# Bevacizumab Products for the Treatment of Neoplastic Disease (Avastin®, bevacizumab-awwb [Mvasi®] and bevacizumab-bvzr [Zirabev™])

**NDC CODE(S)**
50242-0060-XX AVASTIN 100 MG/4ML Solution (GENENTECH)
50242-0060-XX AVASTIN 25MG/ML Solution (GENENTECH)
50242-0061-XX AVASTIN 25MG/ML Solution (GENENTECH)
55513-0206-XX MVASI 25MG/ML (4ML) Solution (AMGEN)
55513-0207-XX MVASI 25MG/ML (16ML) Solution (AMGEN)
00069-0315-XX ZIRABEV 100 MG/4ML Solution (PFIZER U.S.)
00069-0342- XX ZIRABEV 400 MG/16ML Solution (PFIZER U.S.)

## DESCRIPTION

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody which binds to human vascular endothelial growth factor (VEGF). VEGF normally interacts with receptors (Flt-1 and KDR) on the surface of endothelial cells and leads to endothelial cell proliferation and new blood vessel formation. By binding to VEGF, bevacizumab halts interaction with these receptors, resulting in reduction of microvascular growth and inhibition of metastatic disease progression.

Biosimilar products are biological products that are highly similar to an existing FDA-approved innovator product and have no clinically meaningful differences from the innovator product. The differences in the biosimilars must be proven to be in the clinically inactive components of the biosimilars, e.g., stabilizers or buffers.

At present, two products have been approved as biosimilar to bevacizumab, bevacizumab-awwb (Mvasi®) and bevacizumab-bvzr (Zirabev™). Their clinical use mirrors that of bevacizumab.

**Note: This policy does not address the use of bevacizumab products for the treatment of disorders of the eye. Preauthorization is not required when used in the treatment of eye disorders.**

## POLICY

- Bevacizumab products for the treatment of the following neoplastic conditions is considered ***medically necessary*** if the medical appropriateness criteria are met: **(See Medical Appropriateness below.)**
  - Breast cancer
  - Central nervous system cancer
  - Cervical cancer
  - Colorectal cancer
  - Endometrial Carcinoma (Uterine Neoplasms)
  - Hepatocellular Carcinoma
  - Malignant Pleural Mesothelioma
  - Neurofibromatosis
  - Non-small cell lung cancer
  - Ovarian cancer
  - Renal cell carcinoma
  - Small bowel adenocarcinoma
  - Soft tissue sarcoma
  - Vulvar cancer
- Bevacizumab products for the treatment of other conditions/diseases is considered ***investigational***

## MEDICAL APPROPRIATENESS

**INITIAL APPROVAL CRITERIA**

- Patient is at least 18 years of age; **AND**
- Patient is currently on bevacizumab (Avastin®) therapy; **OR**
- Patient has a contraindication to, inadequate response to or intolerable side effects from a prior trial of one of the following:
  - Bevacizumab-awwb (Mvasi®); **OR**
  - Bevacizumab-bvzr (Zirabev™)

**Universal Criteria**

- Patient has no recent history of hemoptysis (i.e., the presence of ≥2.5 mL of blood in sputum) OR any grade 3-4 hemorrhage; **AND**
- Patient must not have had a surgical procedure within the preceding 28 days or have a surgical wound that has not fully healed; **AND**

**Colorectal Cancer (CRC)**

- Will not be used as part of adjuvant treatment; **AND**
  - Patient has metastatic, unresectable, or advanced disease; **AND**
    - Used as first- or second-line therapy in combination with a fluoropyrimidine- (e.g., 5-fluorouracil/5-FU or capecitabine) or irinotecan-based regimen; **OR**
  - Used in combination with a fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based regimen (if not used first line) as subsequent therapy for advanced or metastatic disease that has progressed on a first-line bevacizumab containing regimen

