

UTILIZATION MANAGEMENT MEDICAL POLICY

- POLICY:** Oncology (Injectable) – Bevacizumab Products Utilization Management Medical Policy
- Avastin[®] (bevacizumab intravenous infusion – Genentech)
 - Alysmsys[®] (bevacizumab-maly intravenous infusion – Amneal)
 - Mvasi[™] (bevacizumab-awwb intravenous infusion – Amgen)
 - Vegzelma[™] (bevacizumab-adcd intravenous infusion – Celltrion)
 - Zirabev[™] (bevacizumab-bvzr intravenous infusion – Pfizer)

REVIEW DATE: 03/22/2023

OVERVIEW

Bevacizumab is a recombinant humanized monoclonal antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF), a key mediator of angiogenesis.¹ Bevacizumab is indicated for the following uses:

- **Cervical cancer** in combination with paclitaxel and cisplatin OR paclitaxel and topotecan for persistent, recurrent, or metastatic disease.
- **Colorectal cancer**, metastatic:
 - In combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment.
 - In combination with fluoropyrimidine-irinotecan-based or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab-containing regimen.

Limitation of use: Bevacizumab is not indicated for adjuvant treatment of colon cancer.

- **Glioblastoma**, for treatment of recurrent disease in adults.
- **Hepatocellular carcinoma**, in combination with Tecentriq[®] (atezolizumab intravenous infusion) for the treatment of unresectable or metastatic disease in patients who have not received prior systemic therapy.
- **Non-small cell lung cancer (NSCLC)**, for non-squamous disease, in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent, or metastatic disease.
- **Ovarian (epithelial), fallopian tube, or primary peritoneal cancer:**
 - Recurrent disease that is platinum-resistant in combination with paclitaxel, Doxil[®] (doxorubicin liposome intravenous infusion), or topotecan, in patients who received no more than two prior chemotherapy regimens.
 - Recurrent disease that is platinum-sensitive in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by bevacizumab as a single agent.
 - In combination with carboplatin and paclitaxel, followed by bevacizumab as a single agent, for stage III or IV disease in patients following initial surgical resection.
- **Renal cell carcinoma**, metastatic, in combination with interferon alfa.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of bevacizumab for uses other than ophthalmic conditions. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing document in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the

duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with bevacizumab as well as the monitoring required for adverse events and long-term efficacy, approval requires bevacizumab to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of bevacizumab is recommended in those who meet one of the following criteria:

FDA-Approved Indications

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- 1. Central Nervous System Tumors.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

Note: For pediatric patients see Pediatric Central Nervous System Tumors.

A) Patient is ≥ 18 years of age; AND

B) Patient has tried at least one previous therapy; AND

Note: Examples are temozolomide capsules or injection, etoposide, carmustine, radiotherapy.

C) Patient has ONE of the following (i, ii, iii, iv, v, vi, or vii):

i. Anaplastic gliomas; OR

ii. Astrocytoma; OR

iii. Glioblastoma; OR

iv. Intracranial and spinal ependymoma (excluding subependymoma); OR

v. Meningiomas; OR

vi. Oligodendroglioma; OR

vii. Symptoms due to one of the following (a, b, or c):

a) Radiation necrosis; OR

b) Poorly controlled vasogenic edema; OR

c) Mass effect; AND

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 10 mg/kg administered intravenously not more frequently than once every 2 weeks.

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- 2. Cervical Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following (i or ii):

i. Patient has recurrent or metastatic cervical cancer; OR

ii. Patient has persistent, recurrent, or metastatic small cell neuroendocrine carcinoma of the cervix; AND

C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 15 mg/kg administered intravenously not more frequently than once every 3 weeks.

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- 3. Colon, Rectal, or Appendiceal Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has recurrent, advanced or metastatic colon, rectal, or appendiceal cancer; AND

- C) The medication is used in combination with a chemotherapy regimen; AND

Note: Examples of chemotherapy are 5-fluorouracil with leucovorin, and may include one or both of oxaliplatin, irinotecan; capecitabine with or without oxaliplatin; irinotecan with or without oxaliplatin.

