

Policy Name	Policy Number	Scope
Bevacizumab (Avastin and biosimilars Alymsys, Mvasi, Vegzelma, and Zirabev)	MP-RX-FP-13-23	<input checked="" type="checkbox"/> MMM MA <input checked="" type="checkbox"/> MMM Multihealth

Service Category

- | | |
|--|---|
| <input type="checkbox"/> Anesthesia | <input type="checkbox"/> Medicine Services and Procedures |
| <input type="checkbox"/> Surgery | <input type="checkbox"/> Evaluation and Management Services |
| <input type="checkbox"/> Radiology Procedures | <input type="checkbox"/> DME/Prosthetics or Supplies |
| <input type="checkbox"/> Pathology and Laboratory Procedures | <input checked="" type="checkbox"/> Part B Drugs |

Service Description

This document addresses the use of Bevacizumab agents (Avastin and the biosimilars Alymsys, Mvasi, Vegzelma, and Zirabev), approved by the Food and Drug Administration (FDA) for the treatment of oncologic conditions and other non-ophthalmologic indications. This document does not address the ophthalmologic uses of intraocular bevacizumab. Bevacizumab is a monoclonal antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF).

Background Information

Bevacizumab (Avastin) is a recombinant humanized monoclonal IgG1 antibody that inhibits angiogenesis by binding to and inhibiting the biological activity of human vascular endothelial growth factor (VEGF). VEGF is a protein that plays a critical role in the formation of new blood vessels (angiogenesis), which tumors need to grow and metastasize. By inhibiting VEGF, bevacizumab reduces the vascular supply to tumors, thereby inhibiting their growth.

Central Nervous System Cancer

While bevacizumab is FDA approved to treat recurrent glioblastoma, NCCN recommends bevacizumab in a number of central nervous system cancers which have failed to respond to radiation therapy. NCCN specifically recommends bevacizumab in high grade (World Health Organization [WHO] Grade III/IV) gliomas which would include: anaplastic astrocytoma, glioma, oligoastrocytoma, and oligodendroglioma; glioblastomas; and glioblastoma multiforme. NCCN also recommends bevacizumab as a single agent for meningiomas in certain circumstances. NCCN additionally recommends bevacizumab for management of symptoms driven by radiation therapy necrosis of the central nervous system.

Colorectal Cancer

Bevacizumab is FDA approved to treat metastatic colorectal cancer in combination with 5-fluorouracil-based chemotherapy, irinotecan, or oxaliplatin. The FDA label points out that bevacizumab should not be used in the adjuvant treatment of colon cancer based on two studies in stage II or III colon cancer which did not show efficacy of this agent in the adjuvant setting (de Gramont 2012, Allegra 2013). Bevacizumab in combination with chemotherapy may be used in the first-line setting or as subsequent therapy. Within the non-first line setting, NCCN guidelines and the FDA approved indication suggest continuing bevacizumab following progression on a

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bevacizumab-containing regimen. NCCN additionally recommends adding bevacizumab following progression on an initial regimen that did *not* contain bevacizumab. The CAIRO3 study (Simkens 2015) studied induction therapy (capecitabine, oxaliplatin, and bevacizumab) followed by either maintenance with bevacizumab + capecitabine or observation, followed by re- induction after first progression. The group receiving maintenance therapy showed prolonged second progression free survival, supporting the efficacy of bevacizumab after progression on bevacizumab in this disease state. NCCN guidelines also recommend the combination of bevacizumab with trifluridine and tipiracil (Lonsurf) in individuals who have progressed through standard therapies; including those who have previously received bevacizumab therapy.

Within the guidelines, NCCN recommends that appendiceal adenocarcinoma be treated with chemotherapy according to colon cancer guidelines. Similarly, it is recommended that anal adenocarcinoma, a rare histologic form of anal cancer, may be treated according to guidelines for rectal cancer. Guidelines for squamous cell anal cancer, the most common type of anal cancer, do not currently include bevacizumab among recommended treatments.

Mesothelioma

NCCN recommends bevacizumab in the treatment of unresectable malignant pleural mesothelioma. It is recommended as first line in combination with pemetrexed and either cisplatin or carboplatin followed by single agent bevacizumab until disease progression. Studies cited in these recommendations included patients with Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2 with no evidence of bleeding or thrombosis (Zalcman 2016, Ceresoli 2013).

