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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FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Alymsys® (bevacizumab -maly) Injection for intravenous use	**Colorectal cancer** • Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first0 or second-line treatment • Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin- based		29

Agent(s)	FDA Indication(s)	Notes	Ref#
	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		
	Non-squamous non-small cell lung cancer • Unresectable, locally advanced, recurrent, or metastatic non- squamous non-small-cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment		
	Glioblastoma • Recurrent glioblastoma in adults		
	Renal cell carcinoma • Metastatic renal cell carcinoma in combination with interferon alfa		
	Cervical cancer 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	**Colorectal cancer** • Metastatic colorectal cancer in combination with intravenous 5- fluorouracil-based chemotherapy for first or second-line treatment • Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan		1

Agent(s)	FDA Indication(s)	Notes	Ref#
	or fluoropyrimidine-oxaliplatin based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen Limitations of Use: Avastin is not indicated for adjuvant treatment of colon cancer		
	Non-small cell lung cancer • Unresectable, locally advanced, recurrent or metastatic non- squamous non-small cell lung cancer (NSCLC), in combination with carboplatin and paclitaxel for first-line treatment		
	Glioblastoma • Recurrent glioblastoma in adults		
	Renal cell carcinoma • Metastatic renal cell carcinoma in combination with interferon alfa		
	Cervical cancer • 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		

Agent(s)	FDA Indication(s)	Notes	Ref#
	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	**Colorectal cancer** • Metastatic colorectal cancer with intravenous fluorouracil-based chemotherapy for first or second-line treatment • Metastatic colorectal cancer, 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		2
	Non-small cell lung cancer • Unresectable, locally advanced, recurrent or metastatic non- squamous non-small cell lung cancer (NSCLC), in combination with carboplatin and paclitaxel for first line treatment		
	Glioblastoma • Recurrent glioblastoma in adults		
	Renal cell carcinoma • Metastatic renal cell carcinoma with interferon alfa		
	Cervical cancer • Persistent, recurrent or metastatic cervical cancer, in combination with paclitaxel		

Agent(s)	FDA Indication(s)	Notes	Ref#
	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 chemoptherapy regimens • In combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by Mvasi as a single agent, for platinum-sensitive recurrent disease		
Vegzelma® (bevacizumabadcd) Injection for intravenous use	**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		30
	Non-small cell lung cancer • Unresectable, locally		

Agent(s)	FDA Indication(s)	Notes	Ref#
	advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment		
	Glioblastoma • Recurrent glioblastoma in adults		
	Renal cell carcinoma • Metastatic renal cell carcinoma in combination with interferon alfa		
	Cervical cancer • 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® (bevacizuma-bvzr)	**Colorectal cancer** • Metastatic colorectal cancer in combination with intravenousfluorouracil-		11

Agent(s)	FDA Indication(s)	Notes	Ref#
Intravenous injection	based chemotherapy for first or second-line treatment • Metastatic colorectal cancer, 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-small cell lung cancer Unresectable, locally advanced, recurrent or metastatic non– squamous non–small cell lung cancer (NSCLC), in combination with carboplatin and paclitaxel for first line treatment		
	Glioblastoma • Recurrent glioblastoma in adults		
	Renal cell carcinoma • Metastatic renal cell carcinoma in combination with interferon alfa		
	Cervical cancer • 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 Zirabev as a single agent, for stage III or IV disease following initial surgical resection		

Agent(s)	FDA Indication(s)	Notes	Ref#
	• In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who have 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

ONCOLOGY Metastatic colorectal cancer	Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States.(3,4) 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 by about 50% from peak mortality rates.(3,4) Colorectal cancer screening falls into two broad categories: structural tests (e.g., colonoscopy) and stool/fecal-based tests.(5)
ONCOLOGY-Nonsquamous non-small cell lung cancer	Lung cancer is the leading cause of cancer death and the second most common cancer among men and women in the United States. Lung cancers are grouped into two main types: small cell and non-small cell. Non- small cell lung cancer (NSCLC) is much more common than small cell (85-90% vs 10- 15% respectively). Treatment of lung cancer includes surgery, radiation therapy, and systemic therapy and/or a combination of these treatments. NCCN guidelines state broad molecular profiling is a key component of the improvement of care of patients with NSCLC with the goal of identifying rare driver mutations for which effective drugs may be available.(6)
ONCOLOGY-Glioblastoma(7)	lethal brain tumor with only a third of patients surviving for one year and less than 5% living beyond 5 years. 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. Radiation and chemotherapy/systemic therapy should follow surgery.