- D) The medication is prescribed by or in consultation with an oncologist.

Dosing: Approve one of the following dosing regimens (A, B, or C):

A) 5 mg/kg administered intravenously not more frequently than once every 2 weeks; OR

B) 10 mg/kg administered intravenously not more frequently than once every 2 weeks; OR

C) 7.5 mg/kg administered intravenously not more frequently than once every 3 weeks.

4. Hepatocellular Carcinoma. Approve for 1 year if the patient meets the following criteria (A, B, C, D, E, and F):

A) Patient is ≥ 18 years of age; AND

B) Patient meets ONE of the following (i or ii):

i. Patient has unresectable or metastatic hepatocellular carcinoma; OR

ii. According to the prescriber, the patient is not a surgical candidate; AND

C) Patient has Child-Pugh Class A disease; AND

D) The medication is used in combination with Tecentriq (atezolizumab intravenous infusion); AND

E) Patient has not received prior systemic therapy; AND

F) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 15 mg/kg administered intravenously not more frequently than once every 3 weeks.

5. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient does not have a history of recent hemoptysis; AND

C) Patient has recurrent, advanced, or metastatic non-squamous non-small cell lung cancer (NSCLC) and meets ONE of the following criteria (i, ii, iii, iv, or v):

Note: Non-squamous NSCLC includes adenocarcinoma, large cell, or NSCLC not otherwise specified.

i. The NSCLC tumor is negative or unknown for actionable mutations and the patient meets ONE of the following criteria (a, b, or c):

Note: Examples of actionable mutations include sensitizing epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) fusions, *RET* rearrangement positive, *MET* exon 14 skipping, *NTRK* gene fusion positive, *BRAF V600E* mutation positive, and ROS proto-oncogene 1 (*ROS1*) rearrangement positive.

a) The medication is used as initial therapy in combination with other systemic therapies; OR
Note: Examples of systemic therapies are cisplatin, carboplatin, Tecentriq (atezolizumab intravenous infusion), pemetrexed, paclitaxel.

b) The medication is used as continuation maintenance therapy and meets ONE of the following [(1), (2), or (3)]:

(1) The medication is used as a single agent; OR

(2) The medication is used in combination with Tecentriq, if Tecentriq was used in combination with bevacizumab for first-line therapy; OR

(3) The medication is used in combination with pemetrexed, if pemetrexed was used in combination with bevacizumab for first-line therapy; OR