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

- Used as first-line therapy for recurrent, locally advanced, unresectable, or metastatic disease in combination with carboplatin and paclitaxel**; OR**
- Used for recurrent, advanced, or metastatic disease (excluding locoregional recurrence or symptomatic local disease with no evidence of disseminated disease) or mediastinal lymph node recurrence with prior radiation therapy; **AND**
  - Used as first-line therapy**; AND**
    - Used for one of the following:
      - EGFR, ALK, ROS1, BRAF, MET exon 14 skipping mutation, and RET rearrangement negative tumors* and PD-L1 < 1% in patients with PS ≤ 1; **OR**
      - EGFR, ALK, ROS1, BRAF, MET exon 14 skipping mutation, and RET rearrangement negative tumors* and PD-L1 ≥ 1% in patients with PS ≤ 2; **OR**
      - BRAF V600E-mutation, NTRK gene fusion, MET exon 14 skipping mutation, or RET rearrangement positive tumors in patients with PS ≤ 1; **AND**
    - Used in combination with:
      - Pemetrexed and either carboplatin or cisplatin *(excluding use in PD-L1 ≥ 1%)*; **OR**
      - Atezolizumab, carboplatin, and paclitaxel; **OR**
  - Used as subsequent therapy in patients with PS ≤ 1; **AND**
    - Used for one of the following:
      - EGFR, ALK, or ROS1 positive tumors and prior targeted therapy§; **OR**
      - BRAF V600E-mutation, NTRK gene fusion, MET exon 14 skipping mutation, or RET rearrangement positive tumors; **OR**

        - PD-L1 expression-positive (PD-L1 ≥ 1%) tumors that are EGFR, ALK, ROS1, BRAF, MET exon 14 skipping mutation, and RET negative* with prior PD-1/PD-L1 inhibitor therapy but no prior platinum-doublet chemotherapy; **AND**
    - Used in combination with:
        - Carboplatin and paclitaxel; **OR**
        - Pemetrexed and either carboplatin or cisplatin; **OR**
        - Atezolizumab, carboplatin, and paclitaxel (excluding use in patients who have received prior PD-1/PD-L1 inhibitor therapy); **OR**
- Used as continuation maintenance therapy *(bevacizumab must have been included in patient's first-line chemotherapy regimen)* in patients who achieved a tumor response or stable disease after first-line systemic therapy; **AND**
    - Used as a single agent; **OR**
    - Used in combination with pemetrexed following a first-line bevacizumab/pemetrexed/platinum chemotherapy regimen; **OR**
    - Used in combination with atezolizumab following a first-line atezolizumab/carboplatin/paclitaxel/bevacizumab regimen; **OR**
- Used in combination with erlotinib for sensitizing EGFR mutation positive disease as continuation of therapy following disease progression on erlotinib with bevacizumab for asymptomatic disease, symptomatic brain lesions, or isolated symptomatic systemic lesions

** Note: If there is insufficient tissue to allow testing for all of the EGFR, ALK, ROS1, BRAF, MET, and RET, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.*

**Cervical Cancer**

- Patient has persistent, recurrent, or metastatic disease**; AND**
- Used in combination with paclitaxel AND either cisplatin, carboplatin, or topotecan

**Breast Cancer**

- Patient has recurrent or metastatic disease; **AND**
- Patient has a high tumor burden, rapidly progressive disease, or visceral crisis; **AND**
- Used in combination with paclitaxel; **AND**
- Patient has human epidermal growth factor receptor 2 (HER2)-negative disease; **AND**
    - Disease is hormone receptor-negative; **OR**
    - Disease is hormone receptor-positive with visceral crisis or refractory to endocrine therapy

**Renal Cell Carcinoma (RCC)**

- Used in combination with interferon alfa for metastatic disease; **OR**
- Patient has metastatic or relapsed disease; **AND**
    - Used as a single agent in patients with non-clear cell histology; **OR**
    - Used in combination with everolimus in patients with non-clear cell histology; **OR**
    - Used in combination with erlotinib in patients with non-clear cell histology papillary disease including hereditary leiomyomatosis and renal cell cancer (HLRCC)

**Central Nervous System (CNS) Cancer**

- Used for symptom management related to radiation necrosis, poorly controlled vasogenic edema, or mass effect as single-agent short-course therapy; **AND**
  - Patient has a diagnosis of one of the following other CNS cancers:
    - Infiltrative Supratentorial Astrocytoma/Oligodendroglioma (Low-Grade, WHO Grade II); **OR**
    - Primary CNS Lymphoma; **OR**
    - Meningiomas; **OR**
    - Brain or Spine metastases; **OR**
    - Medulloblastoma; **OR**
    - Glioblastoma or Anaplastic Gliomas; **OR**
    - Intracranial or Spinal Ependymoma (excluding subependymoma); **OR**
- Used as a single agent **OR** in combination with one of the following: carmustine, lomustine, or temozolomide in patients with recurrent Anaplastic Gliomas or recurrent Glioblastoma; **OR**
- Used as a single agent for progressive or recurrent Intracranial and Spinal Ependymoma (excluding subependymoma) after prior radiation therapy; **OR**
- Used as a single agent for patients with surgically inaccessible recurrent or progressive Meningioma when radiation is not possible

