

**Clinical Policy: Bevacizumab (Avastin, Mvasi, Zirabev)**

Reference Number: CP.PHAR.93

Effective Date: 12.01.11

Last Review Date: 11.20

Line of Business: Commercial, HIM, Medicaid

[Coding Implications](#)[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

**Description**

Bevacizumab (Avastin<sup>®</sup>), bevacizumab-awwb (Mvasi<sup>®</sup>), bevacizumab-bvzr (Zirabev<sup>™</sup>) are vascular endothelial growth factor-specific angiogenesis inhibitors.

**FDA Approved Indication(s)**

Avastin, Mvasi, and Zirabev are indicated for the treatment of:

- Metastatic colorectal cancer, in combination with intravenous 5-fluorouracil (5-FU)-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
- Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer (NSCLC), in combination with carboplatin and paclitaxel for first-line treatment
- Recurrent glioblastoma in adults
- Metastatic renal cell carcinoma (RCC) in combination with interferon alfa
- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan

Avastin and Zirabev are also indicated for the treatment of:

- Epithelial ovarian, fallopian tube, or primary peritoneal cancer:
  - In combination with carboplatin and paclitaxel, followed by Avastin/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 Avastin/Zirabev as a single agent, for platinum-sensitive recurrent disease

Avastin is also indicated for the treatment of:

- Hepatocellular carcinoma (HCC) in combination with atezolizumab for patients with unresectable or metastatic HCC who have not yet received prior systemic therapy.

Limitation(s) of use: Bevacizumab-products are not indicated for adjuvant treatment of colon cancer.

**Policy/Criteria**

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

It is the policy of health plans affiliated with Centene Corporation<sup>®</sup> that Avastin, Mvasi, and Zirabev are **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria****A. FDA-Approved Indications (must meet all):**

1. Diagnosis of one of the following (a-g):
  - a. Colorectal cancer;
  - b. Non-squamous non-small cell lung cancer;
  - c. Glioblastoma;
  - d. Metastatic renal cell carcinoma;
  - e. Cervical cancer;
  - f. Epithelial ovarian, fallopian tube, or primary peritoneal cancer;
  - g. Hepatocellular carcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age  $\geq$  18 years;
4. Member meets one of the following (a-g):
  - a. For colorectal cancer, used in combination with one of the following (i, ii, iii):
    - i. 5-FU based chemotherapy;
    - ii. Irinotecan and oxaliplatin;
    - iii. Irinotecan if previously received adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months;
  - b. For non-squamous non-small cell lung cancer, prescribed as one of the following (i-v):
    - i. Single agent therapy;
    - ii. In combination with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease;
    - iii. In combination with pemetrexed;
    - iv. In combination with Tecentriq<sup>®</sup>;
    - v. In combination with erlotinib for sensitizing EGFR mutation-positive histology, recurrent, advanced, or metastatic disease;
  - c. For glioblastoma, patient has recurrent disease;
  - d. For metastatic renal cell carcinoma, used as a single-agent or in combination with interferon alfa, everolimus, or erlotinib (for advanced papillary renal cell carcinoma including hereditary leiomyomatosis and renal cell cancer (HLRCC));
  - e. For cervical cancer, used in combination with paclitaxel and cisplatin, carboplatin, or topotecan for the treatment of persistent, recurrent, or metastatic disease;
  - f. For epithelial ovarian, fallopian tube, or primary peritoneal cancer, one of the following (i, ii, iii, or iv):
    - i. Prescribed in combination with carboplatin and paclitaxel, followed by bevacizumab as a single agent, for one of the following (1 or 2):

1. Stage III or IV disease following initial surgical resection;
2. Stage II-IV high-grade serous, low-grade serous, endometrioid (Grade 1/2/3), clear cell carcinoma, or carcinosarcoma;
- ii. For platinum-resistant recurrent disease, prescribed in combination with paclitaxel, pegylated liposomal doxorubicin, topotecan, or cyclophosphamide;
- iii. For platinum-sensitive recurrent disease, prescribed in combination with carboplatin and paclitaxel, or carboplatin and gemcitabine, or carboplatin and liposomal doxorubicin, followed by bevacizumab as a single agent;
- iv. Prescribed as a single agent for clinical relapse in patients with stage II-IV malignant sex cord-stromal tumors;
- g. For HCC, used in combination with Tecentriq<sup>®</sup> as first-line systemic therapy;
5. For Avastin requests, member meets one of the following (a or b):
  - a. Medical justification supports inability to use Mvasi or Zirabev (e.g., contraindications to the excipients);\*  
*\*Prior authorization may be required for Mvasi and Zirabev*
  - b. Request is for Stage IV or metastatic cancer for a State with regulations against step therapy in advanced oncology settings (*see Appendix E*);
6. Request meets one of the following (a or b):\*
  - a. Dose does not exceed 15 mg/kg IV every 3 weeks or 10 mg/kg IV every 2 weeks (*see Appendix F for dose rounding guidelines*);
  - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**

