Medical Policy

BlueCross BlueShield Kansas
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Title: Bevacizumab Medical Drug Criteria Program Summary for Oncological Applications

Professional / Institutional
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Current Effective Date: December 23, 2024

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FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Alymsys® (bevacizumab-maly) Intravenous injection	**Metastatic colorectal cancer** • In combination with intravenous 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 bevacizumab product-containing regimen Limitations of Use: Alymsys is not indicated for adjuvant treatment of colon cancer		29

Agent(s)	FDA Indication(s)	Notes	Ref#
	Non-squamous non-small cell lung cancer • In combination with carboplatin and paclitaxel for first-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic non-squamous non-small-cell lung cancer **Recurrent Glioblastoma in adults** **Metastatic renal cell carcinoma** • In combination with interferon alfa **Persistent, recurrent, or metastatic cervical cancer** • In combination with paclitaxel and cisplatin, or paclitaxel and topotecan **Epithelial ovarian, fallopian tube, or primary peritoneal cancer** • In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens		
Avastin® (bevacizumab) Intravenous injection	**Metastatic colorectal cancer** • In combination with intravenous 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 bevacizumab product-containing regimen Limitations of Use: Avastin is not indicated for adjuvant treatment of colon cancer **Non-squamous non-small cell lung cancer** • In combination with carboplatin and paclitaxel for first-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic non-squamous non-small-cell lung cancer (NSCLC) **Recurrent glioblastoma in adults** **Metastatic renal cell carcinoma**		1

Agent(s)	FDA Indication(s)	Notes	Ref#
	• In combination with interferon alfa **Persistent, recurrent, or metastatic cervical cancer** • In combination with paclitaxel and cisplatin, or paclitaxel and topotecan **Epithelial ovarian, fallopian tube or primary peritoneal cancer** • In combination with carboplatin and paclitaxel, followed by Avastin as a single agent, for stage III or IV disease following initial surgical resection • In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens • In combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by Avastin as a single agent, for platinum-sensitive recurrent disease **Hepatocellular carcinoma** • In combination with atezolizumab for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy		
Mvasi® (bevacizumab-awwb) Intravenous injection	**Metastatic colorectal cancer** • In combination with intravenous 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 bevacizumab product-containing regimen Limitations of Use: Mvasi is not indicated for adjuvant treatment of colon cancer **Non-squamous non-small cell lung cancer** • In combination with carboplatin and paclitaxel for first-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic non-squamous non-small-cell lung cancer (NSCLC) **Recurrent glioblastoma in adults**		2

Agent(s)	FDA Indication(s)	Notes	Ref#
	Metastatic renal cell carcinoma • In combination with interferon alfa **Persistent, recurrent, or metastatic cervical cancer** • In combination with paclitaxel and cisplatin, or paclitaxel and topotecan **Epithelial ovarian, fallopian tube or primary peritoneal cancer** • In combination with carboplatin and paclitaxel, followed by Mvasi as a single agent, for stage III or IV disease following initial surgical resection • In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens • In combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by Mvasi as a single agent, for platinum-sensitive recurrent disease		
Vegzelma® (bevacizumab-adcd) Intravenous injection	**Metastatic colorectal cancer** • In combination with intravenous 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 bevacizumab product-containing regimen Limitations of Use: Vegzelma is not indicated for adjuvant treatment of colon cancer **Non-squamous non-small cell lung cancer** • In combination with carboplatin and paclitaxel for first-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic non-squamous non-small-cell lung cancer (NSCLC) **Recurrent glioblastoma in adults** **Metastatic renal cell carcinoma** • In combination with interferon alfa		30

