Clinical Policy: Bevacizumab (Alymsys, Avastin, Avzivi, Mvasi, Vegzelma, Zirabev)

Reference Number: CP.PHAR.93
Effective Date: 12.01.11
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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®) and its biosimilars [bevacizumab-maly (Alymsys®), bevacizumab-tnjn (Avzivi®), bevacizumab-awwb (Mvasi®), bevacizumab-adcd (Vegzelma™), bevacizumab-bvzr (Zirabev™)] are vascular endothelial growth factor-specific angiogenesis inhibitors.

FDA Approved Indication(s)

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

- Metastatic colorectal cancer (CRC), in combination with intravenous 5-fluorouracil (5-FU)-based chemotherapy for first- or second-line treatment
- Metastatic CRC, 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
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer:
  - In combination with carboplatin and paclitaxel, followed by Avastin/Mvasi/Vegzelma 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/Mvasi/Vegzelma/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® that Avastin, Alymsys, Avzivi, Mvasi, Vegzelma, 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. CRC;
   b. Non-squamous NSCLC;
   c. Glioblastoma;
   d. Metastatic RCC;
   e. Cervical cancer;
   f. Epithelial ovarian, fallopian tube, or primary peritoneal cancer;
   g. HCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a-g):
   a. For CRC, disease is advanced, metastatic, or unresectable and bevacizumab is used in combination with one of the following (i-vi):
      i. 5-FU/leucovorin or capecitabine-based chemotherapy;
      ii. IROX (irinotecan and oxaliplatin);
      iii. FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin);
      iv. Irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan);
      v. FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin);
      vi. Lonsurf® if previously progressed through all available regimens;
   b. For recurrent, advanced, or metastatic non-squamous NSCLC, prescribed as one of the following (i-v):
      i. Single agent therapy;
      ii. In combination with carboplatin and paclitaxel for first line treatment;
      iii. In combination with pemetrexed;
      iv. In combination with Tecentriq®;
      v. In combination with erlotinib for sensitizing EGFR mutation-positive histology;
   c. For glioblastoma, member has recurrent disease or requires symptom management;
   d. For metastatic RCC, used as a single-agent or in combination with everolimus or erlotinib (for advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer);
   e. For persistent, recurrent, or metastatic cervical cancer, used in one of the following ways (i, ii or iii):
      i. As a single agent;

ii. In combination with paclitaxel and cisplatin, carboplatin, or topotecan;
iii. In combination with Keytruda®, paclitaxel, and cisplatin/carboplatin for PD-L1-postive disease;

f. For epithelial ovarian, fallopian tube, or primary peritoneal cancer, one of the following (i-vi):
i. Prescribed in combination with a platinum agent (e.g., carboplatin, oxaliplatin) and chemotherapy, followed by bevacizumab as a single agent, for Stage IB-IV disease;
ii. Prescribed for maintenance in combination with Lynparza® for stage II-IV disease;
iii. Prescribed in combination with Zejula® as targeted therapy for platinum-sensitive persistent disease or recurrence;
iv. For platinum-resistant disease, prescribed in combination with paclitaxel, pegylated liposomal doxorubicin, topotecan, gemcitabine, or cyclophosphamide;
v. For platinum-sensitive disease, prescribed in combination with carboplatin and paclitaxel, or carboplatin and gemcitabine, or carboplatin and liposomal doxorubicin, followed by bevacizumab as a single agent;
vi. Prescribed as a single agent;

g. For unresectable or metastatic HCC, used in combination with Tecentriq as first-line systemic therapy, and:
i. HCC is classified as Child-Pugh class A or B;

5. For Alymsys, Avastin, Avzivi, or Vegzelma requests, member meets one of the following (a or b):
a. Member must use Mvasi or Zirabev, unless both are contraindicated or clinically significant adverse effects are experienced;*
**Prior authorization may be required for Mvasi and Zirabev*
b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain 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 – 12 months or duration of request, whichever is less

B. Oncology - Non-FDA-Approved Adult Indications (off-label) (must meet all)**:**
1. Diagnosis of one of the following conditions (a-m):
a. Adult glioma of one of the following types (i, ii, or iii):
i. Oligodendroglioma that is IDH-mutant, 1p19q codeleted;
ii. IDH-mutant astrocytoma;
iii. Circumscribed glioma;
b. Ampullary adenocarcinoma – intestinal type;
c. Endometrial carcinoma;

d. Intracranial and spinal ependymoma;
e. Peritoneal mesothelioma;
f. Pleural mesothelioma;
g. Medulloblastoma;
h. Meningioma;
i. Metastatic spine tumors or brain metastases;
j. Primary central nervous system lymphoma;
k. Small bowel adenocarcinoma;
l. Soft tissue sarcoma – solitary fibrous tumor or angiosarcoma;
m. Vulvar cancer – adenocarcinoma or squamous cell carcinoma;

