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Section:	Prescription Drugs	**Effective Date:**	July 1, 2022
Subsection:	Antineoplastic Agents	**Original Policy Date:**	February 1, 2008
Subject:	Bevacizumab	**Page:**	1 of 13

Last Review Date: June 16, 2022

Bevacizumab

Description

Avastin (bevacizumab)

Alymsys* (bevacizumab-maly), **Mvasi** (bevacizumab-awwb), **Zirabev** (bevacizumab-bvzr)

Preferred products for claims adjudicated through the pharmacy benefit: Mvasi and Zirabev

*This medication is included in this policy but is not available on the market as of yet

Background

Neoplastic tissue originates as host-derived cells that proliferate atypically due to loss of ability to control growth. Vascular endothelial growth factor (VEGF) is an important regulating factor of both normal and abnormal angiogenesis (the formation of new blood cells). VEGF interacts with two different receptor tyrosine kinases, VEGFR-1 and VEGFR-2 to alter angiogenesis. Anti-VEGF pharmacotherapies have been developed with a goal of inhibiting tumor angiogenesis and thereby inhibiting growth and metastasis. Bevacizumab is a VEGF inhibitor that binds to human VEGF preventing the interaction of VEGF with its receptors (Flt-1, KDR) on the surface of endothelial cells (1-12).

Regulatory Status

FDA-approved indications: Bevacizumab is an angiogenesis inhibitor indicated for: (5-9)

1. Metastatic colorectal cancer for the first- or second-line treatment of patients with

metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil–based chemotherapy.

2. 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-containing regimen.
3. Non-squamous non-small cell lung cancer (NSCLC), with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent, or metastatic disease.
4. Glioblastoma, as a single agent for adult patients with progressive disease following prior therapy.
5. Metastatic renal cell carcinoma in combination with interferon alfa.
6. Metastatic carcinoma of the cervix, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease
7. Epithelial ovarian, fallopian tube, or primary peritoneal cancer:
    a. In combination with carboplatin and paclitaxel, followed by bevacizumab as a single agent, for stage III or IV disease following initial surgical resection
    b. In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens
    c. In combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by bevacizumab as a single agent, for platinum-sensitive recurrent disease
    d. In combination with olaparib for the maintenance treatment of adult patients with advanced cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:
        i. a deleterious or suspected deleterious BRCA mutation, and/or
        ii. genomic instability
8. Hepatocellular carcinoma (HCC)
    a. In combination with atezolizumab for the treatment of unresectable or metastatic HCC who have not received prior systemic therapy

Limitations of Use:
Bevacizumab is not indicated for adjuvant treatment of colon cancer (5-9).

Off-Label Uses:
In comparative trials and uncontrolled case series report improvements in visual acuity and decreased retinal thickness by optical coherence tomography following treatment with

intravitreal bevacizumab for ocular diseases resulting from intravitreal neovascularization (11-12).

Bevacizumab carries a warning for GI perforations including wound-healing complications and hemorrhage. The reported incidence of GI perforations was 2% and hemorrhage was 31%. In both instances, fatalities occurred. The drug is only approved to be started 28 days after surgery and until the surgical wound is fully healed to prevent wound-healing complications (5-8).

Related policies

Cyramza, Lucentis, Susvimo, VEGF Inhibitors, Zaltrap

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Bevacizumab may be considered **medically necessary** for the treatment of patients 18 years of age or older with colorectal cancer, non-squamous non-small cell lung cancer, glioblastoma multiforme, renal cell carcinoma, epithelial ovarian, fallopian tube, primary peritoneal cancer, cervical cancer, hepatocellular carcinoma or ocular neovascular disease; and if the conditions indicated below are met.

Bevacizumab may be considered **investigational** in patients less than 18 years of age and for all other indications.