Agent(s)	FDA Indication(s)	Notes	Ref#
	Persistent, recurrent, or metastatic cervical cancer • In combination with paclitaxel and cisplatin, or paclitaxel and topotecan **Epithelial ovarian, fallopian tube or primary peritoneal cancer** • In combination with carboplatin and paclitaxel, followed by Vegzelma as a single agent, for stage III or IV disease following initial surgical resection • In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens • In combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by Vegzelma as a single agent, for platinum-sensitive recurrent disease		
Zirabev® (bevacizumab-bvzr) Intravenous injection	**Metastatic colorectal cancer** • In combination with intravenous 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 bevacizumab product-containing regimen Limitations of Use: Zirabev is not indicated for adjuvant treatment of colon cancer **Non-squamous non-small cell lung cancer** • In combination with carboplatin and paclitaxel for first-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic non-squamous non-small-cell lung cancer (NSCLC) **Recurrent glioblastoma in adults** **Metastatic renal cell carcinoma** • In combination with interferon alfa **Persistent, recurrent, or metastatic cervical cancer** • In combination with paclitaxel and cisplatin, or paclitaxel and topotecan		11

Agent(s)	FDA Indication(s)	Notes	Ref#
	Epithelial ovarian, fallopian tube or primary peritoneal cancer • In combination with carboplatin and paclitaxel, followed by Zirabev as a single agent, for stage III or IV disease following initial surgical resection • In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens • In combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by Zirabev as a single agent, for platinum-sensitive recurrent disease		

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Cervical cancer	While cervical cancer rates are decreasing in the United States following the introduction of screening, it remains a major world health problem for assigned female at birth (AFAB) individuals. It is the fourth most common cancer in AFAB individuals worldwide (and leading cause of cancer death in AFAB individuals) with 85% of cases occurring in developing countries because screening is not available to many. Persistent human papillomavirus (HPV) infection is the most important factor in the development of cervical cancer. In countries with a high incidence of cervical cancer, the prevalence of chronic HPV is approximately 10% to 20%, whereas the prevalence in low-incidence countries is 5% to 10%. Immunization against HPV prevents infection with the types of HPV against which the vaccine is designed and, thus, is expected to prevent specific HPV cancer. Other epidemiologic risk factors associated with cervical cancer are a history of smoking, parity, oral contraceptive use, early age of onset of coitus, larger number of sexual partners, history of sexually transmitted disease, certain autoimmune diseases, and chronic immunosuppression.(9) Recommendations by stage are based on the revised 2018 International Federation of Gynecology and Obstetrics (FIGO) staging. The primary treatment of early-stage cervical cancer is either surgery or radiation therapy (RT). Surgery is typically reserved for early-stage disease, fertility-preservation, and smaller lesions, such as stage IA, IB1, IB2, and selected IIA1. The Panel agrees that concurrent chemoradiation is generally the primary treatment of choice for stages IB3 to IVA disease. Chemoradiation can also be used for patients who are not candidates for hysterectomy. Effective treatment for cervical cancer (including surgery and concurrent chemoradiation) can yield cures in 80% of patients with early-stage disease (stages I–II) and in 60% of patients with stage III disease. The hope is that immunization against HPV (using vaccines) will prevent persistent infection with the types of HPV against which the vaccine is designed and will therefore prevent specific HPV cancer.(9)