**Ovarian Cancer**

- Patient has malignant stage II-IV sex cord-stromal tumors; **AND**
  - Used as single agent therapy for clinically relapsed disease; **OR**
- Patient has epithelial ovarian or fallopian tube or primary peritoneal cancer †; **AND**
  - Patient has persistent or recurrent disease; **AND**
    - Bevacizumab has not been used previously; **AND**
    - Patient is not experiencing an immediate biochemical relapse (i.e., rising CA-125 without radiographic evidence of disease); **AND**
      - If platinum sensitive, used as a single agent or in combination niraparib or in combination with carboplatin **AND** either gemcitabine, paclitaxel † or PEGylated liposomal-doxorubicin; **OR**
      - If platinum resistant, used as a single agent or in combination with one of the following: oral cyclophosphamide, PEGylated liposomal doxorubicin, paclitaxel, or topotecan; **OR**
  - Used for rising CA-125 levels or clinical relapse in patients who have received no prior chemotherapy in combination with paclitaxel and carboplatin; **OR**
  - Used as maintenance therapy; **AND**
    - Used as a single agent or in combination with olaparib following primary therapy including bevacizumab; **OR**
    - Used as a single agent following recurrence therapy with chemotherapy plus bevacizumab for platinum-sensitive disease; **OR**
    - Used in combination with paclitaxel and carboplatin for stable disease following neoadjuvant therapy as continued maintenance therapy; **OR**
  - Used as neoadjuvant therapy for endometrioid or serous histology in combination with paclitaxel and carboplatin; **AND**
    - Patient is a poor surgical candidate or has a low likelihood of optimal cytoreduction; **OR**
  - Used as adjuvant therapy in combination with paclitaxel and carboplatin; **AND**
    - Patient has pathologic stage II-IV disease; **OR**
    - Patient is a poor surgical candidate or has a low likelihood of optimal cytoreduction; **AND**
      - Patient has endometrioid or serous histology; **AND**
      - Used after interval debulking surgery (IDS) in patients with a response or stable disease to neoadjuvant therapy

**Soft Tissue Sarcoma**

- Used as a single agent for angiosarcoma; **OR**
- Used in combination with temozolomide for solitary fibrous tumor

**Endometrial Carcinoma (Uterine Neoplasms)**

- Used as a single agent therapy for disease that has progressed on prior cytotoxic chemotherapy; OR
- Used in combination with carboplatin and paclitaxel for advanced and recurrent disease

**Malignant Pleural Mesothelioma (MPM)***

- Patient has unresectable disease OR clinical stage IIIB or IV disease, sarcomatoid, or medically inoperable tumors; **AND**
- Used in combination with pemetrexed and cisplatin or carboplatin as initial therapy, followed by single-agent maintenance bevacizumab; **OR**

**peritoneal, pericardial, and tunica vaginalis testis mesothelioma will be evaluated on a case-by-case basis*

**Vulvar Cancer**

- Used in combination with paclitaxel and cisplatin for squamous cell carcinoma; **AND**
- Patient has unresectable locally advanced, metastatic, or recurrent disease

**Small Bowel Adenocarcinoma**

- Used as initial therapy; **AND**
- Patient has locally advanced or metastatic disease; **AND**
- Used in combination with a fluoropyrimidine-based regimen

**Hepatocellular Carcinoma (HCC)**

- Used as first-line therapy in combination with atezolizumab; **AND**
- Patient has Child-Pugh Class A disease; **AND**
- Patient has locally advanced, unresectable, inoperable, or metastatic disease