Prior-Approval Requirements

Age 18 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Metastatic colorectal cancer

   AND ONE of the following:
   a. 1st line treatment
      i. Concurrent intravenous 5-Fluorouracil-based chemotherapy

b. 2nd line treatment with **ONE** of the following regimens:
    1) Fluoropyrimidine-irinotecan based chemotherapy
    2) Fluoropyrimidine-oxaliplatin based chemotherapy
    3) 5-Fluorouracil-based chemotherapy

2. Non-Squamous non-small cell lung cancer
    a. 1st line treatment
    b. Unresectable, locally advanced, recurrent or metastatic
    c. Concurrent therapy with carboplatin and paclitaxel

3. Glioblastoma multiforme (GBM)
    a. Single agent therapy
    b. Progressive disease following prior therapy

4. Metastatic renal cell carcinoma
    a. Concurrent therapy with interferon-alfa

5. Epithelial ovarian, fallopian tube, or primary peritoneal cancer and **ONE** of the following:
    a. Initial surgical resection
        i. Stage III or IV disease
        ii. Used in combination with paclitaxel and carboplatin for up to 6 cycles followed by bevacizumab as single agent therapy
    b. Platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer
        i. Concurrent therapy with **ONE** of the following:
            1) Paclitaxel
            2) Pegylated liposomal doxorubicin
            3) Topotecan
    c. Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer
        i. Concurrent therapy with **ONE** of the following
            1) Carboplatin and paclitaxel followed by bevacizumab as a single agent
            2) Carboplatin and gemcitabine followed by bevacizumab as a single agent

d. Advanced disease
    i. Used in combination with olaparib
        1) Patient has had a complete or partial response to platinum-based chemotherapy
        2) Cancer is associated with homologous recombination deficiency (HRD) positive status defined by at least **ONE** of the following:
            a. Deleterious or suspected deleterious BRCA mutation
            b. Genomic instability

6. Persistent, recurrent, or metastatic cervical cancer
    a. Concurrent therapy with **ONE** of the following:
        i. Paclitaxel and cisplatin
        ii. Paclitaxel and topotecan

7. Unresectable or metastatic hepatocellular carcinoma (HCC)
    a. Used in combination with atezolizumab
    b. Patient has not received prior systemic therapy

AND the following for **ALL** indications:

1. **Avastin only:** Patient **MUST** have tried **BOTH** of the preferred products (Mvasi and Zirabev) if adjudicated through the pharmacy benefit unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

Avastin Only

Age 18 years of age or older

Diagnosis

Patient must have the following:

1. Ocular disease resulting from intravitreal neovascularization, including:
    a. Neovascular (Wet) Age-Related Macular Degeneration (AMD)
    b. Diabetic Macular Edema
    c. Macular edema secondary to retinal vascular occlusion

d. Progressive high myopia
e. Ocular histoplasmosis
f. Proliferative diabetic retinopathy
g. Retinopathy of prematurity
h. Angioid streaks
i. Neovascular glaucoma

AND the following:

1. **NOT** to be used in combination therapy with other Vascular Endothelial Growth Factor (VEGF) Inhibitors for ocular indications (see Appendix 1)

Prior – Approval *Renewal* Requirements

Age 18 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Metastatic colorectal cancer

   AND ONE of the following:
   a. 1st line treatment
      i. Concurrent intravenous 5-Fluorouracil-based chemotherapy

   b. 2nd line treatment with **ONE** of the following regimens:
      i. Fluoropyrimidine-irinotecan based chemotherapy
      ii. Fluoropyrimidine-oxaliplatin based chemotherapy
      iii. 5-Fluorouracil-based chemotherapy