Colorectal cancer	Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States.(3-5) Overall, the incidence of colon and rectal cancers per 100,000 people has steadily decreased by a rate of 3% per year and mortality from colorectal cancer has decreased more than 50% from peak mortality rates.(3,4) These improvements in incidence of and mortality from CRC are thought to be a result of cancer prevention and earlier diagnosis through screening and better treatment modalities.(3-5) Modeling suggests that approximately 63% of CRC deaths can be attributed to non-screening.(5) Recommended systemic therapy options for advanced or metastatic disease depend on whether the patient is appropriate for intensive therapy; the biomarker status of the tumor; and for patients with progressive disease, the choice of initial therapy.(3,4) The NCCN Guidelines for CRC screening place patients into three groups depending on their risk of getting CRC based on several factors (e.g., age, family history, race/ethnicity). Current technology for CRC screening falls into two broad categories: structural tests (e.g., colonoscopy) and stool/fecal-based tests. Colonoscopy is the most complete screening procedure and is considered the current gold standard for assessing the sensitivity of detecting neoplasia for other screening modalities.(5)
Glioblastoma	Glioblastoma is the most common malignant brain tumor in adults, which is highly invasive and virtually incurable. Brain metastases can also be quite variable. These patients may have one or dozens of brain metastases, and they may have a malignancy that is highly responsive or, alternatively, highly resistant to radiation therapy (RT) or systemic therapy. Moreover, patients with brain metastases may have rapidly progressive systemic disease or no systemic cancer at all. Because of this marked heterogeneity, the prognostic features and treatment options for primary and metastatic brain tumors must be carefully reviewed on an individual basis and sensitively communicated to each patient. NCCN recommends maximal safe resection, if feasible, as the first step in therapy. The goals of surgery are to obtain a diagnosis, alleviate symptoms related to increased intracranial pressure or compression, increase survival, and decrease the need for corticosteroids. Unfortunately, nearly all glioblastomas recur. Postoperative adjuvant RT is appropriate if symptoms persist after incomplete resection or biopsy. Systemic therapy is reserved for cases where both surgery and RT are contraindicated. Specific regimens are dependent on primary tumor type.(7)
Hepatocellular carcinoma	Hepatobiliary cancers are highly lethal cancers including a spectrum of invasive carcinomas arising in the liver (hepatocellular carcinoma; HCC), gall bladder, and bile ducts (intrahepatic and extrahepatic cholangiocarcinoma [CCA]). Gallbladder cancer and CCAs are collectively known as biliary tract cancers. In 2023, it was estimated that 41,210 people in the United States would be diagnosed with liver cancer and intrahepatic bile duct cancer. The major risk factors for the development of HCC are cirrhosis and chronic liver disease, regardless of etiology. Specific risk factors include viral infections caused by hepatitis B virus (HBV) and/or hepatitis C virus (HCV), chronic alcohol consumption, particular comorbidities or other conditions such as non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), genetic hemochromatosis (GH), coinfection with HBV/HVC, and HIV. Globally, HBV is the leading cause of HCC incidence and mortality.(14) HCC is associated with a poor prognosis as many patients with HCC are diagnosed at an advanced stage. Complete resection of the tumor in

	well-selected patients is currently the best available potentially curative treatment. Liver transplantation is a curative option for select resectable patients. Locoregional therapies (ablation, arterially directed therapies, and RT) are often the initial approach for patients with HCC who are not candidates for surgery or liver transplantation. A number of agents are recommended for subsequent-line systemic therapy for patients with disease progression.(14)
Non-squamous non-small cell lung cancer	Lung cancer is the leading cause of cancer-related death in the United States. In 2024, an estimated 234,580 new cases of lung and bronchial cancer will be diagnosed, and 125,070 people. World Health Organization (WHO) divides lung cancer into two major classes based on its biology, therapy and prognosis: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC is more common accounting for more than 80% of all lung cancer cases and it includes two major types: 1) non-squamous, including adenocarcinoma, large-cell carcinoma, and other subtypes; and 2) squamous cell (epidermoid) carcinoma. Surgery, radiation therapy, and systemic are most commonly used to treat patients with NSCLC alone or in combination. NCCN guidelines recommend broad molecular profiling to identify rare driver mutations for which targeted therapies may be available to ensure that patients receive the most appropriate treatment.(6)
Ovarian, fallopian tube, peritoneal cancer	Ovarian neoplasms consist of several histopathologic entities, with epithelial ovarian cancer accounting for the majority of malignant ovarian neoplasms (about 90%). Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States and is the country's fifth most common cause of cancer mortality in females. Primary treatment for presumed ovarian, fallopian tube, or primary peritoneal cancer usually consists of appropriate surgical staging and debulking surgery, followed in most (but not all) patients by systemic chemotherapy. Postoperative observation is an option for select patients with stage I disease, depending on cancer histologic type and substage. Adjuvant systemic chemotherapy is considered an essential component of care for most patients after primary surgery.(10)
Renal cell carcinoma	Kidney and renal pelvis cancers comprise approximately 4.1% of all new cancers, with a median age at diagnosis of 65 years. Approximately 85% of kidney tumors are renal cell carcinoma (RCC). The initial approach to a patient with presumed RCC needs to consider the extent of the disease, as well as the patient's age and comorbidity. Surgical resection remains an effective therapy for clinically localized RCC. Unfortunately, many RCCs are clinically silent for much of their natural history. Thus, the diagnosis if frequently not made until the disease is locally advanced (and unresectable) or has metastasized. After surgical excision, 20% to 30% of patients with localized tumors experience relapse. For most patients with localized RCC, the benefits of adjuvant treatment after nephrectomy in those who have undergone a complete resection of their tumor are not yet clearly established. Adjuvant radiation therapy after nephrectomy has not shown benefit, even in patients with nodal involvement or incomplete tumor resection. Systemic therapy is recommended for those patients that are determined to be appropriate.(8)
Non-oncology indications	For the purposes of the non-oncology criteria, indications deemed appropriate are those supported in the allowed compendia (American Society of Health-System Pharmacists [AHFS], DrugDex level of evidence 1 or 2a), in addition to eye disorders based on recommended use from the American Academy of Ophthalmology (AAO) preferred practice patterns. **Diabetic retinopathy (DR), diabetic macular edema (DME)**

