**AVASTIN (bevacizumab)**

**Line(s) of Business:**
- HMO; PPO; QUEST Integration
- Akamai Advantage

**Original Effective Date:** 10/01/2012

**Current Effective Date:** 05/01/2017

**TBD** 03/01/2018

**POLICY**

**A. INDICATIONS**

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

**FDA-Approved Indications**

- Recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer
  - Platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan for patients who received no more than 2 prior chemotherapy regimens
  - Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, either in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by Avastin as a single agent
- Cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease
- Metastatic colorectal cancer:
  - In combination with intravenous 5-fluorouracil-based chemotherapy for first- or second-line treatment
  - In combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen
- Non-squamous non-small cell lung cancer (NSCLC), with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease
- Glioblastoma, as a single agent for adult patients with progressive disease following prior therapy
- Metastatic renal cell carcinoma with interferon alfa

**Compendial Uses**

- Breast cancer
  - in combination with pacilataxel for recurrent or metastatic human epidermal growth factor receptor 2 (HER2)-negative disease
  - with symptomatic visceral disease or visceral crisis
that is hormone receptor-negative or hormone receptor-positive and endocrine therapy refractory

- Central nervous system (CNS) cancers
  - Adult intracranial and spinal ependymoma, consider as single agent treatment for disease progression
  - Anaplastic gliomas, treatment for recurrent disease as a single agent or in combination with irinotecan, carmustine, lomustine, or temozolomide.
  - Glioblastoma treatment for recurrent disease as a single agent or in combination with irinotecan, carmustine, lomustine, temozolomide.

- Cervical cancer, first line in combination with paclitaxel and cisplatin,- carboplatin, or topotecan for local/regional recurrence or metastatic disease,

- Colon/rectal cancer,
  - in combination with capecitabine or with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), FOLFIRI (fluorouracil, leucovorin, and irinotecan), CapeOX (capecitabine and oxaliplatin), FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan), or 5-FU/LV (fluorouracil and leucovorin) regimen
    - as primary treatment for locally unresectable or medically inoperable disease
    - for unresectable synchronous liver and/or lung metastases that remain unresectable — after primary systemic therapy
    - as primary treatment for synchronous abdominal/peritoneal metastases that are nonobstructing, or following local therapy for patients with imminent or existing obstruction
    - for unresectable synchronous metastases of other sites
    - as primary treatment for unresectable metachronous metastases in patients who have not received previous adjuvant FOLFOX or CapeOX within the past 12 months
    - for unresectable metachronous metastases that remain unresectable after primary treatment
  - Initial treatment for unresectable synchronous liver and/or lung metastases in combination with
    - FOLFOX (fluorouracil, leucovorin, and oxaliplatin) regimen
    - FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen
    - FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin and irinotecan) regimen
    - CapeOX (capecitabine and oxaliplatin) regimen
  - Preferred anti-angiogenic therapy as primary treatment for patients with unresectable metachronous metastases and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months
    - in combination with irinotecan
    - in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen
  - Subsequent therapy after first progression of unresectable advanced or metastatic disease
as the preferred anti-angiogenic agent in combination with irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen for disease previously treated with oxaliplatin-based therapy without irinotecan
- in combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) regimen for disease previously treated with irinotecan-based therapy without oxaliplatin
- as the preferred anti-angiogenic agent in combination with irinotecan or FOLFIRI for patients previously treated with fluoropyrimidine therapy without irinotecan or oxaliplatin
- in combination with FOLFOX, CapeOX, or irinotecan and oxaliplatin for patients previously treated with fluoropyrimidine therapy without irinotecan or oxaliplatin
- preferred anti-angiogenic therapy as primary treatment for patients with unresectable metachronous metastases and previous adjuvant FOLEX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months

- Endometrial carcinoma
  - Single agent for disease that has progressed on prior cytotoxic chemotherapy

