BlueCross BlueShield of North Carolina

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# Corporate Medical Policy

# Oncologic Uses of Bevacizumab (Avastin®) and Bevacizumab Biosimilars

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## Description of Procedure or Service

Bevacizumab (Avastin®) is a humanized monoclonal antibody directed against vascular endothelial growth factor-A (VEGF-A). Vascular endothelial growth factors (VEGFs) and their receptors (VEGF-Rs) contribute to tumor growth and metastasis by promoting angiogenesis.

VEGFs and their receptors (VEGF-Rs) contribute to tumor growth and metastasis by promoting angiogenesis, the growth of new vasculature. Without angiogenesis, nutrients, oxygen and other essential molecules reach malignant cells only by passive diffusion from pre-existing blood vessels, which would limit most tumors to diameters of several millimeters. A VEGF mutation in tumors also correlates with tumor size. Certain normal physiologic processes (e.g., embryonic development, menstruation, wound healing) require angiogenesis, and some non-cancer pathologic processes are linked to angiogenesis (e.g., macular degeneration, atherosclerosis, psoriasis).

Bevacizumab, a vascular endothelial growth factor-specific angiogenesis inhibitor, is used in the treatment of a variety of cancers. Bevacizumab (Avastin) was first approved by the U.S. Food and Drug Administration (FDA) in February 2004 and is indicated for the treatment of the following indications: metastatic colorectal cancer; unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer; recurrent glioblastoma in adults; metastatic renal cell carcinoma; persistent, recurrent, or metastatic cervical cancer; epithelial ovarian, fallopian tube, or primary peritoneal cancers; and unresectable or metastatic hepatocellular carcinoma.

The following biosimilars to bevacizumab have been approved by the FDA for the same labeled indications as the parent drug, Avastin (bevacizumab) for the treatment of: metastatic colorectal cancer; unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer; recurrent glioblastoma in adults; metastatic renal cell carcinoma; and persistent, recurrent, or metastatic cervical cancer.

- FDA approved September 2017, Mvasi™ (bevacizumab-awwb)
- FDA approved June 2019, Zirabev™ (bevacizumab-bvzr)

This policy addresses labeled and off-label indications for oncologic uses of bevacizumab and bevacizumab biosimilars. This policy does not address treatment of non-oncologic indications or disorders, including ocular use.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

# Oncologic Uses of Bevacizumab (Avastin®) and Bevacizumab Biosimilars

## Policy

**BCBSNC will provide coverage for oncologic uses of bevacizumab (Avastin®) and bevacizumab biosimilars (bevacizumab-awwb, bevacizumab-bvzr) when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.**

## Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When Oncologic Uses of Bevacizumab (Avastin®) and Bevacizumab Biosimilars are covered

Bevacizumab (Avastin) and bevacizumab biosimilars (bevacizumab-awwb, bevacizumab-bvzr) may be considered medically necessary when the following criteria are met:

1. If the request is for bevacizumab (Avastin) or non-preferred bevacizumab biosimilars, then both of the following criteria are met:
    a. The patient has a documented serious adverse event that required medical intervention to both preferred bevacizumab biosimilar products [bevacizumab-awwb (Mvasi), bevacizumab-bvzr (Zirabev)] that is not anticipated with the requested product; **AND**
    b. The prescriber has completed and submitted an FDA MedWatch Adverse Event Reporting Form; **AND**

2. Bevacizumab (Avastin) and bevacizumab biosimilars (bevacizumab-awwb, bevacizumab-bvzr) will be used for the following oncologic indications:

    a. Treatment of metastatic colorectal cancer:

        i. When used in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment*, OR
        ii. When used 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*, OR
        iii. When used as first-line therapy, in combination with oxaliplatin and capecitabine (NCCN 2A); **AND**
        iv. Bevacizumab will not be used as adjuvant treatment for colon cancer.*

    b. Treatment of unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer when used in combination with carboplatin and paclitaxel for first-line treatment.*

    c. Treatment of recurrent glioblastoma in adult patients.*

    d. Treatment of metastatic renal cell carcinoma when used in combination with interferon alfa.*

e. Treatment of persistent, recurrent, or metastatic cervical cancer when used in combination with paclitaxel and cisplatin, or paclitaxel and topotecan.*

f. Treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer in the following instances:

   i. When used in combination with carboplatin and paclitaxel, followed by bevacizumab as a single agent, for stage III or IV disease following initial surgical resection*, OR
   ii. When used in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens*, OR
   iii. When used in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by bevacizumab as a single agent, for platinum-sensitive recurrent disease.*

g. Treatment of unresectable or metastatic hepatocellular carcinoma when used in combination with atezolizumab in patients who have not received prior systemic chemotherapy.*

h. Treatment of malignant pleural mesothelioma, as first-line therapy for unresectable disease, in combination with pemetrexed and cisplatin (NCCN 1) or pemetrexed and carboplatin. (NCCN 2A)

i. Treatment of recurrent or metastatic, HER2-negative breast cancer, as first-line therapy, in combination with paclitaxel. (NCCN 2A)

*Indicates an indication approved by the U.S. Food and Drug Administration.

Use of bevacizumab (Avastin) and bevacizumab biosimilars (bevacizumab-awwb, bevacizumab-bvzr) may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either:

- In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); **OR**

- In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached.

## When Oncologic Uses of Bevacizumab (Avastin®) and Bevacizumab Biosimilars are not covered

Bevacizumab (Avastin) and bevacizumab biosimilars (bevacizumab-awwb, bevacizumab-bvzr) are considered **investigational** for oncologic uses when the above criteria are not met.