Cervical, Vulvar, and Endometrial Carcinoma

Bevacizumab is FDA approved to treat persistent, recurrent, or metastatic cervical cancer in combination with paclitaxel and topotecan or paclitaxel and cisplatin. This was approved based on a study that excluded patients that were candidates for curative therapy by means of pelvic exenteration (Tewari 2014). NCCN additionally recommends bevacizumab in combination with paclitaxel and either cisplatin, carboplatin, or topotecan for the treatment of advanced, recurrent, or metastatic disease. Keytruda (pembrolizumab) is FDA approved, in combination with chemotherapy and bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer. NCCN also recommends bevacizumab in advanced, recurrent, or metastatic vulvar cancer in combination with paclitaxel and either carboplatin (2B) or cisplatin (2A). Within the uterine neoplasms NCCN guidelines, it is recommended that bevacizumab be used for endometrial carcinoma in combination with paclitaxel and carboplatin for advanced or recurrent disease. The evidence behind this recommendation (Rose 2017) also studied bevacizumab maintenance after original combination with paclitaxel + carboplatin and found a favorable overall response rate. Bevacizumab is also recommended as single agent therapy for disease that has progressed on prior cytotoxic chemotherapy, but recommendation was based on a phase 2 trial of 52 participants.

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Hepatocellular Carcinoma

Bevacizumab is FDA approved in combination with atezolizumab for the treatment of unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy. NCCN considers this combination a preferred first line treatment for individuals who have Child-Pugh Class A liver function based on the clinical trial population.

Non-Small Cell Lung Cancer (NSCLC)

Bevacizumab is FDA approved for the treatment of unresectable, locally advanced, recurrent, or metastatic non-squamous NSCLC in combination with carboplatin and paclitaxel. For initial therapy, NCCN also recommends bevacizumab in combination with carboplatin+paclitaxel, carboplatin+pemetrexed, or cisplatin+pemetrexed (i.e. platinum based therapy and a taxane or pemetrexed) OR in combination with atezolizumab, carboplatin, and paclitaxel for recurrent, advanced, or metastatic disease in those with no history of hemoptysis. It should be noted that NCCN recommends these treatments as first-line in patients without treatment-driving mutations. In the presence of these mutations, patients should be treated with targeted therapy first (i.e. tyrosine kinase inhibitors).

NCCN also recommends bevacizumab as maintenance therapy as a single agent, or in combination with atezolizumab or pemetrexed. However, the trial that assessed the efficacy in combination with pemetrexed (Barlesi 2013, 2014) found that although participants had longer progression free survival (PFS), the 1-year and 2-year overall survival differences did not meet statistical significance. In addition, the health-related quality of life (HRQOL) was not improved in the bevacizumab + pemetrexed arm (Rittmeyer 2013). Consequently, there is a lack of evidence in the peer-reviewed literature to support the efficacy of this combination over bevacizumab alone.

Ovarian Cancer

Bevacizumab is FDA approved to treat epithelial ovarian, fallopian tube, or primary peritoneal cancer, in combination with certain chemotherapy regimens, followed by bevacizumab monotherapy until disease progression. Bevacizumab is also approved as adjuvant therapy after surgical resection in combination with chemotherapy. NCCN also recommends bevacizumab as a single agent for recurrent disease that is either platinum-sensitive or platinum-resistant. NCCN only recommends bevacizumab as part of combination chemotherapy when used in the adjuvant setting. In contrast to NCCN recommendations for maintenance therapy for colon cancer, it is specifically not recommended as maintenance therapy for ovarian cancer in patients who did not receive a primary treatment regimen containing bevacizumab. Bevacizumab is FDA approved as a single agent for maintenance therapy. NCCN additionally recommends the combination with olaparib as maintenance therapy for those with BRCA 1/2 mutation (category 1) or for BRCA wild-type or unknown (category 2A). The trial investigating this use (Ray-coquard 2019) showed progression free survival (PFS) advantage in those with *and* without BRCA mutations, with a more pronounced advantage in BRCA+ tumors. In patients with homologous recombination deficiency (HRD)- positive tumors, PFS was extended in the combination (bevacizumab + olaparib) group compared to bevacizumab alone. HRD includes but is not limited to tumors with BRCA mutations. Those

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with HRD-positive, BRCA-negative disease also showed a PFS advantage leading to FDA approval in the expanded HRD-positive population.

NCCN also recommends the use of bevacizumab in the neoadjuvant setting for ovarian cancer. However, it is noted that neoadjuvant chemotherapy remains controversial and should only be considered in those with advanced, unresectable disease who have been assessed by a gynecologic oncologist. In addition, the only literature cited involving bevacizumab is an unpublished, phase II abstract.

NCCN recommends combination use of bevacizumab and niraparib in recurrent platinum-sensitive disease, but this use is under investigation (Mirza 2019). NCCN notes that single agent bevacizumab or single agent niraparib are preferred in this setting.