2. Non-Squamous non-small cell lung cancer
   a. Concurrent therapy with carboplatin and paclitaxel

3. Glioblastoma multiforme (GBM)
   a. Single agent therapy

4. Metastatic renal cell carcinoma
   a. Concurrent therapy with interferon-alfa

5. Epithelial ovarian, fallopian tube, or primary peritoneal cancer and **ONE** of the following:
    a. Status post initial surgical resection
        i. Single agent therapy
    b. Platinum- sensitive recurrent
        i. Single agent therapy
    c. Platinum-resistant recurrent
        i. Concurrent therapy with **ONE** of the following:
            1) Paclitaxel
            2) Pegylated liposomal doxorubicin
            3) Topotecan
    d. Advanced disease
        i. Used in combination with olaparib

6. Persistent, recurrent, or metastatic cervical cancer
    a. Concurrent therapy with **ONE** of the following:
        i. Paclitaxel and cisplatin
        ii. Paclitaxel and topotecan

7. Unresectable or metastatic hepatocellular carcinoma (HCC)
    a. Used in combination with atezolizumab

AND the following for **ALL** indications:

1. **Avastin only:** Patient **MUST** have tried **BOTH** of the preferred products (Mvasi and Zirabev) if adjudicated through the pharmacy benefit unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

Avastin Only

Age 18 years of age or older

Diagnoses

Patient must have the following:

1. Ocular disease resulting from intravitreal neovascularization, including:

a. Neovascular (Wet) Age-Related Macular Degeneration (AMD)
b. Diabetic Macular Edema
c. Macular edema secondary to retinal vascular occlusion
d. Progressive high myopia
e. Ocular histoplasmosis
f. Proliferative diabetic retinopathy
g. Retinopathy of prematurity
h. Angioid streaks
i. Neovascular glaucoma

AND the following:

1. **NOT** to be used in combination therapy with other Vascular Endothelial Growth Factor (VEGF) Inhibitors for ocular indications (see Appendix 1)

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Bevacizumab is a Vascular Endothelial Growth Factor (VEGF) inhibitor. Bevacizumab binds to human vascular endothelial growth factor (VEGF) and prevents interaction of VEGF with its receptors (Flt-1, KDR) on the surface of endothelial cells. Bevacizumab is medically necessary for the treatment of angiogenesis-dependent neoplasms as approved by the FDA. There is also an evidence base to support the off-label intravitreal use of bevacizumab for the treatment of ocular disease resulting from neovascularization (1-12).

Prior authorization is required to ensure the safe, clinically appropriate and cost-effective use of bevacizumab while maintaining optimal therapeutic outcomes.

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Policy History

Date	Action
February 2008	Addition to PA
July 2008	Recent studies for the treatment of glioblastoma with combination bevacizumab/irinotecan have shown promising results. Conclusions of several studies have been that the treatment is well tolerated and active against recurrent malignant gliomas. A 6-month progression-free survival among 35 patients was 46%. The 6-month overall survival was 77%. The National Comprehensive Cancer Network recommends bevacizumab with irinotecan for recurrent/salvage therapy of glioblastoma. Bevacizumab has reportedly become the standard of care at the Duke Brain Tumor Institute.