**Medicaid/HIM** – 6 months

**Commercial** – Length of Benefit

**B. Oncology - Non-FDA-Approved Indications (off-label) (must meet all):**

1. Diagnosis of one of the following conditions (a-m):
  - a. Anaplastic gliomas;
  - b. Breast cancer;
  - c. Endometrial carcinoma;
  - d. Intracranial and spinal ependymoma;
  - e. Low-grade (WHO Grade II) infiltrative supratentorial astrocytoma/ oligodendroglioma;
  - f. Malignant pleural mesothelioma;
  - g. Medulloblastoma;
  - h. Meningioma;
  - i. Metastatic spine tumors or brain metastases;
  - j. Primary central nervous system cancers;
  - k. Small bowel adenocarcinoma;
  - l. Soft tissue sarcoma – solitary fibrous tumor or angiosarcoma;
  - m. Vulvar cancer – squamous cell carcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age  $\geq$  18 years;
4. For Avastin requests, medical justification supports inability to use Mvasi or Zirabev (e.g., contraindications to the excipients);

*\*Prior authorization may be required*

5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).\*

*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**

**Medicaid/HIM** – 6 months

**Commercial** – Length of Benefit

**C. Ophthalmology - Non-FDA-Approved Indications (off-label) (must meet all):**

1. Diagnosis of one of the following conditions (a-g):
  - a. Neovascular (wet) age-related macular degeneration;
  - b. Macular edema following retinal vein occlusion;
  - c. Diabetic macular edema;
  - d. Proliferative diabetic retinopathy;
  - e. Neovascular glaucoma;
  - f. Choroidal neovascularization associated with: angioid streaks, no known cause, inflammatory conditions, high pathologic myopia, or ocular histoplasmosis syndrome;
  - g. Diabetic retinopathy associated with ocular neovascularization (choroidal, retinal, iris);
2. Age  $\geq$  18 years;
3. Request is for bevacizumab intravitreal solution;
 

*\*Requests for IV formulations of Avastin, Mvasi, and Zirabev will not be approved*
4. Request meets one of the following (a or b):
  - a. Dose does not exceed 2.5 mg/dose;
  - b. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration:**

**Medicaid/HIM** – 6 months

**Commercial** – Length of Benefit

**D. Other diagnoses/indications**

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**II. Continued Therapy**

**A. All Indications in Section I (must meet all):**

1. Member meets one of the following (a or b):
  - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
  - b. Documentation supports that member is currently receiving Avastin, Mvasi, or Zirabev for a covered oncology indication listed in section I and has received this medication for at least 30 days;

2. Member is responding positively to therapy;
3. For Avastin requests for non-ophthalmology uses, member meets one of the following (a or b):
  - a. Medical justification supports inability to use Mvasi or Zirabev (e.g., contraindications to the excipients);\*  
*\*Prior authorization may be required for Mvasi and Zirabev*
  - b. Request is for Stage IV or metastatic cancer for a State with regulations against step therapy in advanced oncology settings (*see Appendix E*);
4. If request is for a dose increase, request meets one of the following (a or b):\*
  - a. New dose does not exceed 15 mg/kg IV every 3 weeks or 10 mg/kg IV every 2 weeks (*see Appendix F for dose rounding guidelines*);
  - b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).  
*\*Prescribed chemotherapy regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**

Medicaid/HIM – 6 months

Commercial – Length of Benefit

**B. Other diagnoses/indications (must meet 1 or 2):**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.

**Approval duration: Duration of request or 6 months (whichever is less);** or

2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**III. Diagnoses/Indications for which coverage is NOT authorized:**

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

**IV. Appendices/General Information***Appendix A: Abbreviation/Acronym Key*

5-FU: fluorouracil

FDA: Food and Drug Administration

FOLFIRI: fluorouracil, leucovorin,  
irinotecanFOLFOX: fluorouracil, leucovorin,  
oxaliplatin

HCC: hepatocellular carcinoma

HLRCC: hereditary leiomyomatosis and  
renal cell cancerNCCN: National Comprehensive Cancer  
Network*Appendix B: Therapeutic Alternatives*