Renal Cell Carcinoma

Bevacizumab is FDA approved to treat metastatic renal cell carcinoma in combination with interferon alfa. NCCN also recommends bevacizumab as a single agent or in combination with everolimus in non-clear cell histology as well as in combination with erlotinib for non-clear cell histology in selected patients with advanced papillary renal cell carcinoma including hereditary leiomyomatosis and renal cell cancer (HLRCC).

Soft Tissue Sarcoma

NCCN recommends that bevacizumab be used as a single agent treatment of angiosarcoma, a vascular tumor which is a type of soft tissue sarcoma. NCCN also recommends that bevacizumab be used in combination with temozolomide for the treatment of solitary fibrous tumor, another type of soft tissue sarcoma.

Small Bowel Adenocarcinoma

NCCN recommends that bevacizumab be used in combination with 5-fluorouracil-based (including capecitabine) regimen as initial therapy for advanced or metastatic small bowel adenocarcinoma. This use also includes ampullary adenocarcinoma.

Biosimilar Agents

Biosimilar products must be highly similar to the reference product and there must be no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. Biosimilars must utilize the same mechanism of action (MOA), route of administration, dosage form and strength as the reference product; and the indications proposed must have been previously approved for the reference product. The potential exists for a biosimilar product to be approved for one or more indications for which the reference product is licensed based on extrapolation of data intended to demonstrate biosimilarity in one indication. Sufficient scientific justification for extrapolating data is necessary for FDA approval. Factors and issues that should be considered for extrapolation include the MOA for each indication, the pharmacokinetics, bio-

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distribution, and immunogenicity of the product in different patient populations, and differences in expected toxicities in each indication and patient population.

Alymsys (bevacizumab-maly), Mvasi (bevacizumab-awwb) and Zirabev (bevacizumab-bvzr) are FDA approved biosimilar agents to Avastin. They share the same FDA approved uses as Avastin, with some exceptions. All of the biosimilars are not approved for Hepatocellular Carcinoma, Alymsys is not approved for adjuvant treatment of colon cancer, and Mvasi is not approved for Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer. We are awaiting the updates on Alymsys from NCCN. At this time, NCCN guidelines do support the use of both Mvasi and Zirabev biosimilars in these cancers. FDA approval of Mvasi was based on analytical data, a clinical pharmacology program including a pharmacokinetic study comparing Mvasi, Avastin, and EU-approved bevacizumab, and a single comparative clinical study. The clinical study was a randomized, double-blind, comparative clinical study of 642 patients with non-small cell lung cancer (NSCLC) receiving platinum-based chemotherapy. Finally, approval was supported through scientific justification for extrapolation of biosimilarity to the other indications which were not directly studied in Mvasi. Zirabev was also compared to EU-approved bevacizumab in a double-blind, randomized, comparative phase 3 study of 719 patients with NSCLC. Results of this study have not been published to date, but Zirabev did received FDA approval for biosimilarity in all indications besides Hepatocellular Carcinoma. Since all Avastin biosimilars, Alymsys, Mvasi and Zirabev have demonstrated biosimilarity to Avastin for FDA indications, it is reasonable that biosimilarity can be extrapolated to other FDA indications, and off-label indications, as well. NCCN guidelines support the use of biosimilar agents for all FDA approved and off label uses of bevacizumab.

Definitions and Measures

- 5FU-based: A treatment regimen that includes fluorouracil (5-FU) or capecitabine.
- Adenocarcinoma: Cancer originating in cells that line specific internal organs and that have gland-like (secretory) properties
- Adjuvant therapy: Treatment given after the primary treatment to increase the chances of a cure; may include chemotherapy, radiation, hormone or biological therapy.
- Anal cancer: Cancer originating in the tissues of the anus; the anus is the opening of the rectum (last part of the large intestine) to the outside of the body.
- Colon cancer: Cancer originating in the tissues of the colon (the longest part of the large intestine). Most colon cancers are adenocarcinomas that begin in cells that make and release mucus and other fluids.
- Colorectal cancer: Cancer originating in the colon (the longest part of the large intestine) or the rectum (the last several inches of the large intestine before the anus).
- ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual’s disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:
 - 0 = Fully active, able to carry on all pre-disease performance without restriction