	Diabetic retinopathy (DR) is the most common cause of blindness in working-aged adults worldwide. Visual loss from DR may be secondary to macular edema, which includes retinal thickening and edema of the macula. Other causes may be hemorrhage from new vessels, retinal detachment and neovascular glaucoma. It is believed that chronic hyperglycemia is the main reason for DR. Diabetic macular edema (DME) is a common cause of visual impairment globally. The underlying progressive retinal microvascular damage is associated with upregulation of VEGF and a multitude of other inflammatory pathways. There is a range of findings, symptoms, and rate of progression in DR patients necessitating individualistic treatment approaches. Macular edema can occur at any stage of DR. When macular edema does occur, it manifests itself through retinal thickening and edema of the macula. This can cause associated capillary leakage and if near the macula and not treated can cause loss of visual acuity. Initial treatments options are anti-VEGF agents or laser treatment (focal photocoagulation). Studies have been completed with combination treatment of anti-VEGF and focal photocoagulation suggesting that less frequent treatments are needed. Longer-term studies are still needed to determine the optimal regimen in varying degrees of macular edema. Intravitreal triamcinolone injection is an option for macular edema; however, treatment response in DME is transient and requires repeated injections.(27,28) **Macular edema following retinal vein occlusion (RVO)** Retinal vein occlusion (Branch Retinal Vein Occlusion [BRVO], Central Retinal Vein Occlusion [CRVO]) are vascular occlusions of either the branch or central retinal vein resulting in potential vision changes and long-term sequelae. Both CRVO an BRVO are related to occlusion of retinal vein, however the cause of the occlusion differs based on location.(26) • CRVO occurs when a thrombus occludes the central retinal vein near the lamina cribrosa • RVO occurs when a thrombus occurs at the arteriovenous crossing point secondary to atherosclerosis of the retinal artery causing compression of the retinal vein The risk factors for CRVO are:(26) • Hypertension • Open angle glaucoma • Diabetes mellitus The risk factors for BRVO are:(26) • Hypertension • Cardiovascular disease • Open angle glaucoma • High body mass index (not diabetes mellitus) **Neovascular (wet) age-related macular degeneration (AMD/nAMD)**