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.*

| Drug Name   | Dosing Regimen  | Dose Limit/<br>Maximum Dose |
|---|---|-----------------------------|
| <b><i>Metastatic carcinoma of the colon or rectum</i></b>   |   |                             |
| FOLFOX4 = Infusional 5-FU/leucovorin/ oxaliplatin   | Oxaliplatin 85 mg/m <sup>2</sup> IV over 2 hours day 1; leucovorin 200 mg/m <sup>2</sup> IV over 2 hours days 1 & 2, followed by 5-FU 400 mg/m <sup>2</sup> IV bolus over 2-4 minutes, followed by 600 mg/m <sup>2</sup> IV 5-FU continuous infusion over 22 hours on days 1 & 2. Repeat cycle every 14 days. | Varies                      |
| FOLFIRI = Infusional 5-FU/ leucovorin/Camptosar <sup>®</sup> (irinotecan)   | Camptosar 180 mg/m <sup>2</sup> IV over 90 minutes day 1; Leucovorin 400 mg/m <sup>2</sup> IV over 2 hours day 1 followed by 5-FU 400 mg/m <sup>2</sup> IV bolus over 2-4 minutes, followed by 2.4 gm/m <sup>2</sup> IV 5-FU continuous infusion over 46 hours. Repeat cycle every 14 days.                   | Varies                      |
| capecitabine (Xeloda <sup>®</sup> )   | 2500 mg/m <sup>2</sup> PO BID for 2 weeks; repeat cycles of 2 weeks on and 1 week off.<br>For patients who cannot tolerate intensive therapy.   | Varies                      |
| IROX = oxaliplatin/ Camptosar (irinotecan)  | Oxaliplatin 85 mg/m <sup>2</sup> IV followed by Camptosar 200 mg m <sup>2</sup> IV over 30-90 minutes every 3 weeks   | Varies                      |
| Camptosar (irinotecan)  | 180 mg/m <sup>2</sup> IV every 2 weeks or 300-350 mg/m <sup>2</sup> IV every 3 weeks  | Varies                      |
| <b><i>NSCLC</i></b>   |   |                             |
| cisplatin<br>carboplatin<br>paclitaxel<br>docetaxel<br>vinorelbine<br>gemcitabine<br>etoposide<br>irinotecan<br>vinblastine<br>mitomycin<br>ifosfamide<br>pemetrexed disodium (Alimta <sup>®</sup> ) (2 <sup>nd</sup> line)<br>erlotinib (Tarceva <sup>®</sup> )<br>Tecentriq <sup>®</sup> (atezolizumab) | Various doses   | Varies                      |

| Drug Name                                    | Dosing Regimen  | Dose Limit/<br>Maximum Dose |
|--|---|-----------------------------|
| <b><i>Ovarian Cancer</i></b>                 |   |                             |
| carboplatin and paclitaxel                   | Carboplatin dosed at an area under the curve (AUC) of 5-7.5 and paclitaxel 175 mg/m <sup>2</sup> IV over 3 hours given every 3 weeks for 6 courses.   | Varies                      |
| docetaxel taxotere and carboplatin           | Docetaxel, 60-75 mg/m <sup>2</sup> IV over 1 hour plus carboplatin dosed at AUC of 5 to 6 every 3 weeks.  | Varies                      |
| <b><i>Glioblastoma Multiforme</i></b>        |   |                             |
| temozolomide (Temodar <sup>®</sup> )         | Maintenance phase cycles: 150 mg-200 mg/m <sup>2</sup> PO days 1-5. Repeat every 28 days.   | Varies                      |
| carmustine (Bicnu <sup>®</sup> )             | 150 mg to 200 mg/m <sup>2</sup> IV on day 1. Repeat every 6-8 weeks for one year or tumor progression.  | Varies                      |
| <b><i>Cervical Cancer</i></b>                |   |                             |
| cisplatin/paclitaxel                         | Paclitaxel: 135 mg/m <sup>2</sup> IV as a continuous infusion over 24 hours day 1<br><br>Cisplatin: 50 mg/m <sup>2</sup> IV on day 2<br><br>Repeat cycle every 21 days for up to a total of 6 cycles; responders may continue beyond 6 cycles | Varies                      |
| carboplatin/paclitaxel                       | Paclitaxel: 175 mg/m <sup>2</sup> IV followed by carboplatin AUC 5-6 IV<br><br>Repeat every 21 days for up to 6 cycles  | Varies                      |
| cisplatin/topotecan (Hycamtin <sup>®</sup> ) | Topotecan: 10.75 mg/m <sup>2</sup> /day IV on days 1, 2, and 3<br><br>Cisplatin: 50 mg/m <sup>2</sup> IV on day 1 only<br><br>Repeat cycle every 21 days for up to a total of 6 cycles; responders may continue beyond 6 cycles               | Varies                      |



| Drug Name                           | Dosing Regimen   | Dose Limit/<br>Maximum Dose |
|-------------------------------------|--|-----------------------------|
| topotecan<br>(Hycamtin®)/paclitaxel | <p>Paclitaxel: 135 mg/m<sup>2</sup> IV continuous infusion over 24 hours day 1</p> <p>Topotecan: 0.75 mg/m<sup>2</sup>/day IV on days 1, 2, and 3</p> <p>Repeat cycle every 21 days for up to a total of 6 cycles; responders may continue beyond 6 cycles</p> | Varies                      |