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- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
- 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5 = Dead
- **Hormonal therapy:** Treatment that adds, blocks, or removes hormones. Agents that slow or stop the growth of certain cancers, synthetic hormones or other drugs may be given to block the body's natural hormones.
- **Line of Therapy:**
 - First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
 - Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
 - Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.
- **Locally advanced cancer:** Cancer that has spread only to nearby tissues or lymph nodes.
- **Maintenance therapy:** Designed to maintain a condition to prevent a relapse.
- **Melanoma:** A type of cancer that begins in the melanocytes. Melanoma is also referred to as malignant melanoma and cutaneous melanoma.
- **Metastasis:** The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.
- **Neoadjuvant therapy:** Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy.
- **Non-small cell lung cancer:** A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of non-small cell lung cancer are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma.
- **One line of therapy:** Single line of therapy.
- **Primary treatment:** The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. Also called first-line therapy, induction therapy, and primary therapy.
- **Rectal cancer:** Cancer originating in tissues of the rectum (the last several inches of the large intestine closest to the anus).
- **Refractory Disease:** Illness or disease that does not respond to treatment.
- **Relapse or recurrence:** After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.
- **Taxane:** A type of mitotic inhibitor and antimicrotubule drug used to treat cancer that blocks cell growth by stopping mitosis (cell division).

Medical Policy

Healthcare Services Department

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- Unresectable: Unable to be removed with surgery.
- Vascular endothelial growth factor (VEGF): A substance made by cells that stimulates new blood vessel formation.

Approved Indications

	Avastin (bevacizumab)	AlymSYS (bevacizumab- maly)	Mvasi (bevacizumab- awwb)	Vegzelma (bevacizumab- adcd)	Zirabev (bevacizumab- bvzr)
Central Nervous System Cancer	Y	Y	Y	Y	Y
Cervical Cancer	X	X	X	X	X
Colorectal Cancer	X	X	X	X	X
Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	X	X	Y	X	X
Hepatobiliary Carcinoma	X	Y	Y	Y	Y
Malignant Mesothelioma	Y	Y	Y	Y	Y
Non-small Cell Lung Cancer	X	X	X	X	X
Recurrent Glioblastoma	X	X	X	X	X
Renal Cell Carcinoma	X	X	X	X	X
Small Bowel Adenocarcinoma	Y	Y	Y	Y	
Soft Tissue Sarcoma	Y	Y	Y	Y	Y
Vulvar Cancer	Y	Y	Y	Y	Y

X= FDA Approved Use; Y= Off-label indication

Other Uses

- Bevacizumab is not FDA approved or supported by NCCN recommendations for treatment of *prostate cancer, carcinoid tumors, metastatic melanoma or metastatic adenocarcinoma of the pancreas*. In addition, NCCN notes that studies have shown that combination with more than one biologic agent is not associated with improved outcomes and can cause increased toxicity, specifically regarding the addition of Erbitux (cetuximab) or Vectibix (panitumumab) to a bevacizumab-containing regimen (Tol 2009, Hecht 2009). NCCN strongly recommends against the use of therapy involving concurrent combination of an anti-

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EGFR agent and an anti-VEGF agent. NCCN also gives a category 2A recommendation for combination use with atezolizumab as first line therapy in those with NSCLC and targeted oncogene (i.e., BRAF, MET, or NTRK) positive tumors in certain circumstances. NCCN recommends the combination with pemetrexed as subsequent therapy after prior PD-1/PD-L1 inhibitor but no prior platinum- containing chemotherapy. Published data for these uses is lacking.

- B. *Neurofibromatosis type 2 (NF2)* is a genetic condition characterized by benign tumors which can grow and cause progressive hearing loss. Management typically includes surgery; and there are treatment modalities, such as bevacizumab, under investigation. Evidence largely includes retrospective reviews and small case series. A more recent systematic review (Lu 2019) pooled data from a number of sources for the use of bevacizumab in vestibular schwannoma caused by NF2. Of 162 evaluable tumors, response included partial regression in 41% [95% CI 31- 51%], no change in 47% [95% CI 39-55%], and tumor progression in 7% [95% CI 1-15%]. In addition, hearing improvement only occurred in 20% [95% CI 9-33%] and serious toxicity occurred in 17% [CI 10-26%]. The optimal timing, ideal clinical candidate, and long term safety and efficacy for bevacizumab in NF2 is unknown.
- C. *Hereditary hemorrhagic telangiectasia (HHT or Osler-Weber-Rendu syndrome)* causes inappropriate blood vessel growth leading to a variety of clinical manifestations, including recurrent bleeding (epistaxis). Reported evidence for bevacizumab in this disease is limited including case reports, retrospective reviews, and observational studies with short follow-up. Reports include intranasal injection, intranasal spray, and IV bevacizumab (Steinger 2018, Dupuis- Girod 2016, Iyer 2018). Randomized controlled trials are needed to confirm the effectiveness, safety, and patient selection for bevacizumab in HHT.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9035	Injection, bevacizumab, 10 mg [Avastin]
Q5107	Injection, bevacizumab-awwb, biosimilar, (Mvasi), 10 mg
Q5118	Injection, bevacizumab-bvzr, biosimilar, (Zirabev), 10 mg
Q5126	Injection, bevacizumab-maly, biosimilar, (Alymsys), 10 mg
Q5129	Injection, bevacizumab-adcd, biosimilar, (Vegzelma) 10 mg
ICD-10	Description
C17.0-C17.9	Malignant neoplasm of small intestine
C18.0-C20	Malignant neoplasm of colon, rectosigmoid junction, rectum
C21.2-C21.8	Malignant neoplasm of cloacogenic zone, overlapping sites of rectum, anus