Except as noted above, treatment with bevacizumab and bevacizumab biosimilars is considered **investigational** for all other cancers including, but not limited to, advanced adenocarcinoma of the pancreas, prostate cancer, colon cancer as adjuvant therapy, and advanced gastric cancer.

# Oncologic Uses of Bevacizumab (Avastin®) and Bevacizumab Biosimilars

Bevacizumab (Avastin) and bevacizumab biosimilars (bevacizumab-awwb, bevacizumab-bvzr) are considered investigational when used for:

1. Non-cancer indications; **OR**

2. When criteria are not met regarding FDA labeling **OR** strong endorsement/support by nationally recognized compendia, as stated under "When Oncologic Uses of Bevacizumab (Avastin®) and Bevacizumab Biosimilars are covered."

## Policy Guidelines

Bevacizumab and bevacizumab biosimilars (bevacizumab-awwb, bevacizumab-bvzr) are administered as an intravenous infusion. Bevacizumab and bevacizumab biosimilars should not be administered for 28 days following major surgery and until surgical wounds are fully healed.

The recommended dosing regimens for bevacizumab (Avastin) and bevacizumab biosimilars (bevacizumab-awwb, bevacizumab-bvzr) is as follows:

Metastatic colorectal cancer:
- 5 mg/kg every 2 weeks with bolus-IFL (irinotecan, 5-fluorouracil, leucovorin)
- 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 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

Additional recommended dosing regimens for bevacizumab (Avastin) are as follows:

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:
- 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:
- 15 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
- 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 1200 mg of atezolizumab every 3 weeks

The FDA has issued warnings in patients receiving bevacizumab and bevacizumab biosimilars for gastrointestinal perforations, surgery and wound healing complications, and hemorrhage. Other warnings and precautions include arterial thromboembolic events (ATE) and venous thromboembolic events (VTE), hypertension, congestive heart failure (CHF), posterior reversible encephalopathy syndrome (PRES), renal injury and proteinuria, infusion-related reactions, embryo-fetal toxicity, and ovarian failure.

Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy (CMP), "Investigational (Experimental) Services."

Please refer to CMP "Investigational (Experimental) Services" for a summary of evidence standards from nationally recognized compendia.

## Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable codes*: *C9257, J9035, Q5107, Q5118, S0353, S0354*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

Genentech, Inc. Avastin (bevacizumab) injection, for intravenous use. Highlights of prescribing information. June 2019. Available at: https://www.gene.com/download/pdf/avastin_prescribing.pdf. Last accessed November 2019.

Amgen Inc. Mvasi (bevacizumab-awwb) injection, for intravenous use. Highlights of prescribing information. June 2019. Available at: https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/mvasi/mvasi_pi_hcp_english.pdf. Last accessed November 2019.

Pfizer Biosimilars. Zirabev (bevacizumab-bvzr) injection, for intravenous use. Highlights of prescribing information. June 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761099s000lbl.pdf. Last accessed November 2019.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Colon Cancer, version 3.2019. Revised September 26, 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed October 2019.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Rectal Cancer, version 3.2019. Revised September 26, 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed October 2019.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Breast Cancer, version 3.2019. Revised September 6, 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed October 2019.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Malignant Pleural Mesothelioma, version 2.2019. Revised April 1, 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mpm.pdf. Accessed October 2019.

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Genentech, Inc. Avastin (bevacizumab) injection, for intravenous use. Highlights of prescribing information. October 2020. Available at: https://www.gene.com/download/pdf/avastin_prescribing.pdf. Last accessed November 2020.

Specialty Matched Consultant Advisory Panel 11/2020

## Policy Implementation/Update Information

11/12/19 New policy developed. Bevacizumab (Avastin) and bevacizumab biosimilars (bevacizumab-awwb, bevacizumab-bvzr) may be considered medically necessary for the following FDA approved oncologic uses: metastatic colorectal cancer; unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer; recurrent glioblastoma in adults; metastatic renal cell carcinoma; persistent, recurrent, or metastatic cervical cancer; and epithelial ovarian, fallopian tube, or primary peritoneal cancers; and for the following off-label indications: malignant pleural mesothelioma and HER2-negative breast cancer, when the medical criteria and guidelines are met. Added HCPCS codes C9257, J9035, Q5107, Q5118, S0353, and S0354 to Billing/Coding section. References added. Medical Director review 11/2019. **Policy notification given 11/12/2019 for effective date 1/14/2020**. (krc)

10/27/20 Added the following requirements to "When Covered" section: "If the request is for bevacizumab (Avastin) or non-preferred bevacizumab biosimilars, then both of the following criteria are met: patient has a documented serious adverse event that required medical intervention to both preferred bevacizumab biosimilar products [bevacizumab-awwb (Mvasi), bevacizumab-bvzr (Zirabev)] that is not anticipated with the requested product AND prescriber has completed and submitted an FDA MedWatch Adverse Event Reporting Form." Minor typographical and formatting changes made throughout for clarity. Medical Director review 10/2020. **Policy notification given 10/27/2020 for effective date 1/1/2021**. (krc)

12/31/20 Added the following indication to "When Covered" section: unresectable or metastatic hepatocellular carcinoma when used in combination with atezolizumab in patients who have not received prior systemic chemotherapy. Removed statement regarding off-label use of bevacizumab biosimilars for epithelial ovarian, fallopian tube, or primary peritoneal cancer. Reference added. Specialty Matched Consultant Advisory Panel review 11/18/2020. (krc)