- c) The medication is used as subsequent therapy in combination with other systemic therapies; OR
Note: Examples of systemic therapies are cisplatin, carboplatin, pemetrexed, paclitaxel.
 - ii. The tumor is positive for (*EGFR*) exon 19 deletion or exon 21 *L858R* mutations and the patient meets ONE of the following (a or b):
 - a) The medication is used as first-line or continuation maintenance therapy in combination with erlotinib; OR
 - b) The medication is used as subsequent therapy following prior targeted therapy; OR
Note: Examples of targeted therapy include Gilotrif (afatinib tablet), Tagrisso (osimertinib tablet), erlotinib, Iressa (gefitinib tablet), Vizimpro (dacomitinib tablet).
 - iii. Patient meets all of the following (a, b, and c):
 - a) The medication is used first-line; AND
 - b) The medication is used in combination with other systemic therapies; AND
Note: Examples include carboplatin plus paclitaxel or pemetrexed; cisplatin plus pemetrexed; and Tecentriq plus carboplatin and paclitaxel.
 - c) The tumor is positive for ONE of the following mutations [(1), (2), or (3)]:
 - (1) *EGFR* exon 20 mutation; OR
 - (2) *KRAS G12C* mutation; OR
 - (3) *ERBB2* (HER2) mutation; OR
 - iv. Patient meets all of the following (a, b, and c):
 - a) The medication is used as first-line or subsequent therapy; AND
 - b) The medication is used in combination with other systemic therapies; AND
Note: Examples include carboplatin plus paclitaxel or pemetrexed; cisplatin plus pemetrexed; and Tecentriq plus carboplatin and paclitaxel.
 - c) The tumor is positive for ONE of the following mutations [(1), (2), (3), or (4)]:
 - (1) *BRAF V600E* mutation; OR
 - (2) *NTRK1/2/3* gene fusion positive; OR
 - (3) *MET* exon 14 skipping mutation; OR
 - (4) *RET* rearrangement positive; OR
 - v. Patient meets all of the following (a, b, c, and d):
 - a) The medication is used as subsequent therapy; AND
 - b) The medication is used in combination with other systemic therapies; AND
Note: Examples include carboplatin plus paclitaxel or pemetrexed; cisplatin plus pemetrexed; and Tecentriq plus carboplatin and paclitaxel.
 - c) The tumor is positive for ONE of the following mutations [(1), (2), or (3)]:
 - (1) *EGFR S768I, L861Q*, and/or *G719X* mutation; OR
 - (2) *ALK* rearrangement positive; OR
 - (3) *ROS1* rearrangement positive; AND
 - d) Patient has previously received targeted drug therapy for the specific mutation; AND
Note: Examples of targeted drug therapy include Gilotrif (afatinib tablet), Tagrisso (osimertinib tablet), erlotinib, Iressa (gefitinib tablet), Vizimpro (dacomitinib tablet), Xalkori (crizotinib capsule), Rozlytrek (entrectinib capsule), or Zykadia (ceritinib tablet).
- D)** The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 15 mg/kg administered intravenously not more frequently than once every 3 weeks.

6. Ovarian, Fallopian Tube, or Primary Peritoneal Cancer. Approve for 1 year if the patient meets the following criteria (A and B):

- A) Patient is ≥ 18 years of age; AND

B) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve one of the following doses (A or B):

A) Up to 15 mg/kg administered intravenously not more frequently than once every 3 weeks; OR

B) 10 mg/kg administered intravenously not more frequently than once every 2 weeks.

7. **Renal Cell Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient is \geq 18 years of age; AND

B) Patient has relapsed, metastatic, or stage IV renal cell cancer; AND

C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 10 mg/kg administered intravenously not more frequently than once every 2 weeks.¹

Other Uses with Supportive Evidence

8. **Ampullary Adenocarcinoma.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

A) Patient is \geq 18 years of age; AND

B) Patient has intestinal type disease; AND

C) The medication is used in combination with chemotherapy; AND

Note: Examples of chemotherapy include FOLFOX (leucovorin, fluorouracil, oxaliplatin), FOLFIRI (leucovorin, fluorouracil, irinotecan), FOLFOXIRI (leucovorin, fluorouracil, oxaliplatin, irinotecan), and CapeOX (capecitabine, oxaliplatin).

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 7.5 mg/kg administered intravenously not more frequently than once every 3 weeks.

9. **Endometrial Carcinoma.** Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient is \geq 18 years of age; AND

B) Patient has recurrent, advanced, or metastatic disease; AND

C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 15 mg/kg administered intravenously not more frequently than once every 3 weeks.

10. **Mesothelioma.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

A) Patient is \geq 18 years of age; AND

B) Patient has one of the following (i, ii, iii, or iv):

i. Malignant pleural mesothelioma; OR

ii. Malignant peritoneal mesothelioma; OR

iii. Pericardial mesothelioma; OR

iv. Tunica vaginalis testis mesothelioma; AND

C) Patient meets ONE of the following (i or ii):

i. Bevacizumab will be used in combination with a chemotherapy regimen; OR

Note: Examples of chemotherapy are pemetrexed, cisplatin, carboplatin.

- ii. Bevacizumab will be used in combination with Tecentriq (atezolizumab intravenous infusion);
AND

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 15 mg/kg administered intravenously not more frequently than once every 3 weeks.