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C22.0-C22.9	Hepatocellular carcinoma
C24.1	Malignant neoplasm of ampulla of Vater
C33	Malignant neoplasm of trachea
C34.00-C34.92	Malignant neoplasm of bronchus and lung
C45.0-C45.9	Mesothelioma
C48.0-C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C49.0-C49.9	Malignant neoplasm of other connective and soft tissue [angiosarcoma, hemangiopericytoma]
C51.0-C51.9	Malignant neoplasm of vulva
C53.0-C53.9	Malignant neoplasm of cervix uteri
C54.0-C55	Malignant neoplasm of corpus uteri, uterus part unspecified
C56.1-C56.9	Malignant neoplasm of ovary
C57.00-C57.9	Malignant neoplasm of other and unspecified female genital organs
C64.1-C64.9	Malignant neoplasm of kidney, except renal pelvis
C65.1-C65.9	Malignant neoplasm of renal pelvis
C71.0-C71.9	Malignant neoplasm of brain
C78.00-C78.02	Secondary malignant neoplasm of lung
C78.4-C78.5	Secondary malignant neoplasm of small intestine, large intestine and rectum
C79.00-C79.02	Secondary malignant neoplasm of kidney and renal pelvis
C79.60-C79.62	Secondary malignant neoplasm of ovary
C79.81	Secondary malignant neoplasm of breast
I67.89	Other cerebrovascular disease [radiation necrosis]
T66.XXXS	Radiation sickness, unspecified, sequela
Z51.11-Z51.12	Encounter for antineoplastic chemotherapy, immunotherapy
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.048	Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus
Z85.068	Personal history of other malignant neoplasm of small intestine
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.3	Personal history of malignant neoplasm of breast
Z85.43	Personal history of malignant neoplasm of ovary
Z85.528	Personal history of malignant neoplasm of kidney
Z85.841	Personal history of malignant neoplasm of brain

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Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member’s medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Bevacizumab (Avastin and biosimilars Alymsys, Mvasi, Vegzelma, and Zirabev)

A. Criteria For Initial Approval

Requests for Avastin (bevacizumab), Alymsys (bevacizumab-maly), Mvasi (bevacizumab-awwb), Vegzelma (bevacizumab-adcd), or Zirabev (bevacizumab-bvzr) may be approved if the following criteria are met:

- i. Individual has a diagnosis of Central Nervous System- Primary Tumor and the following are met (Label, NCCN 2A):
 - A. Individual has failed radiation therapy; **AND**
 - B. Bevacizumab is used in a single line of therapy; **AND**
 - C. The tumor to be treated is World Health Organization (WHO) Grade III/IV glioma which includes but is not limited to:
 - I. Anaplastic astrocytoma; **OR**
 - II. Anaplastic glioma; **OR**
 - III. Ependymoma, progressive or recurrent; **OR**
 - IV. Glioblastoma; **OR**
 - V. Glioblastoma multiforme; **OR**
 - VI. High-grade glioma, recurrent;

OR
- ii. Individual is using bevacizumab to treat symptomatic post-radiation necrosis of the central nervous system (NCCN 2A);

OR

- iii. Individual has a diagnosis of advanced or metastatic colon, rectal, or colorectal, appendiceal, or anal adenocarcinoma and the following are met (Label, NCCN 2A):
 - A. Individual has not progressed on more than two lines of a bevacizumab-containing chemotherapy regimen (Simkens 2015); **AND**
 - B. Bevacizumab is used in combination with 5-fluorouracil-based (including capecitabine) chemotherapy, irinotecan, or oxaliplatin; **OR**
 - C. Bevacizumab is used in combination with trifluridine and tipiracil (Lonsurf) in patients who have progressed through standard therapies;

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OR

iv. Individual has a diagnosis of advanced or metastatic small bowel adenocarcinoma, including ampullary adenocarcinoma, and the following are met (NCCN 2A):

A. Bevacizumab is used in combination with 5-fluorouracil-based (including capecitabine) regimen;

AND

B. Bevacizumab is used as initial therapy or subsequent therapy for disease progression;

AND

C. Bevacizumab is used in a single line of therapy;

OR

v. Individual has a diagnosis of Vulvar Cancer and the following are met (NCCN 2A):