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

#### *Appendix C: Contraindications/Boxed Warnings*

None reported

#### *Appendix D: General Information*

- The FDA revoked the approval of the breast cancer indication for Avastin (bevacizumab) on November 18, 2011. Avastin used for metastatic breast cancer has not been shown to provide a benefit, in terms of delay in the growth of tumors that would justify its serious and potentially life-threatening risks. Nor is there evidence that use of Avastin will either help women with breast cancer live longer or improve their quality of life. More information at: <http://www.fda.gov/NewsEvents/Newsroom/ucm279485.htm>
- Fatal pulmonary hemorrhage can occur in patients with NSCLC treated with chemotherapy and bevacizumab. The incidence of severe or fatal hemoptysis was 31% in patients with squamous histology and 2.3% with NSCLC excluding predominant squamous histology. Patients with recent hemoptysis should not receive bevacizumab.

#### *Appendix E: States with Regulations against Redirections in Stage IV or Metastatic Cancer*

| State | Step Therapy Prohibited? | Notes   |
|-------|--------------------------|---|
| FL    | Yes                      | For stage 4 metastatic cancer and associated conditions.  |
| GA    | Yes                      | For stage 4 metastatic cancer. Redirection does not refer to review of medical necessity or clinical appropriateness.   |
| IA    | Yes                      | For standard of care stage 4 cancer drug use, supported by peer-reviewed, evidence-based literature, and approved by FDA.   |
| LA    | Yes                      | For stage 4 advanced, metastatic cancer or associated conditions. Exception if “clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy. |
| OH    | Yes                      | <i>*Applies to Commercial and HIM requests only*</i><br>For stage 4 metastatic cancer and associated conditions   |
| PA    | Yes                      | For stage 4 advanced, metastatic cancer   |
| TN    | Yes                      | For advanced metastatic cancer and associated conditions  |
| TX    | Yes                      | For stage 4 advanced, metastatic cancer and associated conditions   |



## Appendix F: Dose Rounding Guidelines

| Weight-based Dose Range | Vial Quantity Recommendation                       |
|-------------------------|--|
| ≤ 104.99 mg             | 1 vial of 100 mg/4 mL                              |
| 105 mg-209.99 mg        | 2 vials of 100 mg/4 mL                             |
| 210 mg-314.99 mg        | 3 vials of 100 mg/4 mL                             |
| 315 mg-419.99 mg        | 1 vial of 400 mg/16 mL                             |
| 420 mg-524.99 mg        | 1 vial of 100 mg/4 mL and 1 vial of 400 mg/16 mL   |
| 525 mg-629.99 mg        | 2 vials of 100 mg/4 mL and 1 vial of 400 mg/16 mL  |
| 630 mg-734.99 mg        | 3 vials of 100 mg/4 mL and 1 vial of 400 mg/16 mL  |
| 735 mg-839.99 mg        | 2 vials of 400 mg/16 mL                            |
| 840 mg-944.99 mg        | 1 vials of 100 mg/4 mL and 2 vials of 400 mg/16 mL |
| 945 mg-1,049.99 mg      | 2 vials of 100 mg/4 mL and 2 vials of 400 mg/16 mL |
| 1,050 mg-1,154.99 mg    | 3 vials of 100 mg/4 mL and 2 vials of 400 mg/16 mL |
| 1,155 mg-1,259.99 mg    | 3 vials of 400 mg/16 mL                            |
| 1,260 mg-1,364.99 mg    | 1 vials of 100 mg/4 mL and 3 vials of 400 mg/16 mL |
| 1,365 mg-1,469.99 mg    | 2 vials of 100 mg/4 mL and 3 vials of 400 mg/16 mL |
| 1,470 mg-1,574.99 mg    | 3 vials of 100 mg/4 mL and 3 vials of 400 mg/16 mL |
| 1,575 mg-1,679.99 mg    | 4 vials of 400 mg/16 mL                            |
| 1,680 mg-1,784.99 mg    | 1 vials of 100 mg/4 mL and 4 vials of 400 mg/16 mL |
| 1,785 mg-1,889.99 mg    | 2 vials of 100 mg/4 mL and 4 vials of 400 mg/16 mL |
| 1,890 mg-1,994.99 mg    | 3 vials of 100 mg/4 mL and 4 vials of 400 mg/16 mL |
| 1,995 mg-2,099.99 mg    | 5 vials of 400 mg/16 mL                            |