11. Neovascular or Vascular Ophthalmic Conditions. Approve for 3 years.

Note: Examples of neovascular or vascular ophthalmic conditions include diabetic macular edema (includes patients with diabetic retinopathy and diabetic macular edema), macular edema following retinal vein occlusion, myopic choroidal neovascularization, neovascular (wet) age-related macular degeneration, other neovascular diseases of the eye (e.g., neovascular glaucoma, retinopathy of prematurity, sickle cell neovascularization, choroidal neovascular conditions).

12. Pediatric Central Nervous System Tumors. Approve for 1 year if the patient meets the following criteria (A, B, C, D, and E):

A) Patient is < 18 years of age; AND

B) Patient has pediatric-type diffuse high-grade glioma; AND

Note: Examples include diffuse hemispheric glioma, diffuse pediatric-type high-grade glioma, infant-type hemispheric glioma, and diffuse midline glioma.

C) Patient has recurrent or progressive disease; AND

D) The medication is used for palliation; AND

E) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 10 mg/kg administered intravenously not more frequently than once every 2 weeks.

13. Small Bowel Adenocarcinoma. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

A) Patient is \geq 18 years of age; AND

B) Patient has advanced or metastatic disease; AND

C) The medication is used in combination with chemotherapy; AND

Note: Examples of chemotherapy are fluorouracil, leucovorin, and oxaliplatin (FOLFOX), capecitabine and oxaliplatin (CapeOX), fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI).

D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 7.5 mg/kg administered intravenously not more frequently than once every 2 weeks.

14. Soft Tissue Sarcoma. Approve for 1 year if the patient meets BOTH of the following criteria (A, B, and C):

A) Patient is \geq 18 years of age; AND

B) Patient has angiosarcoma or solitary fibrous tumor; AND

C) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 15 mg/kg administered intravenously not more frequently than once every 2 weeks.

15. Vulvar Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):

- A) Patient is \geq 18 years of age; AND
 - B) Patient has advanced, recurrent, or metastatic disease; AND
 - C) Bevacizumab is used in combination with a chemotherapy regimen; AND
- Note: Examples of chemotherapy regimen are cisplatin and paclitaxel, carboplatin and paclitaxel.
- D) The medication is prescribed by or in consultation with an oncologist.

Dosing. Approve 15 mg/kg administered intravenously not more frequently than once every 3 weeks.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of bevacizumab products is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	<p>Central Nervous System Tumors: Added “Symptoms due to radiation necrosis, poorly controlled vasogenic edema, or mass effect” as additional options for approval.</p> <p>Colon or Rectal Cancer: Added “recurrent” as additional descriptor in “Patient has recurrent, advanced, or metastatic colon or rectal cancer.” Removed requirement that bevacizumab is not used for adjuvant treatment of colon cancer.</p> <p>Non-Small Cell Lung Cancer (NSCLC): Added “recurrent” as additional descriptor in “Patient has recurrent, advanced, or metastatic non-squamous cell NSCLC. Added “exon 19 deletion or L858R” as additional descriptor to “NSCLC tumor is positive for epidermal growth factor receptor (EGFR) exon 19 deletion or L858R mutations.” Added tumor is positive for one of the following mutations: EGFR exon 20 mutation, KRAS G12C mutation, BRAF V600E, NTRK1/2/3 gene fusion, MET exon 14 skipping mutation, and RET rearrangement; and bevacizumab is used in combination other systemic therapies. Added Note with list of examples of systemic therapies.</p> <p>Breast Cancer: Removed breast cancer from Other Uses with Supportive Evidence due to National Comprehensive Cancer Network withdrawing its recommendations for bevacizumab for the treatment of breast cancer.</p> <p>Endometrial Cancer: Removed requirement that the patient has progressed on prior chemotherapy and added requirement that the patient has recurrent, advanced, or metastatic disease.</p> <p>Mesothelioma: Removed Malignant Pleural from the condition of approval. Added malignant peritoneal mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma as additional options for approval. Added “bevacizumab will be used in combination with Tecentriq” as an additional option for approval.</p>	03/16/2022
Selected Revision	Product: Added Alymsys to the list of bevacizumab products.	06/15/2022
Selected Revision	Product: Added Vegzelma to the list of bevacizumab products.	11/16/2022
Annual Revision	<p>Central Nervous System Tumors: A requirement was added that the patient is ≥ 18 years of age. A Note was added for pediatric patients to refer to the Pediatric Central Nervous System Tumors criteria. Astrocytoma and oligodendroglioma were added as additional options for approval.</p> <p>Cervical Cancer: A requirement was added that the patient is ≥ 18 years of age. The option of approval was added that the patient has persistent, recurrent, or metastatic small cell neuroendocrine carcinoma of the cervix.</p> <p>Colon, Rectal, or Appendiceal Cancer: Appendiceal was added to the condition of approval. A requirement was added that the patient is ≥ 18 years of age. Appendiceal</p>	03/22/2023