- Non-Squamous Non-Small Cell Lung Cancer
  - Treatment in combination with carboplatin and paclitaxel or pemetrexed or in combination with cisplatin and pemetrexed for recurrence or metastases in patients with performance status 0-1, tumors of nonsquamous cell histology, and no history of recent hemoptysis as
    - first-line therapy for EGFR, ALK, ROS1, BRAF, and PD-L1 negative or unknown
    - first-line or subsequent therapy for BRAF V600E-mutation positive tumors
    - subsequent therapy for sensitizing EGFR mutation-positive tumors and prior erlotinib, afatinib, gefitinib, or osimertinib therapy
    - subsequent therapy for ALK rearrangement-positive tumors and prior crizotinib, ceritinib, alectinib, or brigatinib therapy
    - subsequent therapy for ROS1 rearrangement-positive tumors and prior crizotinib therapy
    - subsequent therapy for PD-L1 expression-positive (≥50%) tumors and EGFR, ALK, ROS1, and BRAF negative or unknown and prior pembrolizumab therapy
  - Continuation maintenance therapy if given first line with chemotherapy for recurrence or metastasis in patients with performance status 0-2, tumors of nonsquamous cell histology, and no history of recent hemoptysis who achieve tumor response or stable disease following first-line chemotherapy
    - as a single agent
    - in combination with pemetrexed if previously used with a first-line pemetrexed/platinum chemotherapy regimen

- Malignant pleural mesothelioma
  - Used in combination with cisplatin and pemetrexed followed by single-agent maintenance bevacizumab as treatment of
    - unresectable clinical stage I-III disease and tumors of epithelial histology
Clinical stage IV disease, tumors of sarcomatoid or mixed histology, or medically inoperable tumors in patients with performance status (PS) 0-2

- Non-small cell lung cancer
- Ovarian cancer
  - Malignant sex cord-stromal tumors as a single agent for clinical relapse in patients with stage II-IV disease
  - Therapy for persistent or recurrent epithelial ovarian cancer/ fallopian tube cancer
    - as preferred therapy if platinum-sensitive, in combination with carboplatin and gemcitabine
    - if platinum-sensitive, in combination with carboplatin and paclitaxel
    - as preferred therapy if platinum-resistant, in combination with liposomal doxorubicin, weekly paclitaxel, or topotecan
    - as preferred therapy as a single agent
  - Therapy for persistent disease or recurrence
    - maintenance therapy for platinum-sensitive persistent disease or recurrence following response to combination therapy with
      - carboplatin, gemcitabine, and bevacizumab
      - carboplatin, paclitaxel, and bevacizumab
- Renal Cancer
  - For relapse or stage IV disease
    - in combination with interferon alfa-2b as first-line therapy for predominant clear cell histology
    - as single-agent systemic therapy for non-clear cell histology
- Soft tissue sarcoma
  - Angiosarcoma as a single agent
  - Solitary Fibrous Tumor/Hemangiopericytoma in combination with temozolomide for the treatment of solitary fibrous tumor and hemangiopericytoma
- Ophthalmic-related disorders
  - Choroidal neovascularization (CNV)
  - Wet age-related macular degeneration (AMD)
  - Macular Branch and central retinal vein occlusion with macular edema due to retinal vein occlusion (RVO)
  - Diabetic macular edema
  - OcULAR neovascularization (choroidal, retinal, iris) associated with proliferative diabetic retinopathy
  - Neovascular glaucoma
  - Retinopathy of prematurity

B. REQUIRED DOCUMENTATION
The following information may be necessary to initiate the prior authorization review:
- All approvable oncologic diagnoses
  - Current oncology notes, clinical notes (including previous treatment history), and any pertinent pathology reports and/or imaging studies
- All approvable oncologic diagnoses for continuation therapy
  - Documentation demonstrating lack of disease progression on therapy
- Breast cancer
  - Human epidermal growth factor receptor 2 (HER2) test result
  - Hormone receptor (HR) test result
- NSCLC
  - Documentation of previous treatment history where applicable