## V. Dosage and Administration

| Indication                               | Dosing Regimen  | Maximum Dose   |
|--|---|--|
| Metastatic colorectal cancer             | 5 mg/kg or 10 mg/kg once every 14 days as an IV infusion in combination with a 5-FU based chemotherapy regimen until disease progression is detected.<br>5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks when used in combination with a fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy regimen in patients who have progressed on a first-line Avastin-containing regimen | 15 mg/kg IV every 3 weeks or 10 mg/kg IV every 2 weeks |
| Non-squamous, non-small cell lung cancer | 15 mg/kg IV infusion every 3 weeks with carboplatin/paclitaxel  | 15 mg/kg IV every 3 weeks or 10 mg/kg IV every 2 weeks |

| Indication  | Dosing Regimen  | Maximum Dose   |
|---|---|--|
| Ovarian cancer  | 15 mg/kg IV infusion every 3 weeks  | 15 mg/kg IV every 3 weeks or 10 mg/kg IV every 2 weeks |
| Platinum resistant ovarian cancer   | 10 mg/kg intravenously every 2 weeks with weekly paclitaxel, liposomal doxorubicin, or topotecan            | 15 mg/kg IV every 3 weeks or 10 mg/kg IV every 2 weeks |
| HCC   | 15 mg/kg IV every 3 weeks plus Tecentriq 1,200 mg IV on the same day  | 15 mg/kg IV every 3 weeks                              |
| Clear cell renal carcinoma  | 10 mg/kg IV every 2 weeks with interferon alfa  | 15 mg/kg IV every 3 weeks or 10 mg/kg IV every 2 weeks |
| Glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma | 10 mg/kg IV every 2 weeks   | 15 mg/kg IV every 3 weeks or 10 mg/kg IV every 2 weeks |
| Soft tissue sarcoma   | 15 mg/kg IV infusion every 3 weeks  | 15 mg/kg IV every 3 weeks or 10 mg/kg                  |
| Cervical cancer   | 15 mg/kg IV infusion every 3 weeks (in combination with paclitaxel and either cisplatin or topotecan) until | 15 mg/kg IV every 3 weeks or 10 mg/kg                  |
| Neovascular (wet) macular degeneration  | 1.25 to 2.5 mg administered by intravitreal injection every 4 weeks   | 2.5 mg/dose  |
| Neovascular glaucoma  | 1.25 mg administered by intravitreal injection every 4 weeks  | 2.5 mg/dose  |
| Macular edema secondary to retinal vein occlusion                             | 1 mg to 2.5 mg administered by intravitreal injection every 4 weeks   | 2.5 mg/dose  |
| Proliferative diabetic retinopathy  | 1.25 mg administer by intravitreal injection 5 to 20 days before vitrectomy                                 | 2.5 mg/dose  |
| Diabetic macular edema  | 1.25 mg administered by intravitreal injection  | 2.5 mg/dose  |

| Indication   | Dosing Regimen   | Maximum Dose  |
|--|--|---|
| Malignant mesothelioma of pleura   | 15 mg/kg IV (plus pemetrexed 500 mg/m <sup>2</sup> IV and cisplatin 75 mg/m <sup>2</sup> IV) every 21 days for up to 6 cycles, followed by maintenance bevacizumab 15 mg/kg every 21 days until disease progression or unacceptable toxicity. All patients should receive folic acid 400 mcg orally daily and vitamin B12 1000 mcg IM every 3 weeks, both beginning 7 days prior to pemetrexed and continuing for 3 weeks following the last pemetrexed dose (off-label dosage). | 2.5 mg/dose   |
| Metastatic colorectal cancer in previously untreated elderly patients ineligible for oxaliplatin- or irinotecan-based chemotherapy | 7.5 mg/kg IV on day 1 with capecitabine 1,000 mg/m <sup>2</sup> orally twice daily on days 1 to 14, given every 3 weeks until disease progression.   | 15 mg/kg IV every 3 weeks or 10 mg/kg IV every 2 weeks. |