	<p>was added to the requirement that the patient has recurrent, advanced, or metastatic disease.</p> <p>Hepatocellular Carcinoma: A requirement was added that the patient is ≥ 18 years of age. A requirement was added that the patient has Child-Pugh Class A disease. Criteria were added that the patient has unresectable or metastatic hepatocellular carcinoma and according to the prescriber, the patient is not a surgical candidate as options for approval.</p> <p>Non-Small Cell Lung Cancer (NSCLC): A requirement was added that the patient is ≥ 18 years of age. A requirement was added that the patient does NOT have a history of recent hemoptysis. Adenocarcinoma, large cell or NSCLC not otherwise specified were moved to a Note. For NSCLC that is negative for actionable mutations, continuation maintenance therapy was added as an option of approval. In combination with other systemic therapies was added to the subsequent therapy option for approval. To the epidermal growth factor receptor exon 19 deletion or exon 21 L858R mutations option for approval, exon 21 descriptor was added. As first-line or continuation maintenance therapy was added to the in combination with erlotinib option of approval. The medication is used as subsequent therapy following prior targeted therapy was added as an option of approval. The medication is used for first-line treatment was added as an option of approval. ERBB2 was added as an option of approval for first-line therapy. Requirements for first-line or subsequent therapy (based on genetic markers) were added. Separately, requirements for subsequent therapy (based on genetic markers) were added.</p> <p>Ovarian, Fallopian Tube, or Primary Peritoneal Cancer: A requirement was added that the patient is ≥ 18 years of age. The descriptor “up to” was added to the recommended dose.</p> <p>Renal Cell Carcinoma: A requirement was added that the patient is ≥ 18 years of age. The descriptor of “advanced” was removed from requirement that the patient has relapsed, metastatic, or stage IV disease.</p> <p>Ampullary Adenocarcinoma: This was added as a new condition of approval.</p> <p>Endometrial Carcinoma: A requirement was added that the patient is ≥ 18 years of age. The frequency of dosing was changed from once every 2 weeks to once every 3 weeks.</p> <p>Mesothelioma: A requirement was added that the patient is ≥ 18 years of age. Bevacizumab was removed if used as a single agent for maintenance therapy as an option of approval.</p> <p>Pediatric central Nervous System Tumors: This was added new condition of approval.</p> <p>Small Bowel Adenocarcinoma: A requirement was added that the patient is ≥ 18 years of age. A requirement was added that the patient has advanced or metastatic disease.</p> <p>Soft Tissue Sarcoma: A requirement was added that the patient is ≥ 18 years of age.</p> <p>Vulvar Cancer: Squamous cell carcinoma was removed from the condition of approval. A requirement was added that the patient is ≥ 18 years of age. A requirement was added that the patient has advanced, recurrent, or metastatic disease. The descriptor “up to” was removed from the recommended dosing regimen. The frequency of dosing was changed from once every 2 weeks to once every 3 weeks.</p>	
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