2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. For Alymsys, Avastin, Avzivi, or Vegzelma requests, member meets one of the following (a or b):
   a. Member must use Mvasi or Zirabev, unless both are contraindicated or clinically significant adverse effects are experienced;*
      **Prior authorization may be required for Mvasi and Zirabev*
   b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings *(see Appendix E)*;
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 – 12 months or duration of request, whichever is less

C. Oncology - Non-FDA-Approved Pediatric Indications (off-label) (must meet all)**:**
1. Diagnosis of difuse high-grade glioma;
2. Prescribed by or in consultation with an oncologist;
3. Age < 18 years;
4. For Alymsys, Avastin, Avzivi, or Vegzelma requests, member meets one of the following (a or b):
   a. Member must use Mvasi or Zirabev, unless both are contraindicated or clinically significant adverse effects are experienced;*
      **Prior authorization may be required for Mvasi and Zirabev*
   b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings (*see Appendix E*);
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 – 12 months or duration of request, whichever is less

D. 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 ≥ 18 years;
3. Request is for bevacizumab intravitreal solution;
   **Requests for IV formulations of Avastin, Alymsys, Avzivi, Mvasi, Vegzelma, and Zirabev will not be approved*
4. Request meets one of the following (a or b):
   a. Dose does not exceed 2.5 mg per 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 – 12 months or duration of request, whichever is less

E. Other diagnoses/indications (must meet all)**:**

1. For Alymsys, Avastin, Avzivi, or Vegzelma requests for non-ophthalmology uses, member meets one of the following (a or b):
   a. Member must use Mvasi or Zirabev, unless both are contraindicated or clinically significant adverse effects are experienced;*
      **Prior authorization may be required for Mvasi and Zirabev*
   b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings *(see Appendix E)*;
2. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
3. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 2 above does not apply, refer to the off-label use policy for the relevant line

of business: 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, b, or c):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B*);
   c. Documentation supports that member is currently receiving Alymsys, Avastin, Avzivi, Mvasi, Vegzelma, 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 Alymsys, Avastin, Avzivi, or Vegzelma requests for non-ophthalmology uses, member meets one of the following (a or b):
   a. Member must use Mvasi or Zirabev, unless both are contraindicated or clinically adverse effects are experienced;*
      **Prior authorization may be required for Mvasi and Zirabev*
   b. Request is for treatment associated with 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 – 12 months or duration of request, whichever is less

B. Other diagnoses/indications (must meet 1 and either 2 or 3)**:**

1. For Alymsys, Avastin, Avzivi, or Vegzelma requests for non-ophthalmology uses, member meets one of the following (a or b):
   a. Member must use Mvasi or Zirabev, unless both are contraindicated or clinically significant adverse effects are experienced;*
      **Prior authorization may be required for Mvasi and Zirabev*
   b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings *(see Appendix E);*
2. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

3. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 2 above does not apply, refer to the off-label use policy for the relevant line of business: 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
CapeOX: capecitabine, oxaliplatin
CRC: colorectal cancer
FDA: Food and Drug Administration
FOLFIRI: fluorouracil, leucovorin, irinotecan
FOLFIRINOX: fluorouracil, leucovorin, irinotecan, oxaliplatin
FOLFOX: fluorouracil, leucovorin, oxaliplatin
HCC: hepatocellular carcinoma
IDH: isocitrate dehydrogenase gene
IROX: irinotecan, oxaliplatin
NCCN: National Comprehensive Cancer Network
NSCLC: non-small cell lung cancer
PD-L1: programmed death-ligand 1
RCC: renal cell carcinoma