May 2009	FDA has approved Avastin treatment of glioblastoma, as a single agent for patients with progressive disease following prior therapy. Prior to the FDA approval the studies for the treatment of glioblastoma involved the combination therapy of bevacizumab/irinotecan. Due to the FDA approval of treating glioblastoma without concurrent irinotecan therapy in some cases the criteria is being updated to remove IV irinotecan as a requirement for approval.
August 2009	FDA has approved Avastin treatment of metastatic renal cell carcinoma (mRcc) with concurrent administration of interferon-alfa.
January 2010	The use of bevacizumab to treat wet AMD has been demonstrated to be safe and effective and is widely accepted in clinical practice. The clinical literature supports the use of bevacizumab in the following ocular conditions characterized by neovascularization: diabetic macular edema, macular edema secondary to retinal vascular occlusion, progressive high myopia, proliferative diabetic retinopathy, retinopathy of prematurity, angioid streaks, neovascular glaucoma and ocular histoplasmosis. Practicing ophthalmologists consulted also report general acceptance of the use of bevacizumab for these conditions. Use of bevacizumab as monotherapy for polypoidal choroidal vasculopathy, which is genetically linked to AMD, has been found in some cases to result in a treatment-refractory response. Decreased efficacy is possibly due to bevacizumab being unable to reach the location of the PCV or PCV development resulting from a non-VEGF source.
November 2011	Approved indication of breast cancer deleted, based on loss of FDA approval for breast cancer.
May 2012	The CATT two year study was released in 2012 and showed that Avastin and ranibizumab have similar efficacy in the treatment of neovascular AMD. Monthly dosing results in minimally better visual outcomes than 'as needed' dosage. However, the clinical difference is so small that 'as needed' dosing may be quite appropriate for some patients in certain social and financial situations. Avastin is associated with a higher rate of non-specific serious systemic adverse events. The significance of this finding is unclear and may be related to the overall advanced age of the study participants.[8] (Consultant ophthalmologist assessment.)
September 2012	Annual editorial and reference update
December 2012	Added recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancers to approved indications, to align with NCCN Guidelines.

January 2013	FDA added a new indication of metastatic colorectal cancer, with fluoropyrimidine- irinotecan- or fluoropyrimidine- oxaliplatin- based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen. Editorial review and reference update.
June 2013	Annual editorial review and reference update
December 2013	Annual editorial review and update
August 2014	Addition of new FDA approved indication to treat patients with persistent, recurrent or late-stage cervical cancer.
September 2014	Annual review and reference update.
November 2014	Change to include the new indication for platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan
March 2015	Annual editorial review and update
December 2015	Annual editorial review and reference update
June 2016	Annual editorial review and reference update Policy number change from 5.04.04 to 5.21.04
January 2017	Addition of the diagnosis of platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with carboplatin and paclitaxel or in combination with carboplatin and emcitabine, followed by Avastin as a single agent to criteria
March 2017	Annual review
June 2017	Annual editorial review
September 2017	Annual review
June 2018	Annual editorial review and reference update
July 2018	Addition of the diagnosis of initial surgical resection of epithelial ovarian, fallopian tube, or primary peritoneal cancer to criteria
September 2018	Annual review
June 2019	Annual editorial review and reference update. Renamed policy Bevacizumab. Addition of biosimilar Mvasi
July 2019	Addition of biosimilar Zirabev
September 2019	Annual editorial review and reference update
December 2019	Annual review. Addition of requirement to trial preferred product for all diagnoses other than ocular diseases. Changed ocular disease indications to Avastin only per SME
March 2020	Annual review and reference update
May 2020	Addition of indication: used in combination with olaparib (Lynparza) for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD) positive

	status defined by either: a deleterious or suspected deleterious BRCA mutation, and/or genomic instability
June 2020	Annual review and reference update. Addition of indication: hepatocellular carcinoma
December 2020	Annual review and reference update. Added Zirabev as a preferred product
March 2021	Annual editorial review and reference update. Under Avastin only: Added requirement for no dual therapy with other VEGF inhibitors for ocular indications to align with other VEGF Inhibitor policies. Added Appendix 1. Clarification added to the t/f, intolerance, C/I to preferred products requirement indicating that it only applies to claims adjudicated through the pharmacy benefit
July 2021	Removed Macugen from Appendix 1 due to being discontinued
September 2021	Annual review and reference update
March 2022	Annual editorial review and reference update. Vabysmo and Susvimo added to Appendix 1
June 2022	Annual editorial review and reference update. Addition of biosimilar Alymsys to policy

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 16, 2022 and is effective on July 1, 2022.

Appendix 1 - List of VEGF Inhibitors for Ocular Indications

Generic Name	Brand Name
aflibercept	Eylea
bevacizumab	Avastin
brolucizumab-dbll	Beovu
faricimab-svoa	Vabysmo
ranibizumab	Lucentis
ranibizumab	Susvimo