ONCOLOGY -Renal cell carcinoma(8)	Renal cell carcinoma (RCC) comprises approximately 4.1% of all new cancers, with a median age at diagnosis of 64 years. 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. If diagnosed early, surgical resection can be curative. 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. In addition, many patients have disease recurrence after initial resection. Systemic therapy is recommended for those patients that are determined to be appropriate.
ONCOLOGY -Cervical cancer	Cervical cancer rates are decreasing in the United States; however, cervical cancer is a major world health problem for women. 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 in women. 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. Women with cervical cancer limited to the uterus have early-stage disease. Treatment options for these women include modified radical hysterectomy, fertility sparing surgery, or primary radiation therapy with or without chemotherapy.(9) Women with locally advanced cervical cancer (stage IB2 to IVA) have a higher rate of recurrence and worse survival than those with early-stage disease. After surgery alone, the rate of relapse is at least 30%, and five-year survival rates range from 30 to 80% depending on the stage. Treatment for locally advanced cervical cancer include primary chemoradiation, chemotherapy, and radiation therapy.(9)
ONCOLOGY-Ovarian, fallopian tube and peritoneal cancer(10)	Ovarian neoplasms consist of several histopathologic entities; treatment depends on the specific tumor type. Epithelial ovarian cancer comprises approximately 90% of malignant ovarian neoplasms. The National Comprehensive Cancer Network (NCCN) includes less common fallopian tube cancers and peritoneal cancers in the ovarian cancer guidelines because these cancers are managed in a similar manner to epithelial ovarian cancer. Primary treatment for presumed ovarian cancer consists of appropriate surgical staging and debulking surgery, followed in most (but not all) patients by systemic chemotherapy.
ONCOLOGY-Efficacy(1-2,11)	Bevacizumab binds 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.
ONCOLOGY-Safety(1-2,11)	Labeling for bevacizumab contains a boxed warning for gastrointestinal perforations, surgery and wound healing complications, and hemorrhage. Gastrointestinal perforation occurred in 0.3 to 3.2% of treated patients with some fatalities. Increased incidence of wound healing and surgical complications, including serious and fatal complications has been observed in bevacizumab treated patients. Severe or fatal hemorrhage has been shown to occur up to 5-fold more frequently in bevacizumab treated patients
ONCOLOGY-Compendia Supported Indications	For the purposes of the oncology criteria, indications deemed appropriate are those that are supported by NCCN recommended use 1 or 2a.
NON-ONCOLOGY-Neovascular (Wet) Age-related Macular Degeneration (AMD)	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 approved 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. These present significant burdens on the healthcare system and on the 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, and can be refilled periodically, as well as hydrogel platforms that serve to release the drug. The use of biosimilars will also serve to 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, also open a new avenue of therapeutic approaches that can be used for this treatment.(24)
NON-ONCOLOGY-Diabetic retinopathy (DR) and Diabetic Macular Edema (DME)	Diabetic retinopathy is the most common cause of blindness in working-aged adults worldwide. Visual loss from diabetic retinopathy 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 diabetic retinopathy. 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 diabetic retinopathy patients necessitating individualistic treatment approaches. Macular edema can occur at any stage of diabetic retinopathy. 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 as a result. Longer-term studies are still needed to determine the optimal regimen in varying degrees of macular edema. It has been noted that intravitreal triamcinolone injection is an option for macular edema; however, response from treatment in DME is transient and require repeated injections.(27,28)
NON-ONCOLOGY-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)
NON-ONCOLOGY-Bevacizumab	Bevacizumab is commonly used to treat CNV (in AMD and other diseases), DME, and RVO. Interest in bevacizumab for ocular use began due to 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 has put bevacizumab and not ranibizumab in 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.(24,25) Bevacizumab is considered efficacious for treatment of CNV and macular edema by the ophthalmologic community. As this drug has not been FDA approved for ophthalmic indications, classic clinical trials do not uniformly exist, however convincing data has been published for the most commonly treated pathologies.(24) Age-related Macular Degeneration (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.(24) Diabetic Macular Edema (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.(24) Macular Edema due to Retinal Vein Occlusion: 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, which 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.(24)
NON-ONCOLOGY-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)
NON-ONCOLOGY-Safety(1)	Labeling for bevacizumab contains a boxed warning for gastrointestinal perforations, surgery and wound healing complications, and hemorrhage. Gastrointestinal perforation

	occurred in 0.3 to 3.2% of treated patients with some fatalities. Increased incidence of wound healing and surgical complications, including serious and fatal complications has been observed in bevacizumab treated patients. Severe or fatal hemorrhage has been shown to occur up to 5-fold more frequently in bevacizumab treated patients.
NON-ONCOLOGY-Compendia Supported Indications	For the purposes of the non-oncology criteria, indications deemed appropriate are those that are supported by American Society of Health-System Pharmacists (AHFS), DrugDex level of evidence 1 or 2a. In addition, this criteria will allow for use for use in eye disorders based on recommended use in the American Academy of Ophthalmology (AAO) preferred practice pattern.
NON-ONCOLOGY-Use of intravitreal anti-VEGF with intravitreal corticosteroids(13)	Randomized trials have been performed to study the adjunct use of intravitreal corticosteroids and/or anti-VEGF agents in various drug combinations or with verteporfin PDT, following the publication of results from uncontrolled case series. The AAO has concluded that the data do not currently support the use of combination therapy at this time, especially with the long-term side effects of glaucoma and cataracts that are associated with corticosteroid use.