## VI. Product Availability

Single-use vials: 100 mg/4 mL, 400 mg/16 mL

## VII. References

1. Avastin Prescribing Information. South San Francisco, CA: Genentech, Inc. May 2020. Available at: [www.avastin.com](http://www.avastin.com). Accessed July 6, 2020.
2. Mvasi Prescribing Information. Thousand Oaks, CA: Amgen Inc. June 2019. Available at: <https://www.mvasi.com/hcp>. Accessed July 6, 2020.
3. Zirabev Prescribing Information. New York, NY: Pfizer Inc. February 2021. Available at: <http://labeling.pfizer.com/ShowLabeling.aspx?id=11860>. Accessed February 26, 2021.
4. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: [http://www.nccn.org/professionals/drug\\_compendium](http://www.nccn.org/professionals/drug_compendium). Accessed July 6, 2020.
5. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at: <http://www.clinicalpharmacology-ip.com/>.
6. American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern® Guidelines. Age-Related Macular Degeneration. San Francisco, CA: American Academy of Ophthalmology; September 2019. Available at: [www.aao.org/ppp](http://www.aao.org/ppp). Accessed July 6, 2020.
7. American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern® Guidelines. Retinal Vein Occlusions. San Francisco, CA: American Academy of Ophthalmology; September 2019. Available at: [www.aao.org/ppp](http://www.aao.org/ppp). Accessed July 6, 2020.
8. American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern® Guidelines. Diabetic Retinopathy. San Francisco, CA: American Academy of Ophthalmology; September 2019. Available at: [www.aao.org/ppp](http://www.aao.org/ppp). Accessed July 6, 2020.

**Coding Implications**

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

| HCPCS Codes | Description   |
|-------------|---|
| J9035       | Injection, bevacizumab, 10 mg                             |
| C9257       | Injection, bevacizumab, 0.25 mg                           |
| Q5107       | Injection, bevacizumab-awwb, biosimilar, (Mvasi), 10 mg   |
| Q5118       | Injection, bevacizumab-bvcr, biosimilar, (Zirabev), 10 mg |

**ICD-10-CM Diagnosis Codes that Support Coverage Criteria**

The following is a list of diagnosis codes that support coverage for the applicable covered procedure code(s).

| ICD-10-CM Code   | Description   |
|------------------|---|
| A18.53           | Tuberculosis chorioretinitis  |
| C17.0 – C17.9    | Malignant neoplasm of small intestine   |
| C18.0 – C18.9    | Malignant neoplasm of colon   |
| C19              | Malignant neoplasm of rectosigmoid junction   |
| C20              | Malignant neoplasm of rectum  |
| C21.8            | Malignant neoplasm of overlapping sites of rectum, anus and anal canal                      |
| C33              | Malignant neoplasm of trachea   |
| C34.00 – C34.02  | Malignant neoplasm of main bronchus   |
| C34.10 – C34.12  | Malignant neoplasm of upper lobe, bronchus or lung  |
| C34.2            | Malignant neoplasm of middle lobe, bronchus or lung   |
| C34.30 – C34.32  | Malignant neoplasm of lower lobe, bronchus or lung  |
| C34.80 – C34.82  | Malignant neoplasm of overlapping sites of bronchus and lung                                |
| C34.90 – C34.92  | Malignant neoplasm of unspecified part of bronchus or lung                                  |
| C48.0 – C48.8    | Malignant neoplasm of retroperitoneum and peritoneum  |
| C49.0 – C49.9    | Malignant neoplasm of other connective and soft tissue                                      |
| C50.01 – C50.929 | Malignant neoplasm of breast  |
| C53.0 – C53.9    | Malignant neoplasm of cervix uteri  |
| C54.0 – C55      | Malignant neoplasm of corpus uteri  |
| C56.1 – C56.9    | Malignant neoplasm of ovary   |
| C57.0 – C57.9    | Malignant neoplasm of other and unspecified female genital organs                           |
| C64.1 – C64.9    | Malignant neoplasm of kidney, except renal pelvis   |
| C65.1 – C65.9    | Malignant neoplasm of renal pelvis  |
| C70.0 – C70.9    | Malignant neoplasm of meninges  |
| C71.0 – C71.9    | Malignant neoplasm of brain   |
| C72.0 – C72.9    | Malignant of spinal cord, cranial neoplasm nerves and other parts of central nervous system |
| D32.0 – D32.9    | Benign neoplasm of meninges   |
| D42.0 – D42.9    | Neoplasm of uncertain behavior of meninges  |
| E08.311,         | Diabetes mellitus due to underlying condition with  |