**Neurofibromatosis**

- Diagnosed as type 2 (NF2); **AND**
- Patient has bilateral progressive vestibular schwannomas; **AND**
- Patient has progressive hearing loss

| **Genomic Aberration Targeted Therapies**<br>(*not all inclusive, refer to guidelines for appropriate use*) § |
|---|
| • Sensitizing *EGFR* mutation-positive tumors<br>  ○ Afatinib<br>  ○ Dacomitinib<br>  ○ Erlotinib<br>  ○ Gefitinib |

| |
|---|
| ○ Osimertinib |
| • *ALK* rearrangement-positive tumors<br>○ Alectinib<br>○ Brigatinib<br>○ Ceritinib<br>○ Crizotinib<br>○ Lorlatinib |
| • *ROS1* rearrangement-positive tumors<br>○ Ceritinib<br>○ Crizotinib<br>○ Entrectinib |
| • *BRAF* V600E-mutation positive tumors<br>○ Dabrafenib ± Trametinib<br>○ Vemurafenib |
| • *NTRK* Gene Fusion positive tumors<br>○ Entrectinib<br>○ Larotrectinib |
| • *PD-1 / PD-L1* expression-positive tumors (> 1% ~~50%~~)<br>○ Atezolizumab<br>○ Nivolumab ± ipilimumab<br>○ Pembrolizumab |
| • *MET* Exon-14 skipping mutations<br>○ Capmatinib<br>○ Crizotinib |
| • *RET* rearrangement-positive tumors<br>○ Cabozantinib<br>○ Selpercatinib<br>○ Vandetanib |

**RENEWAL CRITERIA**

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in Initial Approval Criteria; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: gastrointestinal perforations and fistulae, surgical/wound healing complications, hemorrhage, arterial and venous thromboembolic events (ATE & VTE), uncontrolled hypertension, posterior reversible encephalopathy syndrome (PRES), nephrotic syndrome, proteinuria, severe infusion reactions, ovarian failure, congestive heart failure (CHF), etc.; **AND**

**CNS Cancers – symptom management (short-course therapy):**

- May NOT be renewed

**Colorectal Cancer (after first-line bevacizumab-containing regimen):**

- Refer to Initial Approval Criteria for criteria

**Malignant Mesothelioma (maintenance therapy):**

- Refer to Initial Approval Criteria for criteria

**Ovarian Cancer (in combination with gemcitabine):**

- May NOT exceed 10 cycles of therapy

**Ovarian Cancer (maintenance therapy):**

- Refer to Initial Approval Criteria for criteria

**Non-Squamous Non-Small Cell Lung Cancer (continuation therapy in combination with erlotinib):**

- Refer to Initial Approval Criteria for criteria

**DOSAGE/ADMINISTRATION**

| INDICATION | DOSE |
|---|---|
| CRC | Administer 5 to 10 mg/kg intravenously every 2 weeks OR 7.5 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity. |
| Small Bowel Adenocarcinoma | Administer 5 mg/kg intravenously every 2 weeks **OR** 7.5 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity. |
| NSCLC & Cervical Cancer | Administer 15 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity. |
| CNS Cancers | ▫ For disease treatment: Administer 10 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity.<br>▫ For symptom management: Administer 5 to 10 mg/kg intravenously every 2 weeks up to 12 weeks duration. |
| RCC | Administer 10 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity. |
| MPM | Administer 15 mg/kg intravenously every 3 weeks in combination with chemotherapy for up to 6 cycles. May follow with maintenance therapy with single-agent bevacizumab 15 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity. |
| Ovarian Cancer | Platinum-sensitive disease:<br>Administer 15 mg/kg intravenously every 3 weeks for up to 8 cycles when used with paclitaxel or up to 10 cycles when used with gemcitabine; followed by single-agent bevacizumab 15 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity.<br>Platinum-resistant disease:<br>Administer 10 mg/kg intravenously every 2 weeks **OR** 15 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity.<br>All other treatment settings:<br>Administer 5 to 10 mg/kg intravenously every 2 weeks **OR** 7.5 to 15 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity. |
| HCC | Administer 15 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity. |
| All Other Oncology Indications | Administer 5 to 10 mg/kg intravenously every 2 weeks OR 7.5 to 15 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity. |

**LENGTH OF AUTHORIZATION**

Coverage will be provided for six months and may be renewed (unless otherwise specified).

- For CNS cancers (symptom management), coverage will be provided for 12 weeks and may NOT be renewed.

**DOSAGE LIMITS**

**Max Units (per dose and over time) [HCPCS Unit]:**

**Oncology indications**

- Small Bowel Adenocarcinoma:
  - 60 billable units per 14 days
- CRC, CNS & RCC:
  - 120 billable units per 14 days
- All other indications:
  - 170 billable units per 21 days
  - 120 billable units per 14 days

## APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

## IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the Medical Policy and a health plan, the express terms of the health plan will govern.

## ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

## SOURCES

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**EFFECTIVE DATE** 6/2/2021

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