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/ Maximum Dose
Metastatic carcinoma of the colon or rectum		
FOLFOX4 = Infusional 5-FU/leucovorin/ oxaliplatin	Oxaliplatin 85 mg/m^2 IV over 2 hours day 1; leucovorin 200 mg/m^2 IV over 2 hours days 1 & 2, followed by 5-FU 400 mg/m^2 IV bolus over 2-4 minutes, followed by 600 mg/m^2 IV 5-FU continuous infusion over 22 hours on days 1 & 2. Repeat cycle every 14 days.	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
FOLFIRI = Infusional 5-FU/ leucovorin/Camptosar® (irinotecan)	Camptosar 180 mg/m^2 IV over 90 minutes day 1; Leucovorin 400 mg/m^2 IV over 2 hours day 1 followed by 5- FU 400 mg/m^2 IV bolus over 2-4 minutes, followed by 2.4 gm/m^2 IV 5- FU continuous infusion over 46 hours. Repeat cycle every 14 days.	Varies
capecitabine (Xeloda®)	2500 mg/m^2 PO BID for 2 weeks; repeat cycles of 2 weeks on and 1 week off. For patients who cannot tolerate intensive therapy.	Varies
IROX = oxaliplatin/Camptosar (irinotecan)	Oxaliplatin 85 mg/m^2 IV followed by Camptosar 200 mg m^2 IV over 30-90 minutes every 3 weeks	Varies
Camptosar (irinotecan)	180 mg/m^2 IV every 2 weeks or 300-350 mg/m^2 IV every 3 weeks	Varies
Lonsurf® (trifluridine and tipiracil)	35 mg/m^2 (based on trifluridine component) PO BID on days 1-5 and 8-12, repeated every 28 days	Trifluridine 80 mg/dose
NSCLC		
Examples of drugs used in single- or multi-drug chemotherapy regimens: • Cisplatin, carboplatin, paclitaxel docetaxel, vinorelbine, gemcitabine, etoposide, irinotecan, vinblastine, mitomycin, ifosfamide, pemetrexed disodium, (Alimta®) erlotinib (Tarceva®), Tecentriq® (atezolizumab)	Various doses	Varies
Ovarian Cancer		
Examples of drugs used in single- or multi-drug chemotherapy regimens: • carboplatin and paclitaxel, docetaxel and carboplatin, Lynparza® (olaparib),	Various doses	Varies
Glioblastoma Multiforme		
temozolomide (Temodar®)	Maintenance phase cycles: 150 mg- 200 mg/m² PO days 1-5. Repeat every 28 days.	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
carmustine (Bicnu®)	150 mg to 200 mg/m² IV on day 1. Repeat every 6-8 weeks for one year or tumor progression.	Varies
Cervical Cancer		
Examples of drugs used in multi-drug chemotherapy regimens: • cisplatin/paclitaxel, carboplatin/paclitaxel, cisplatin/topotecan (Hycamtin®), topotecan/paclitaxel	Various doses	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
- 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 Certain Oncology Settings

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.
MS	Yes	**Applies to HIM requests only** For advanced metastatic cancer and associated conditions
NV	Yes	Stage 3 and stage 4 cancer patients for a prescription drug to treat the cancer or any symptom thereof of the covered person
OH	Yes	**Applies to Commercial and HIM requests only** For stage 4 metastatic cancer and associated conditions
OK	Yes	**Applies to HIM requests only** For advanced metastatic cancer and associated conditions
PA	Yes	For stage 4 advanced, metastatic cancer
TN	Yes	For advanced metastatic cancer and associated conditions

State	Step Therapy Prohibited?	Notes
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 CRC	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. 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

Indication	Dosing Regimen	Maximum Dose
Non-squamous NSCLC	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
Ovarian cancer, stage III or IV disease following initial surgical resection	15 mg/kg IV infusion every 3 weeks with carboplatin/paclitaxel for up to 6 cycles, followed by bevacizumab 15 mg/kg every 3 weeks as a single agent	15 mg/kg IV every 3 weeks or 10 mg/kg IV every 2 weeks
Platinum resistant ovarian cancer	10 mg/kg intravenously every 2weeks with weekly paclitaxel, liposomal doxorubicin, or topotecan	15 mg/kg IV every 3 weeks or 10 mg/kg IV every 2 weeks
Platinum sensitive ovarian cancer	15 mg/kg intravenously every 3 weeks with carboplatin and paclitaxel or with carboplatin and gemcitabine, followed by bevacizumab 15 mg/kg every 3 weeks as a single agent	15 mg/kg IV every 3 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 IV every 2 weeks

Indication	Dosing Regimen	Maximum Dose
Cervical cancer	15 mg/kg IV infusion every 3 weeks (in combination with paclitaxel and either cisplatin or topotecan) until disease progression or unacceptable toxicity	15 mg/kg IV every 3 weeks or 10 mg/kg IV every 2 weeks
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
Malignant mesothelioma of pleura	15 mg/kg IV (plus pemetrexed 500 mg/m(2) IV and cisplatin 75 mg/m(2) 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 CRC 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/m2 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

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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
C9257	Injection, bevacizumab, 0.25 mg
J9035	Injection, bevacizumab, 10 mg
J9999	Not otherwise classified, antineoplastic drugs
Q5107	Injection, bevacizumab-awwb, biosimilar, (Mvasi), 10 mg
Q5118	Injection, bevacizumab-bvcr, biosimilar, (Zirabev), 10 mg
Q5126	Injection, bevacizumab-maly, biosimilar, (Alymsys), 10 mg
Q5129	Injection, bevacizumab-adcd (Vegzelma), biosimilar, 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, E08.3211 – E08.3219,	Diabetes mellitus due to underlying condition with diabetic retinopathy with macular edema