A. Individual has advanced, recurrent, or metastatic disease; **AND**

B. Bevacizumab is used in combination with paclitaxel *and* either cisplatin or carboplatin;

AND

C. Bevacizumab is used in a single line of therapy;

OR

vi. Individual has a diagnosis of Cervical Cancer and the following are met (Label, NCCN 1, 2A):

A. Individual has persistent, recurrent, or metastatic disease; **AND**

B. Bevacizumab is used in a single line of therapy; **AND**

C. Bevacizumab is used in combination with paclitaxel *and* either topotecan, cisplatin, or carboplatin for disease that is not amenable to curative treatment with surgery or radiotherapy (Tewari 2014); **OR**

D. Bevacizumab is used in combination with pembrolizumab, paclitaxel, and a platinum agent; **OR**

E. Bevacizumab is used as a single agent for second-line or subsequent therapy;

OR

vii. Individual has a diagnosis of Endometrial Carcinoma and the following are met (NCCN 2A):

A. Individual has advanced or recurrent disease; **AND**

B. Bevacizumab is used in combination with carboplatin and paclitaxel;

OR

C. Following combination therapy with carboplatin and paclitaxel, bevacizumab is used as single-agent maintenance therapy until disease progression or prohibitive toxicity.

OR

viii. Individual has a diagnosis of Malignant Pleural or Peritoneal Mesothelioma and the following are met (NCCN 2A):

A. Bevacizumab is used as first-line therapy for unresectable disease when:

1. Used in combination chemotherapy with pemetrexed *and* either cisplatin or carboplatin;

AND

2. Individual has an Eastern Cooperative Oncology Group performance status of 0-2 and no history of bleeding or thrombosis (Zalcman 2016, Ceresoli 2013);

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OR

- B. Bevacizumab is used as maintenance therapy for unresectable disease, as a single agent, when:
 1. Bevacizumab was previously administered as an agent in a first-line combination chemotherapy regimen; **AND**
 2. Bevacizumab is used until disease progression*;
 ***Note:** Once disease progression has occurred, bevacizumab is not to be re-instituted

OR

- C. Bevacizumab is used as subsequent systemic therapy, if immunotherapy was administered as first- line treatment in combination with pemetrexed and cisplatin or carboplatin (in those not eligible for cisplatin);

OR

- ix. Individual has a diagnosis of advanced, recurrent, or metastatic non-squamous Non-Small Cell Lung Cancer (NSCLC) and the following are met:
 - A. Individual has a current Eastern Cooperative Oncology Group performance status of 0-2, no history of hemoptysis; **AND**
 - B. Individual is using in combination with platinum-based therapy and either a taxane or pemetrexed;
AND
 - C. Individual is using for one of the following:
 1. As first-line therapy (Label); **OR**
 2. As subsequent therapy if disease has progressed during or following treatment with a targeted agent for the expressed oncogene (including but not limited to, kinase inhibitors that target EGFR, KRAS, ALK, ROS1, BRAF, NTRK, RET, ERBB2 (HER2) or MET mutations) (NCCN 2A);

OR

- x. Individual has a diagnosis of advanced, recurrent, or metastatic non-squamous Non-Small Cell Lung Cancer (NSCLC) and the following are met (NCCN 2A):
 - A. Individual has a current Eastern Cooperative Oncology Group performance status of 0-2, no history of hemoptysis; **AND**
 - B. Individual is using in combination with platinum-based therapy, a taxane, and atezolizumab; **AND**
 - C. Individual is using for one of the following:
 1. As first line therapy if individual does not have presence of actionable molecular markers* (see note below this section);
OR
 2. As subsequent therapy if disease has progressed during or following treatment with a targeted agent for the expressed oncogene (including but not limited to, kinase inhibitors that target EGFR, KRAS, ALK, ROS1, BRAF, NTRK, RET, ERBB2 (HER2) or MET mutations) (NCCN 2A);

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***Note:** Actionable molecular markers include but not limited to EGFR, KRAS, ALK, ROS1, BRAF, NTRK, ERBB2 (HER2), MET and RET mutations. The NCCN panel recommends testing prior to initiating therapy to help guide appropriate treatment. If there is insufficient tissue to allow testing for all of these markers, 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 (NCCN 2A).