C. PRESCRIBER RESTRICTION
- All approvable oncologic diagnoses
  - Avastin must be prescribed by an oncologist.

D. CRITERIA FOR APPROVAL
1. Breast cancer
   Authorization of 3 months may be granted to members who are prescribed Avastin in combination with paclitaxel for the treatment of HER2-negative recurrent or metastatic breast cancer when members have ANY of the following types of disease:
   a. Symptomatic visceral disease
   b. Disease with visceral crisis
   c. HR-negative disease
   d. HR-positive disease refractory to endocrine therapy

2. Cervical cancer
   Authorization of 3 months may be granted for the treatment of persistent, recurrent, or metastatic cervical cancer when Avastin is prescribed in ONE of the following regimens:
   a. Avastin, cisplatin and paclitaxel
   b. Avastin, carboplatin and paclitaxel
   c. Avastin, topotecan and paclitaxel

3. CNS cancer
   3.1. Glioblastoma and anaplastic glioma
       Authorization of 3 months may be granted to members who are prescribed Avastin in combination with irinotecan, carmustine, lomustine, or temozolomide, or as a single agent for recurrent or progressive disease.

   3.2. Adult intracranial and spinal ependymoma (excludes subependymoma)
       Authorization of 3 months may be granted to members who are prescribed Avastin as a single agent for disease progression.

4. Colorectal cancer
   a. Authorization of 3 months may be granted to members who are prescribed Avastin as therapy for T4b colorectal cancer prior to colectomy or rectal cancer stage II or III (T3, N0, M0; any T, N1-2, M0; or T4) and/or locally unresectable or medically inoperable disease and Avastin will be used in combination with capecitabine, FOLFIRI, FOLFOX, CapeOX, FOLFOXIRI, or 5-FU with leucovorin.
Authorization of 3 months may be granted to members who are prescribed Avastin as perioperative/neoadjuvant therapy for resectable synchronous liver and/or lung metastases and Avastin will be used in combination with FOLFIRI, FOLFOX, or CapeOX.

b. Authorization of 3 months may be granted to members who are prescribed Avastin as perioperative (neoadjuvant/adjuvant) therapy for resectable metastases and Avastin will be used in combination with capecitabine, FOLFIRI, FOLFOX, CapeOX, FOLFOXIRI, or 5-FU with leucovorin for members who were previously treated with chemotherapy.

a. Authorization of 3 months may be granted to members who are prescribed Avastin as adjuvant therapy in combination with FOLFOX, FOLFIRI, CapeOX, FOLFOXIRI, or 5-FU with leucovorin.

c. Authorization of 3 months may be granted to members who are prescribed Avastin in combination with irinotecan or FOLFIRI for unresectable metastases with previous adjuvant FOLFOX or CapeOX therapy within the past 12 months.

d. Authorization of 3 months may be granted to members who are prescribed Avastin in combination with capecitabine, FOLFOX, CapeOX, FOLFOXIRI, or 5-FU with leucovorin for unresectable advanced or metastatic disease as initial therapy who can tolerate intensive therapy.

Authorization of 3 months may be granted to members who are prescribed Avastin in combination with infusional 5-FU with leucovorin, or capecitabine for unresectable advanced or metastatic disease as initial therapy who CANNOT tolerate intensive therapy.

e. Authorization of 3 months may be granted when Avastin is prescribed after first progression of unresectable advanced or metastatic disease as ONE of the following:

i. In combination with FOLFIRI or irinotecan for members who were previously treated with an oxaliplatin-based regimen without irinotecan,

ii. In combination with FOLFOX or CapeOX for members who were previously treated with an irinotecan-based regimen without oxaliplatin, OR

iii. In combination with FOLFOX, CapeOX, irinotecan, irinotecan and oxaliplatin, or FOLFIRI for members who were treated with 5-FU with leucovorin or capecitabine regimen.