ICD-10-CM Code	Description
E08.3311 – E08.3319, E08.3411 – E08.3419, E08.3511 – E08.3519	
E09.311, E09.3211 – E09.3219, E09.3311 – E09.3319, E09.3411 – E09.3419, E09.3511 – E093519	Drug or chemical induced diabetes mellitus with diabetic retinopathy with macular edema
E10.311, E10.3211 – E10.3219, E10.3311 – E10.3319, E10.3411 – E10.3419, E10.3511 – E10.3519	Type 1 diabetes mellitus with diabetic retinopathy with macular edema
E11.311, E11.3211 – E11.3219, E11.3311 – E11.3319, E11.3411 – E11.3419, E11.3511 – E11.3519	Type 2 diabetes mellitus with diabetic retinopathy with macular edema
E13.311, E13.3211 – E13.3219, E13.3311 – E13.3319, E13.3411 – E13.3419, 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
Z85.048	Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus

ICD-10-CM Code	Description
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
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	
4Q 2020 annual review: removed AIDS-related Kaposi sarcoma as an off label use as it is no longer NCCN supported; added additional	06.29.20	11.20

Reviews, Revisions, and Approvals	Date	P&T Approval Date
NCCN supported regimens for CRC, 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.		
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	
Ad Hoc update: applied redirection of Avastin to preferred biosimilars to other diagnoses/indications; amended redirection language to "must use" per template update.	03.15.21	
4Q 2021 annual review: added additional NCCN-supported regimens and classifications for CRC, NSCLC, glioblastoma, cervical cancer, and epithelial ovarian, fallopian tube, or primary peritoneal cancer; added criterion that HCC be classified as Child-Pugh class A disease per NCCN; added low-grade WHO grade I glioma to NCCN-supported off-label indication; added Nevada to Appendix E; allowed option to bypass redirection to preferred agent if state regulations apply for section I.B.; references reviewed and updated.	08.15.21	11.21
RT4: updated with Mvasi's FDA-approved indications of epithelial ovarian, fallopian tube, or primary peritoneal cancers.	12.10.21	
Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less	01.20.22	05.22
RT4: added newly FDA-approved biosimilar Alymsys to policy; generalized language for oncology redirection bypass.	05.04.22	
4Q 2022 annual review: added additional NCCN-supported indications of ampullary adenocarcinoma cancer, malignant peritoneal mesothelioma, and pediatric diffuse high-grade glioma; re-classified anaplastic gliomas to astrocytoma and oligodendroglioma per updated NCCN classification; removed breast cancer indication, WHO grade 2 glioma indication, and single-agent therapy option for cervical cancer per NCCN; removed "radiographic and/or clinical relapse", "recurrent", and "carcinosarcoma with… BRCA 1/2 mutation" disease qualifiers for ovarian cancer as there are other clinical scenarios per NCCN; added new regimens for cervical cancer and	10.24.22	11.22

Reviews, Revisions, and Approvals	Date	P&T Approval Date
CRC per NCCN; added legacy Wellcare line of business (WCG.CP.PHAR.93 to retire), aligned initial approval durations as 6 months, and aligned redirection to Mvasi or Zirabev; references reviewed and updated. Template changes applied to other diagnoses/indications and continued therapy section. Added HCPCS code [C9142]. RT4: added Vegzelma biosimilar to policy.		
Updated HCPCS code: removed [C9142] and added [Q5126].	01.06.23	
Added HCPCS code [Q5129].	04.17.23	
Updated Appendix E to include Oklahoma.	06.07.23	
4Q annual review: per NCCN – for CRC added that disease is advanced, metastatic, or unresectable; for cervical cancer added option for single-agent therapy; for RCC removed combination therapy option with interferon alfa; for ovarian cancers simplified bevacizumab combination therapy criterion when used with a platinum and chemotherapy along with corresponding staging update to IB-IV disease, added combination therapy option with gemcitabine for platinum-resistant disease, and removed combination therapy with Zejula; for HCC added Child-Pugh class B option; clarified off-label indication of primary central nervous system cancer is specifically for lymphoma; modified low-grade (WHO Grade I) glioma to circumscribed glioma; revised mesotheliomas to remove "malignant" per terminology change; references reviewed and updated.	08.19.23	11.23
RT4: added newly FDA-approved biosimilar Avzivi to policy; for ovarian cancers, added combination therapy with Zejula per NCCN; created separate section for oncology – non-FDA-approved indications for pediatrics to include diffuse high-grade glioma.	12.14.23	
Updated Appendix E to include Mississippi.	06.05.24	

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.