OR

- xi. Individual has a diagnosis of non-squamous Non-Small Cell Lung Cancer (NSCLC) and the following are met:
 - A. Individual is using as maintenance therapy for advanced, recurrent, or metastatic disease; **AND**
 - B. Bevacizumab was previously administered as an agent in a first-line combination chemotherapy regimen; **AND**
 - C. Individual is using as a single agent or in combination with atezolizumab; **AND**
 - D. May be used until disease progression;

OR

- xii. Individual has a diagnosis of Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer and the following are met:
 - A. Bevacizumab is used for advanced or metastatic disease following initial surgical resection (as adjuvant therapy) when (NCCN 1):
 - 1. Used in combination with other chemotherapy; **AND**
 - 2. Used in a single line of therapy;

OR

- B. Bevacizumab is used for recurrent, metastatic disease that is relapsed or refractory when:
 - 1. Used as a single agent or in combination with other chemotherapy (NCCN 2A, Label); **AND**
 - 2. Used in a single line of therapy;

OR

- xiii. Individual has a diagnosis of Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer and the following are met:
 - A. Bevacizumab is used as maintenance therapy for advanced, recurrent, or metastatic disease; **AND**
 - B. Was previously administered as an agent in a combination chemotherapy regimen ; **AND**
 - C. Used as a single agent; **AND**
 - D. May be used until disease progression;

OR

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- E. Used in combination with olaparib when the following applies (NCCN 1, Lynparza label):
 - 1. Individual has achieved complete clinical remission (CR) or partial remission (PR) to primary therapy; **AND**
 - 2. Individual has a homologous recombination deficiency (HRD) positive status defined by either;
 - a. Deleterious germline and/or somatic BRCA 1/2 mutation with test results confirmed; **OR**
 - b. Genomic instability;

OR

- xiv. Individual has a diagnosis of Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer and the following are met (NCCN 2A):
 - A. Bevacizumab is used in combination with niraparib (Zejula); **AND**
 - B. Individual is using as maintenance therapy for stage II-IV high-grade serous or grade 2/3 endometroid carcinosarcoma; **AND**
 - C. Individual is in complete or partial response; **AND**
 - D. Bevacizumab is used following primary therapy (which included bevacizumab) in those with a germline or somatic BRCA 1/2 mutation;

OR

- xv. Individual has a diagnosis of Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer and the following are met (NCCN 1, 2A):
 - A. Bevacizumab is used as neoadjuvant therapy; **AND**
 - B. Using in combination with carboplatin and either paclitaxel or docetaxel OR with oxaliplatin and docetaxel; **AND**
 - C. Individual is a poor surgical candidate or has a low likelihood of optimal cytoreduction;

OR

- xvi. Individual has a diagnosis of Hepatocellular Carcinoma and the following are met (Label, NCCN 1):
 - A. Individual has advanced, unresectable, or metastatic disease; **AND**
 - B. Individual is using for first-line treatment in combination with atezolizumab; **AND**
 - C. Individual has Child-Pugh Class A liver function (NCCN 2A); **AND**
 - D. Individual has an ECOG performance status of 0-2; **AND**
 - E. Bevacizumab may be used until disease progression;

OR

- xvii. Individual has a diagnosis of Renal Cell Carcinoma (RCC) and the following are met:
 - A. Individual has metastatic RCC and bevacizumab is used in combination with interferon alpha (Label); **OR**
 - B. Individual has relapsed or medically unresectable stage IV disease when:
 - 1. Bevacizumab is used as a single agent in those with non-clear cell histology (NCCN 2A);

OR

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2. Bevacizumab is used in combination with erlotinib or everolimus in those with non-clear cell histology (including papillary RCC and hereditary leiomyomatosis and RCC [HLRCC]) (NCCN 2A);

OR

- xviii. Individual has a diagnosis of Soft Tissue Sarcoma and the following are met (NCCN 2A):
 - A. Bevacizumab is used as a single agent for treatment of angiosarcoma; **OR**
 - B. Bevacizumab is used in combination with temozolomide for the treatment of solitary fibrous tumor.

B. Criteria For Continuation of Therapy

- i. MMM considers continuation of bevacizumab (Avastin), bevacizumab-maly (Almysys), bevacizumab-awwb (Mvasi), bevacizumab-adcd (Vegzelma), and bevacizumab-bvzr (Zirabev) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen, and the recommended duration of therapy has not been exceeded. The following information should be submitted for reauthorization:
 - A. A current oncology note documenting the patient’s response to treatment showing no progression of disease.
 - B. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results (every six months).
- ii. For stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer following initial surgical resection (as adjuvant): Bevacizumab use should be limited to a maximum of 22 cycles.
- iii. For all other oncologic conditions: Bevacizumab may be approved until disease progression or unacceptable toxicity.
 - A. For colorectal cancer: Bevacizumab continuation is considered medically necessary in patients who have progressed on up to two lines of a bevacizumab-containing chemotherapy regimen (after disease progression). In this scenario, continuation of bevacizumab may be approved in combination with:
 1. 5-fluorouracil-based (including capecitabine) chemotherapy, irinotecan, or oxaliplatin; **OR**
 2. Trifluridine and tipiracil (Lonsurf) in patients who have progressed through standard therapies.