| ICD-10-CM Code  | Description   |
|---|---|
| E08.3211 – E08.3219,<br>E08.3311 – E08.3319,<br>E08.3411 – E08.3419,<br>E08.3511 – E08.3519             | diabetic retinopathy with macular edema   |
| E09.311,<br>E09.3211 – E09.3219,<br>E09.3311 – E09.3319,<br>E09.3411 – E09.3419,<br>E09.3511 – E09.3519 | Drug or chemical induced diabetes mellitus with diabetic retinopathy with macular edema |
| E10.311,<br>E10.3211 – E10.3219,<br>E10.3311 – E10.3319,<br>E10.3411 – E10.3419,<br>E10.3511 – E10.3519 | Type 1 diabetes mellitus with diabetic retinopathy with macular edema                   |
| E11.311,<br>E11.3211 – E11.3219,<br>E11.3311 – E11.3319,<br>E11.3411 – E11.3419,<br>E11.3511 – E11.3519 | Type 2 diabetes mellitus with diabetic retinopathy with macular edema                   |
| E13.311,<br>E13.3211 – E13.3219,<br>E13.3311 – E13.3319,<br>E13.3411 – E13.3419,<br>E13.3511 – E13.3519 | Other specified diabetes mellitus with diabetic retinopathy with macular edema          |
| H16.401 – H16.449   | Corneal neovascularization  |
| H30.001 – H30.049   | Focal chorioretinal inflammation  |
| H30.101 – H30.139   | Disseminated chorioretinal inflammation   |
| H30.891 – H30.899   | Other chorioretinal inflammations   |
| H30.90 – H30.93   | Unspecified chorioretinal inflammations   |
| H32   | Chorioretinal disorders in diseases classified elsewhere                                |
| H34.8110 – H 34.8192  | Central retinal vein occlusion  |
| H34.8310 – H34.8392   | Tributary (branch) retinal vein occlusion   |
| H35.051 – H35.059   | Retinal neovascularization, unspecified   |
| H35.141 – H35.169   | Retinopathy of prematurity, stages 3 through 5  |
| H35.3210 – H35.3293   | Exudative age-related macular degeneration  |
| H35.33  | Angioid streaks of macula   |
| H35.81  | Retinal edema   |
| H40.50X0-H40.53X4   | Glaucoma secondary to other eye disorders [associated with vascular disorders of eye]   |
| H44.20-H44.23   | Degenerative myopia   |
| H44.2A1-H44.2A9   | Degenerative myopia with choroidal neovascularization                                   |
| I67.89  | Other cerebrovascular disease   |
| Z85.038   | Personal history of other malignant neoplasm of large intestine                         |

| ICD-10-CM Code | Description   |
|----------------|---|
| Z85.048        | Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus |
| Z85.068        | Personal history of other malignant neoplasm of small intestine                         |
| Z85.118        | Personal history of other malignant neoplasm of bronchus and lung                       |
| Z85.3          | Personal history of malignant neoplasm of breast  |
| Z85.41         | Personal history of malignant neoplasm of cervix uteri                                  |
| Z85.42         | Personal history of malignant neoplasm of other parts of uterus                         |
| Z85.43         | Personal history of malignant neoplasm of ovary   |
| Z85.44         | Personal history of malignant neoplasm of other female genital organs                   |
| Z85.528        | Personal history of other malignant neoplasm of kidney                                  |
| Z85.53         | Personal history of malignant neoplasm of renal pelvis                                  |
| Z85.841        | Personal history of malignant neoplasm of brain   |
| Z85.848        | Personal history of malignant neoplasm of other parts of nervous tissue                 |

| Reviews, Revisions, and Approvals  | Date     | P&T Approval Date |
|--|----------|-------------------|
| New FDA labeled indication added: Platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer. Doses removed. Under renal cell carcinoma, FDA approved use, added 2a/2b subtypes to interferon alpha. Safety criteria limited to black box warnings precluding initiation of therapy. Off-label ocular use is edited to follow supported uses in Micromedex and Clinical Pharmacology (i.e., AMD secondary to choroidal neovascularization, macular edema secondary to branch/central retinal vein occlusion or diabetes, choroidal retinal neovascularization secondary to pathologic myopia or angioid streaks, diabetic retinopathy, retinopathy of prematurity). Choroidal neovascularization associated with no known cause or with inflammation or ocular histoplasmosis syndrome is removed but may be requested under the Global Biopharm policy. Approval duration lengthened to 6 and 12 months. Added ICD-10 appropriate code ranges for eye conditions that now have a new 6 <sup>th</sup> or 7 <sup>th</sup> digit indicating the specific eye. | 03.17    | 04.17             |
| 1Q18 annual review:<br>Policies combined from Medicaid and commercial<br>New policy for HIM<br>Specialist involvement in care added to all indications<br>Added specific criteria for off-label uses for ophthalmic indications<br>Added allowable off-label oncology indications as reflected in the NCCN compendium.<br>Added 2018 codes H44.2A1-H44.2A3<br>References reviewed and updated  | 11.20.17 | 02.18             |