CapeOX = capecitabine and oxaliplatin; FOLFIRI = leucovorin, fluorouracil, and irinotecan; FOLFOX = leucovorin, fluorouracil, and oxaliplatin; FOLFOXIRI = leucovorin, fluorouracil, oxaliplatin, and irinotecan.

5. **Endometrial cancer**
Authorization of 3 months may be granted to members who are prescribed Avastin as a single agent and who have progressed on prior cytotoxic chemotherapy.

6. **Ovarian cancer**

6.1 **Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer**
Authorization of 3 months may be granted to members who meet ALL of the following criteria:

a. Member has persistent or recurrent disease and.
b. Member has not previously received Avastin.

c. Avastin will be used in ONE of the following regimens:
   i. As a single agent, or
   ii. In combination with liposomal doxorubicin, paclitaxel, or topotecan, or
   iii. In combination with carboplatin and either paclitaxel or gemcitabine

### 6.2.2 Malignant sex cord-stromal tumors
Authorization of 3 months may be granted to members in clinical relapse with stage II-IV granulosa cell tumors disease.

### 7. NSCLC
a. The disease is unresectable, locally advanced, recurrent, or metastatic.
b. Member has ECOG performance status (PS) 0-1 (first-line/subsequent therapy) or PS 0-2 (continuation maintenance), tumors of non-squamous cell histology, and no history of recent hemoptysis.
c. Authorization of 3 months may be granted to members who are prescribed Avastin in combination with carboplatin and paclitaxel or pemetrexed or with cisplatin and pemetrexed who meet one of the following:
   i. For tumors with negative/unknown EGFR mutations, ALK gene rearrangements, ROS1 rearrangements or PD-L1 expression (≥50%) Avastin will be used as a first-line therapy (see section d. below for continuation maintenance).
   
   ii. For tumors with sensitizing EGFR mutation ss-positive tumors:
      1) Avastin will be used as a subsequent therapy AND
      2) Member experienced disease progression on prior erlotinib (Tarceva), afatinib (Gilotrif), gefitinib (Iressa) or osimertinib (Tagrisso) therapy.
   iii. For ALK-positive tumors:
      1) Avastin will be used as a subsequent therapy AND
      2) Member experienced disease progression on prior crizotinib (Xalkori), ceritinib (Zykadia), *brigatinib (Alunbrig)* or alectinib (Alecensa) therapy.
   iv. For ROS1-positive tumors:
      1) Avastin will be used as a subsequent therapy AND
      2) Member experienced disease progression on prior crizotinib (Xalkori) therapy.
   v. For PD-L1 expression-positive (≥50%) tumors:
      1) Avastin will be used as a subsequent therapy AND
      2) Member experienced disease progression on prior pembrolizumab (Keytruda) therapy.

d. Authorization of 3 months may be granted to members who are prescribed Avastin as a continuation maintenance therapy when ALL of the following criteria are met:
   i. Members have achieved tumor response or stable disease following first-line chemotherapy.
   ii. Avastin will be used as a single agent or in combination with pemetrexed if previously used with a first-line pemetrexed/platinum chemotherapy regimen.

### 8. Renal cell carcinoma
Authorization of 3 months may be granted for the treatment of relapsed, metastatic or stage IV renal cell carcinoma when Avastin will be used as ONE of the following:
a. Avastin in combination with interferon alfa-2
b. Avastin monotherapy for disease with non-clear cell histology

9. Soft tissue sarcoma
9.1. Angiosarcoma
Authorization of 3 months may be granted to members who are prescribed Avastin as a single agent.

9.2. Solitary fibrous tumor/hemangiopericytoma
Authorization of 3 months may be granted to members who are prescribed Avastin in combination with temozolomide.

