoma. There is also a Phase II study recruiting for its use in pancreatic cancer.

Adverse Reactions

In addition to the Black Box warning, hemorrhage, arterial thromboembolic events, hypertensive crises, reversible posterior leukoencephalopathy syndrome, neutropenia and infection, nephrotic syndrome, and congestive heart failure were also side effects of Avastin. The following additional serious adverse events occurred in at least one subject treated with Avastin in clinical studies or post-marketing experience: polyserositi, pulmonary hypertension, intestinal necrosis, mesenteric venous occlusion, anastomotic ulceration, pancytopeni, and nasal septum perforation.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary for Intravitreal treatment of neovascular (wet) age-related macular degeneration or branched retinal vein occlusion:

HCPCS Codes	Description
C9257	Injection, bevacizumab, 0.25 mg

ICD-9-CM Diagnosis Codes	Description
362.20-362.29	Other proliferative retinopathy
362.36	Venous tributary (branch) occlusion
362.52	Exudative senile macular degeneration

Covered when medically necessary for intravenous infusion for treatment of the specified cancer conditions:

HCPCS Codes	Description
J9035	Injection, bevacizumab, 10 mg

ICD-9-CM Diagnosis Codes	Description
153.0-153.9	Malignant neoplasm of colon
154.0	Malignant neoplasm of rectosigmoid junction
154.1	Malignant neoplasm of rectum
154.8	Malignant neoplasm of rectum, rectosigmoid junction, and anus, other
162.3-162.9	Malignant neoplasm of lung
174.0-174.9	Malignant neoplasm of female breast
175.0-175.9	Malignant neoplasm of male breast
183.0	Malignant neoplasm of ovary
189.0	Malignant neoplasm of kidneys, except pelvis
191.0-191.9	Malignant neoplasm of brain

Experimental/Investigational/Unproven and Not Covered when used in combination with photodynamic therapy (PDT) with verteporfin (Visudyne):

CPT*	Description
67221	Destruction of localized lesion of choroid (eg, choroidal neovascularization); photodynamic therapy (includes intravenous infusion)
67225	Destruction of localized lesion of choroid (eg, choroidal neovascularization); photodynamic therapy, second eye, at single session (List separately in addition to code for primary eye treatment)

HCPCS Codes	Description
J3396	Injection, verteporfin, 0.1mg

*Current Procedural Terminology (CPT®) ©2010 American Medical Association.

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