| Reviews, Revisions, and Approvals  | Date     | P&T Approval Date |
|--|----------|-------------------|
| 4Q 2018 annual review: added Mvasi to the policy; added NCCN Category 2A recommended off-label uses: AIDs-related Kaposi sarcoma, anaplastic gliomas, intracranial and spinal ependymoma, infiltrative supratentorial astrocytoma/oligodendroglioma, medulloblastoma; references reviewed and updated.   | 07.31.18 | 11.18             |
| Added ICD-10 codes C21.8, C33, and C46.0-C46.9   | 03.15.19 |                   |
| Added the following ICD-10 codes for diabetic retinopathy: E08.3521 – E08.3529, E08.3531- E08.3539, E08.3541 – E08.3549, E08.3551 – E08.3559, E08.3591- E08.3599, E09.3521 - E09.3529, E09.3531 – E09.3539, E09.3541 – E09.3549, E09.3551 – E09.3559, E09.3591 – E09.3599, E10.3521 – E10.3529, E10.3531 – E10.3539, E10.3541 – E10.3549, E10.3551 – E10.3559, E10.3591 – E10.3599, E11.3521 – E11.3529, E11.3531 – E11.3539, E11.3541 – E11.3549, E11.3551 – E11.3559, E11.3591 – E11.3599, E13.3521 – E13.3529, E13.3531 – E13.3539, E13.3541 – E13.3549, E13.3551 – E13.3559, E13.3591 – E13.3599 | 06.06.19 |                   |
| RT4: Added biosimilar, Zirabev, to the policy; references reviewed and updated.  | 07.08.19 |                   |
| 4Q 2019 annual review: added NCCN category 2A recommended off-label uses: meningioma, small bowel adenocarcinoma; added additional ICD-10 codes for meningioma per NCCN (D32.0–D32.9, D42.0–D42.9, I67.89); updated glioblastoma, cervical cancer, and epithelial ovarian, fallopian tube, or primary peritoneal cancer FDA-approved indications in approval criteria; updated references reviewed and updated.  | 08.09.19 | 11.19             |
| Added HIM-Medical Benefit line of business; added redirection to Mvasvi for Avastin.   | 12.23.19 |                   |
| Revised Avastin redirection to Mvasi or Zirabev for non-ophthalmology uses per SDC and prior clinical guidance; added HIM line of business; removed HIM-Medical Benefit line of business and non-formulary references related to the HIM line of business.   | 02.19.20 |                   |
| Added requirement for redirection to Mvasi or Zirabev to Section II for continued therapy requests for non-ophthalmology uses; allowed by-passing of redirection if state regulations do not allow step therapy in Stage IV or metastatic cancer settings.   | 04.20.20 | 05.20             |
| RT4 policy update to add criteria for newly FDA-approved indication for first-line therapy for HCC in combination with atezolizumab; references reviewed and updated.  | 06.08.20 |                   |
| Ad Hoc update: for ophthalmology non-FDA approved indications, added requirement that request be for intravitreal Avastin as compounding pharmacies often break standard Avastin vials into smaller dosages specifically for ophthalmic use and there is a temporary CPT code not currently available to biosimilars   | 10.01.20 |                   |



| Reviews, Revisions, and Approvals  | Date     | P&T Approval Date |
|--|----------|-------------------|
| 4Q 2020 annual review: removed AIDS-related Kaposi sarcoma as an off label use as it is no longer NCCN supported; added additional NCCN supported regimens for colorectal cancer, non-squamous non-small cell lung cancer, renal cell carcinoma, cervical cancer, and epithelial ovarian, fallopian tube, or primary peritoneal cancer; added to Section IB metastatic spine tumors or brain metastases and vulvar cancer diagnoses which are supported by NCCN; added appendix F: dose rounding guidelines; added reference to appendix F within criteria; references reviewed and updated. | 06.29.20 | 11.20             |
| Added appendix E.  | 12.11.20 |                   |
| Updated appendix E to include Ohio.  | 02.08.21 |                   |
| RT4: FDA indication language updated for Zirabev to reflect expansion of indication to include epithelial ovarian, fallopian tube, or primary peritoneal cancer; amended language for ophthalmology non-FDA approved indications to be: request is for bevacizumab intravitreal solution; updated reference for HIM off-label use to HIM.PA.154 (replaces HIM.PHAR.21); updated GA in Appendix E.  | 02.26.21 |                   |

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or

regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

**Note:**

**For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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