10. Malignant pleural mesothelioma
Authorization of 3 months may be granted to members who are prescribed Avastin for the treatment of malignant pleural mesothelioma when criteria a. and b. below are met:
   a. Member has one of the following:
      - Unresectable or medically inoperable clinical stage I to III disease with epithelial or mixed histology
      - Clinical stage IV disease
      - Tumor with sarcomatoid histology
      - Medically inoperable disease in patients with an ECOG Performance status of 0 - 2
   b. Avastin is used as a single agent for maintenance therapy or is used in combination with pemetrexed (Alimta) and cisplatin

11. Ophthalmic-related disorders
Authorization of 6 months may be granted to members who are prescribed Avastin for intravitreal injection for ANY of the following retinal disorders:
   - Choroidal neovascularization (CNV) associated with high (pathologic) myopia, ocular histoplasmosis syndrome, angiod streaks, inflammatory conditions, or idiopathic
   - Wet age-related macular degeneration (AMD) (including polypoidal choroidopathy and retinal angiomatus proliferation subtypes of AMD)
   - Macular edema due to branch and central retinal vein occlusion (RVO)
   - Diabetic macular edema
   - Ocular neovascularization (choroidal, retinal, iris) associated with proliferative diabetic retinopathy
   - Neovascular glaucoma, as adjunct
   - Retinopathy of prematurity

E. CONTINUATION OF THERAPY
1. No previous authorization/precertification:
   All members (including new members and members currently receiving treatment without prior authorization) must meet criteria for initial approval in section D.
2. Reauthorization:
   a. All approvable oncologic diagnosis except colorectal cancer
      Members who were previously approved for Avastin by HMSA/CVS may request reauthorizations after their initial approval. Approval for an additional 3 months may be granted if the following information is supplied:
• A current oncology note documenting the patient’s response to treatment showing no progression of disease
• Current imaging studies and other objective measures showing no progression of disease when compared with previous results

Authorization of 3 months may be granted to members who are continuing with Avastin therapy when previously authorized by HMSA/CVS and initial criteria was met.

b. Colorectal cancer

Authorization of 3 months may be granted to members requesting continuation of therapy when Avastin was previously authorized by HMSA/CVS and after first progression of unresectable advanced or metastatic disease and cancer progressed on a first-line Avastin-containing regimen as ONE of the following:
   i. In combination with FOLFIRI or irinotecan for members who were previously treated with an oxaliplatin-based regimen,
   ii. In combination with FOLFOX or CapeOX for members who were previously treated with an irinotecan-based regimen, OR
   iii. In combination with FOLFOX, CapeOX, irinotecan, irinotecan and oxaliplatin, or FOLFIRI for members who were treated with 5-FU with leucovorin or capecitabine regimen.

1. All approvable oncologic diagnoses (except CRC)

Authorization of 3 months may be granted to members requesting authorization for continuation of therapy for all approvable oncologic diagnoses (except CRC) when ALL of the following criteria are met:
   a. Member has not had disease progression.
   b. Previous Avastin therapy was authorized by HMSA or member meets all initial criteria.

2. Colorectal cancer

Authorization of 3 months may be granted to members requesting authorization for continuation of therapy when Avastin is prescribed after first progression of unresectable advanced or metastatic disease and cancer progressed on a first-line Avastin-containing regimen as ONE of the following:
   i. In combination with FOLFIRI or irinotecan for members who were previously treated with an oxaliplatin-based regimen,
   ii. In combination with FOLFOX or CapeOX for members who were previously treated with an irinotecan-based regimen, OR
   iii. In combination with FOLFOX, CapeOX, irinotecan, irinotecan and oxaliplatin, or FOLFIRI for members who were treated with 5-FU with leucovorin or capecitabine regimen.

F. DOSAGE AND ADMINISTRATION

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

G. PROGRAM EXCEPTION – AKAMAI ADVANTAGE

For Akamai Advantage members, the following National Coverage Determination (NCD) applies:
   • Anti-Cancer Chemotherapy for Colorectal Cancer (110.17).
H. ADMINISTRATIVE GUIDELINES
Precertification is required. Please refer to the HMSA medical policy web site for the fax form.

I. IMPORTANT REMINDER
The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that CVS/carem reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

J. REFERENCES