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	Clinical Criteria for Approval
Oncology	

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 is being 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. Information has been provided that indicates the patient has been treated with the requested agent in the past 180 days **OR**
      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 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 is supported by ALL requirements in either FDA labeling or compendia support for the requested agent [i.e., this indication must be supported by ALL requirements in the FDA label or compendia support (e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy)] **OR**

Module	Clinical Criteria for Approval
	B. 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** 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 is supported by ALL requirements in either FDA labeling or compendia support for the requested agent [i.e., this indication must be supported by ALL requirements in the FDA label or compendia support (e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy)]**OR** C. The patient has a diagnosis of glioblastoma AND ONE of the following: 1. ALL 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 **AND** C. ONE of the following: 1. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** 2. The prescriber has provided information in support of using the requested agent for the patient's age **OR** 2. The requested indication is supported by ALL requirements in either FDA labeling or compendia support for the requested agent [i.e., this indication must be supported by ALL requirements in the FDA label or compendia support (e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy)]**OR** D. 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 is supported by ALL requirements in either FDA labeling or compendia support for the requested agent [i.e., this indication must be supported by ALL requirements in the FDA label or compendia support (e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy)] **OR** E. The patient has a diagnosis of cervical cancer AND ONE of the following: 1. ALL of the following:

Module	Clinical Criteria for Approval
	A. The patient's disease is persistent, recurrent, OR metastatic **AND** B. The requested agent will be used in combination paclitaxel and ONE of the following: 1. Cisplatin OR 2. Topotecan **OR** 2. The requested indication is supported by ALL requirements in either FDA labeling or compendia support for the requested agent [i.e., this indication must be supported by ALL requirements in the FDA label or compendia support (e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy)]**OR** F. 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: 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 followed by bevacizumab as a single agent for maintenance therapy **OR** 2. The requested agent will be used in combination with carboplatin and gemcitabine for initial therapy followed by bevacizumab 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 is supported by ALL requirements in either FDA labeling or compendia support for the requested agent [i.e., this indication must be supported by ALL requirements in the FDA label or compendia support (e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy)] **OR**

Module	Clinical Criteria for Approval
	G. 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 is supported by ALL requirements in either FDA labeling or compendia support for the requested agent [i.e., this indication must be supported by ALL requirements in the FDA label or compendia support (e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy)] **OR** H. The patient has another FDA approved indication for the requested agent and route of administration [i.e., this indication must be supported by ALL requirements in the FDA label (e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy)] **OR** I. The patient has another indication that is supported in compendia for the requested agent and route of administration [i.e., this indication must be supported by ALL requirements in the compendia support (e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy)] **AND** 2. If the patient has an FDA approved 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. The prescriber has provided information in support of 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 dose and duration are within FDA labeling or compendia supported dosing

Module	Clinical Criteria for Approval
	Length of Approval: 12 months or for duration of treatment as supported in FDA labeling or compendia, whichever is shorter **Compendia Allowed:** NCCN 1 or 2a recommended use

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.

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 2.2023.
4	National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Rectal Cancer. Version 2.2023.
5	National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Colorectal Cancer Screening. Version 3.2022.
6	National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 3.2023.
7	National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Central Nervous System Cancers. Version 1.2023.
8	National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Kidney Cancer. Version 4.2023.
9	National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Cervical Cancer. Version 1.2023.
10	National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Version 1.2023.
11	Zirabev Prescribing Information. Pfizer Laboratories Div Pfizer Inc. February 2023.
12	Feldman BH, Shah VA, Shah VA, Kim LA, et al. American Academy of Ophthalmology. Bevacizumab. Updated December 20,2022.
13	National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Hepatobiliary Cancers. Version 1.2023.

Number	Reference
14	Leng T, Barash A, Tripathy K, Hsu J, Kamjoo S, Lim JI. American Academy of Ophthalmology. Intravitreal Injections. Status updated on August 4, 2022.
15	Tan CS, Ngo WK, Chay IW, Ting DS, Sadda SR. Neovascular Age-Related Macular Degeneration (nAMD): A Review of Emerging Treatment Options. Clin Ophthalmol. 2022 Mar 25;16:917-933. doi: 10.2147/OPTH.S231913. PMID: 35368240; PMCID: PMC8965014.
16	Feldman BH, Shah VA, Shah VA, Kim LA, Tripathy K, Tsui JC, Elshatory YM. American Academy of Ophthalmology. Age-Related Macular Degeneration. Updated December 9, 2022.
17	Shah VA, Randolph J, Hsu J, Furnani B, Lim JI, Marcet MM. American Academy of Ophthalmology. Retinal Vein Occlusion. Updated October 22, 2022.
18	Jacoba CMP, Mitzner MG, Bhagat N, Zarbin MA, et al. American Academy of Ophthalmology. Diabetic Macular Edema. Update pending.
19	Feldman BH, Shah VA, Tripathy K, Rana HS, et al. American Academy of Ophthalmology. Diabetic Retinopathy. Updated December 2022.
20	Alymsys Prescribing Information. Amneal Pharmaceuticals LLC. April 2022.
21	Vegzelma Prescribing Information. Celltrion USA, Inc. February 2023.