C. Authorization Duration

- i. Initial Approval Duration: Up to 6 months
- ii. Reauthorization Approval Duration: Up to 6 months

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D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

- i. All other non-ophthalmologic indications not included above (Section A: Criteria for Initial Approval); **OR**
- ii. Individuals is using as adjuvant therapy following surgery for stage II or III adenocarcinoma of the colon; **OR**
- iii. Individual is using bevacizumab in combination with the same irinotecan-based regimen that was previously used in combination with ziv-aflibercept; **OR**
- iv. Individual is using for treatment of a single condition with concomitant use of other targeted biologic agents (including, cetuximab, panitumumab, trastuzumab, lapatinib, and ziv-aflibercept); **OR**
- v. Individual is using for the treatment of any of the following:
 - A. Prostate cancer; **OR**
 - B. Carcinoid tumors; **OR**
 - C. Metastatic melanoma; **OR**
 - D. Metastatic adenocarcinoma of the pancreas; **OR**
 - E. Metastatic breast cancer, second line therapy or greater, for example when progression noted following anthracycline and taxane chemotherapy; **OR**
 - F. Neurofibromatosis type 2; **OR**
 - G. AIDS-related Kaposi sarcoma; **OR**
 - H. Pseudoprogression of glioblastoma

Limits or Restrictions

A. Therapeutic Alternatives

This medical policy may be subject to Step Therapy. Please refer to the document published on the MMM Website: <https://www.mmm-pr.com/planes-medicos/formulario-medicamentos>

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B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Bevacizumab dosing is calculated based on the patient’s weight. Quantity limits should align with FDA-approved dosing for each diagnosis.

Indication	Limit
Metastatic colorectal cancer	<ul style="list-style-type: none"> • 5 mg/kg every 2 weeks with bolus-IFL • 10 mg/kg every 2 weeks with FOLFOX4 • 5 mg/ kg every 2 weeks or 7.5 mg/kg every 3 weeks with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy after progression on a first-line bevacizumab product- containing regimen
First-line non-squamous non-small cell lung cancer	15 mg/kg every 3 weeks with carboplatin and paclitaxel
Recurrent glioblastoma	10 mg/kg every 2 weeks
Metastatic renal cell carcinoma	10 mg/kg every 2 weeks with interferon alfa
Persistent, recurrent, or metastatic cervical cancer	15 mg/kg every 3 weeks with paclitaxel and cisplatin, or paclitaxel and topotecan
Stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer following initial surgical resection	15 mg/kg every 3 weeks with carboplatin and paclitaxel for up to 6 cycles, followed by 15 mg/kg every 3 weeks as a single agent, for a total of up to 22 cycles
Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer	<ul style="list-style-type: none"> • 10 mg/kg every 2 weeks with paclitaxel, pegylated liposomal doxorubicin, or topotecan given every week • 15 mg/kg every 3 weeks with topotecan given every 3 weeks
Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer	<ul style="list-style-type: none"> • 5 mg/kg every 3 weeks with carboplatin and paclitaxel for 6-8 cycles, followed by 15 mg/kg every 3 weeks as a single agent

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Indication	Limit
	<ul style="list-style-type: none"> 15 mg/kg every 3 weeks with carboplatin and gemcitabine for 6-10 cycles, followed by 15 mg/kg every 3 weeks as a single agent
Hepatocellular Carcinoma	15 mg/kg after administration of 1,200 mg of atezolizumab every 3 weeks
Exceptions	
None	

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 - iv. Cervical Cancer. V1.2023. Revised January 6, 2023.
 - v. Colon Cancer. V1.2023. Revised March 29, 2023
 - vi. Hepatocellular Carcinoma. V1.2023. Revised March 10, 2023.
 - vii. Malignant Peritoneal Mesothelioma. V1. 2023. December 15, 2022.
 - viii. Malignant Pleural Mesothelioma. V1.2023. December 15, 2022.
 - ix. Uterine Neoplasms. 1.2023. December 22, 2022.
 - x. Ovarian Cancer. 1.2023. Revised December 22 2022.
 - xi. Pediatric Central Nervous System Cancers. V2.2023. Revised October 31, 2022.
 - xii. Kidney Cancer. V4.2023. Revised January 18, 2023.
 - xiii. Soft tissue sarcoma. V1.2023. Revised March 13, 2023.
 - xiv. Small Bowel Adenocarcinoma. V1.2023. Revised January 9, 2023.
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Policy History

Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Policy Inception	Elevance Health’s Medical Policy adoption.	N/A	11/30/2023

Revised: 09/28/2023