	Neovascular age-related macular degeneration (nAMD) is a common world-wide cause of visual loss. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents are an effective means to treat nAMD and reduce its impact on vision compared to either sham treatment or photodynamic therapy. In addition to the FDA labeled anti-VEGF therapies for nAMD, bevacizumab used off-label has been shown to be effective in treating nAMD. While anti-VEGF agents are effective, limitations include the requirement for frequent, often monthly injections, and the need for long-term treatment of nAMD contributing to significant burdens on the healthcare system and on patients. These limitations are partly addressed by exploring different treatment regimens that reduce the frequency of treatments. Newer anti-VEGF drugs have been shown in Phase III clinical trials to have injection intervals as long as 12 or even 16 weeks for a proportion of patients. In addition, reviews of patients with nAMD treated with anti-VEGF have reported deterioration of vision over time with progression of geographic atrophy.(24) There is research on newer drugs that affect other pathways, such as the angiopoietin pathway, which may impact nAMD by extending the treatment interval and reducing the burden of treatment. Other measures include the use of sustained-release implants that release the drug regularly over a period of time, can be refilled periodically, as well as hydrogel platforms that serve to release the drug. The use of biosimilars will also help reduce the cost of treatment for nAMD. A new frontier of gene therapy, primarily targeting genes involved in the transduction of retinal cells to produce anti-VEGF proteins intraocularly may introduce new therapeutic approaches that can be used for this treatment.(24)
Bevacizumab (non-oncology)	Bevacizumab is commonly used to treat CNV (in AMD and other diseases), DME, and RVO. Interest in bevacizumab for ocular use began with the molecular similarity it shares with ranibizumab. Bevacizumab has a long history of safety and efficacy, albeit without FDA approval for ocular use. Based on its affordability, the world health organization (WHO) has put bevacizumab and not ranibizumab in the WHO model list of essential drugs. In ophthalmology, bevacizumab is typically given by transconjunctival intravitreal injections into the posterior segment. Intravitreal injections for retinal pathologies are typically administered at 4-6-week intervals, although this varies widely based on disease and response. Typical dose is 1.25 mg in 0.05 mL in adults, and half that dose in babies.(21) Bevacizumab is considered efficacious for treatment of CNV and macular edema by the ophthalmologic community. Since this drug does not have FDA labeling for ophthalmic indications, classic clinical trials do not uniformly exist. However, convincing data has been published for the most commonly treated pathologies.(21) AMD (neovascular with CNV): The sham injection/untreated arm of the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) trial showed vision loss of 14.9 letters from baseline over 24 months, which is often quoted as the natural history of neovascular AMD. While the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) did not have an untreated arm, it was perhaps the most well-structured clinical trial involving bevacizumab and showed a 7.8 letter gain from baseline with monthly administration. The Inhibit VEGF in the Age-Related Choroidal Neovascularization trial (IVAN) echoed this positive result.(21)

	DME: The Pan-American Collaborative Retina Study Group (PACORES) trial compared monthly intravitreal bevacizumab with macular focal-grid laser photocoagulation (standard of care at that time) and showed an average of 11.86 letters gained with bevacizumab and 3.66 letters gained with focal grid laser over 24-months.(21) Macular Edema due to RVO: The untreated macular edema arm (Group M) of the Central Vein Occlusion Study (CVOS) trial lost approximately 5 letters from baseline. The PACORES trial for central vein occlusion, did not have an untreated arm but had similar inclusion criteria, showed 19 letters of improvement from baseline over 12 months with monthly/as-needed intravitreal bevacizumab.(21) *Efficacy* Bevacizumab and bevacizumab-awwb bind to and inhibits the biological activity of human vascular endothelial growth factor (VEGF). It prevents VEGF from stimulating blood vessel growth to the tumor. Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors on the surface of the endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in vitro models of angiogenesis. Administration of bevacizumab results in reduction of microvascular growth and inhibition of metastatic disease progression.(21)
Concomitant intravitreal anti-VEGF with intravitreal corticosteroids	Meta-analyses were done to evaluate the efficacy and safety of combining intravitreal corticosteroids (IVC) and endothelial growth factor inhibitor (anti-VEGF) for the treatment of neovascular age-related macular degeneration (nAMD) and for the treatment of diabetic macular edema (DME). Anti-VEGF combined with ocular corticosteroids had a significant advantage over anti-VEGF monotherapy within 3 months of DME treatment, which reached the maximum with increasing anti-VEGF injection times to 3. However, with the prolongation of the treatment cycle, the effect of combined therapy after 6 months was no better than monotherapy, and the side effects of combined therapy were more severe.(13) No visual or anatomical benefits are observed in IVC/anti-VEGF group at 6 months. At 12 months, the central macular thickness (CMT) of the IVC/anti-VEGF group is significantly lower than that of the anti-VEGF group. Risk of severe elevation of intraocular pressure is significantly higher when treated by the combination of IVC with anti-VEGF.(12)
Safety	Alymsys, Avastin, Mvasi, Vegzelma, and Zirabev have no FDA labeled contraindications for use.(1,2,11,29,30)

POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Q5126	Alymsys	bevacizumab-maly iv soln	100 MG/4ML ; 400 MG/16ML	M ; N ; O ; Y	N		
J9035	Avastin	bevacizumab iv soln	100 MG/4ML ; 400 MG/16ML	M ; N ; O ; Y	N		
Q5129	Vegzelma	bevacizumab-adcd iv soln	100 MG/4ML ; 400 MG/16ML	M ; N ; O ; Y	N		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Alymsys	bevacizumab-maly iv soln	100 MG/4ML ; 400 MG/16ML	Commercial ; HIM ; ResultsRx
Avastin	bevacizumab iv soln	100 MG/4ML ; 400 MG/16ML	Commercial ; HIM ; ResultsRx
Vegzelma	bevacizumab-adcd iv soln	100 MG/4ML ; 400 MG/16ML	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module: Oncology

Clinical Criteria for Approval

Preferred Agent(s)	Non-Preferred Agent(s)
Mvasi (bevacizumab-awwb) Zirabev (bevacizumab-bvzr)	Alymsys (bevacizumab-maly) Avastin (bevacizumab) Vegzelma (bevacizumab-adcd)

Target Agent(s) will be approved when ALL of the following are met:

1. The requested agent will be used for an oncology indication **AND**
2. ONE of the following:
   A. The requested agent is eligible for continuation of therapy AND ONE of the following:

Agents Eligible for Continuation of Therapy
All Target Agents are eligible for continuation of therapy

1. The patient has been treated with the requested agent within the past 180 days **OR**

Module	Clinical Criteria for Approval
	2. The prescriber states the patient has been treated with the requested agent within the past 180 days AND is at risk if therapy is changed **OR** B. BOTH of the following: 1. ONE of the following: A. The patient has a diagnosis of cervical cancer AND ONE of the following: 1. ALL of the following: A. The patient's disease is persistent, recurrent, OR metastatic **AND** B. The requested agent will be used in combination with paclitaxel and ONE of the following: 1. Cisplatin **OR** 2. Topotecan **OR** 2. The requested indication meets ALL requirements within FDA labeling or allowed compendia for the requested agent (e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy) **OR** B. The patient has a diagnosis of colorectal cancer AND ONE of the following: 1. ALL of the following: A. The patient has metastatic disease **AND** B. The requested agent is being used as first-line or second-line treatment **AND** C. The requested agent will be used in combination with intravenous 5-fluorouracil based chemotherapy **OR** 2. ALL of the following: A. The patient has metastatic disease **AND** B. The patient's disease has progressed on a first line bevacizumab containing regimen **AND** C. The requested agent will be used in combination with fluoropyrimidine-irinotecan OR fluoropyrimidine-oxaliplatin-based chemotherapy **OR** 3. The requested indication meets ALL requirements within FDA labeling or allowed compendia for the requested agent (e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy) **OR** C. The patient has a diagnosis of epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer AND ONE of the following: 1. The patient's disease is platinum-resistant AND ALL of the following: A. The patient has recurrent disease **AND** B. The patient has received no more than 2 prior chemotherapy regimens **AND** C. The requested agent will be used in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan **OR** 2. The patient's disease is platinum-sensitive AND BOTH of the following:

Module	Clinical Criteria for Approval
	A. The patient has recurrent disease **AND** B. ONE of the following: 1. The requested agent will be used in combination with carboplatin and paclitaxel for initial therapy OR as a single agent for maintenance therapy **OR** 2. The requested agent will be used in combination with carboplatin and gemcitabine for initial therapy OR as a single agent for maintenance therapy **OR** 3. The patient has stage III or IV disease AND BOTH of the following: A. The patient has had surgical resection **AND** B. The requested agent will be used in combination with carboplatin and paclitaxel for initial therapy OR as a single agent for maintenance therapy **OR** 4. The requested indication meets ALL requirements within FDA labeling or allowed compendia for the requested agent (e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy) **OR** D. The patient has a diagnosis of glioblastoma AND ONE of the following: 1. BOTH of the following: A. The patient's disease has progressed following prior treatment **AND** B. The requested agent will be used as a single agent **OR** 2. The requested indication meets ALL requirements within FDA labeling or allowed compendia for the requested agent (e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy) **OR** E. The patient has a diagnosis of hepatocellular carcinoma (HCC) AND ONE of the following: 1. ALL of the following: A. The patient's disease is unresectable or metastatic **AND** B. The patient has not received prior systemic therapy **AND** C. The requested agent will be used in combination with atezolizumab **OR** 2. The requested indication meets ALL requirements within FDA labeling or allowed compendia for the requested agent (e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy) **OR** F. The patient has a diagnosis of non-squamous non-small cell lung cancer AND ONE of the following: 1. ALL of the following: A. The patient's disease is unresectable, locally advanced, recurrent, OR metastatic **AND**

Module	Clinical Criteria for Approval
	B. The requested agent is being used as first-line therapy **AND** C. The requested agent will be used in combination with carboplatin and paclitaxel **OR** 2. The requested indication meets ALL requirements within FDA labeling or allowed compendia for the requested agent (e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy) **OR** G. The patient has a diagnosis of renal cell carcinoma AND ONE of the following: 1. BOTH of the following: A. The patient has metastatic disease **AND** B. The requested agent will be used in combination with interferon alfa **OR** 2. The requested indication meets ALL requirements within FDA labeling or allowed compendia for the requested agent (e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy) **OR** H. The patient has another FDA labeled indication for the requested agent and route of administration **OR** I. The patient has another indication that is supported in compendia for the requested agent and route of administration (i.e., indication must be supported in compendia by ALL requirements [e.g., performance status, disease severity, previous failures, monotherapy vs. combination therapy]) **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. If the client has preferred agent(s), then ONE of the following: A. The requested agent is a preferred agent **OR** B. The patient has tried and had an inadequate response to TWO preferred agents (medical records required) **OR** C. The patient has an intolerance or hypersensitivity to TWO preferred agents that is not expected to occur with the requested agent (medical records required) **OR** D. The patient has an FDA labeled contraindication to ALL preferred agents that is not expected to occur with the requested agent (medical records required) **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The requested quantity (dose) is within FDA labeling or supported in compendia for the requested indication **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval**: 12 months or for the duration of therapy in FDA labeling or supported in compendia, whichever is shorter

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

REVISIONS	
Posted 12-01-2023 Effective 01-01-2024	Policy added to the bcbsks.com web site.
12-23-2024	Updated Approval Criteria • Condensed and simplified criteria point language that the requested indication needs to meet ALL requirements of FDA labeling or allowed compendia (e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy) • Removed age requirement under glioblastoma diagnosis as this is assessed later in criteria • Updated epithelial ovarian cancer for platinum-sensitive patients to "OR as a single agent for maintenance therapy" to keep verbiage consistent across this indication
	Medical policy maintained by Prime Therapeutics

REFERENCES

Number	Reference
1	Avastin prescribing information. Genentech Inc. September 2022.
2	Mvasi prescribing information. Amgen Inc. February 2023.
3	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Colon Cancer. Version 4.2024.
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