POLICY: Oncology (Injectable) – Bevacizumab Products
- Avastin® (bevacizumab for intravenous injection – Genentech, Inc.)
- Mvasi™ (bevacizumab-awwb injection for intravenous infusion – Amgen)
- Zirabev™ (bevacizumab-bvzr injection for intravenous infusion – Pfizer)

DATE REVIEWED: 04/01/2020; 06/10/2020 selected revision

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:

1) cervical cancer (persistent, recurrent, or metastatic), in combination with paclitaxel and cisplatin OR paclitaxel and topotecan;
2) metastatic colorectal cancer (mCRC), in combination with intravenous 5-fluorouracil [5-FU]-based chemotherapy for first- or second-line treatment; or for mCRC, in combination with fluoropyrimidine (5-FU, capecitabine)-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;
3) treatment of recurrent glioblastoma in adults;
4) non-squamous non-small cell lung cancer (NSCLC), in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease;
5) recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that is platinum-resistant in combination with paclitaxel, Doxil® (doxorubicin liposome intravenous infusion; i.e., pegylated liposomal doxorubicin), or topotecan for the treatment of patients who received no more than two prior chemotherapy regimens, OR disease that is platinum-sensitive in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by Avastin as a single agent; or in combination with carboplatin and paclitaxel, followed by Bevacizumab as a single agent, in patients with stage III or IV disease following initial surgical resection;
6) metastatic renal cell carcinoma (mRCC) in combination with interferon alfa subcutaneous injection;
7) Hepatocellular carcinoma (HCC): Bevacizumab in combination with Tecentriq (atezolizumab injection for intravenous use) is indicated for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy.

Bevacizumab is available as a solution and is supplied in 100 mg and 400 mg preservative-free, single-use vials that deliver 4 mL and 16 mL of bevacizumab (25 mg/mL), respectively.[1] The dose of bevacizumab is diluted in a total volume of 100 mL of 0.9% sodium chloride injection. The first dose is given as an intravenous (IV) infusion over 90 minutes. The second dose is infused over 60 minutes if the first dose was tolerated, and the third and all subsequent doses are given over 30 minutes, if the 60 minute infusion was tolerated.

Dosing Information

For mesothelioma, the National Comprehensive Cancer Network (NCCN) guidelines recommend intravenous bevacizumab 15 mg per kg on Day 1 given every 3 weeks for 6 cycles in combination with Alimta with cisplatin or carboplatin.[2] This combination therapy may be followed by maintenance bevacizumab 15 mg per kg given every 3 weeks until disease progression. For small bowel adenocarcinoma guidelines recommend bevacizumab dose of either 5 mg/kg or 7.5 mg/kg IV on Day 1, when given in combination with chemotherapy.[3] The dose is repeated once every 2 or 3 weeks. The recommended dosage

for HCC is 15 mg/kg IV bevacizumab after administration of 1,200 mg Tecentriq IV on the same day, every 3 weeks until disease progression or unacceptable toxicity.

Guidelines

The NCCN clinical practice guidelines on **cervical cancer** (version 3.2019 – December 17, 2018) recommend bevacizumab for treatment of local/regional recurrence or Stage IVB or distant metastases in patients with cervical cancer (squamous cell carcinoma or adenocarcinoma) as first-line preferred combination regimen with paclitaxel and cisplatin (category 1), or with carboplatin and paclitaxel (category 2A), or with topotecan and paclitaxel (category 1).[4] It is also recommended for second-line, single-agent therapy (category 2B).

The NCCN clinical practice guidelines on **colon cancer** (version 2.2020 – March 3, 2020) recommendations for bevacizumab treatment are as follows:[5,6]

- In combination with capecitabine or with FOLFOX, FOLFIRI, CapeOX, FOLFOXIRI, OR 5-FU/LV as one of the following (category 2A):
  - As primary treatment for advanced or metastatic disease;
  - For unresectable synchronous metastases to liver and/or lung and other sites;
  - As primary treatment for synchronous abdominal/peritoneal metastases that are non-obstructing, or following local therapy for patients with imminent or existing obstruction;
  - As primary treatment for unresectable metachronous metastases in combination with FOLFIRI or irinotecan.
- Primary treatment for unresectable synchronous liver and/or lung metastases in combination with one of the following: FOLFOX, FOLFIRI, FOLFOXIRI, or CapeOX (category 2A);
- The preferred anti-angiogenic therapy* as primary treatment for patients with unresectable metachronous metastases and previous adjuvant FOLFOX or CapeOX within the past 12 months in combination with irinotecan or FOLFIRI (category 2A);
- As subsequent therapy for advanced or metastatic disease (category 2A):
  - As the preferred anti-angiogenic agent* in combination with irinotecan or FOLFIRI in patients previously receiving oxaliplatin-based therapy without irinotecan;
  - In combination with FOLFOX or CapeOX in patients previously receiving irinotecan-based therapy without oxaliplatin;
  - As the preferred anti-angiogenic agent* in combination with irinotecan or FOLFIRI for patients previously treated with fluoropyrimidine therapy without irinotecan or oxaliplatin; or in combination with FOLFOX or CAPEOX in this population; or irinotecan + oxaliplatin.

The NCCN clinical practice guidelines on **rectal cancer** (version 2.2020 – March 3, 2020) recommendations for bevacizumab treatment are as follows:[6,7]

- In combination with capecitabine or with a FOLFOX, FOLFIRI, FOLFOXIRI, CapeOX or 5-FU/LV regimen for one of the following (All of these are category 2A except adjuvant therapy which is 2B.):
  - Primary therapy for T3, N0, any T, N1-2, or T4 and/or locally unresectable or medically inoperable disease if resection is contraindicated after neoadjuvant therapy;
  - Primary therapy for unresectable synchronous metastases or for medically inoperable disease;
  - After primary treatment with chemoradiation or local therapy for symptomatic unresectable synchronous metastases or medically inoperable disease;
  - Adjuvant therapy after resection and/or local therapy of resectable metachronous metastases for patients who received previous chemotherapy or had growth on neoadjuvant chemotherapy;
  - Primary treatment for unresectable metachronous metastases in patients who have not received previous adjuvant FOLFOX or CapeOX within the past 12 months;

  - Adjuvant therapy for unresectable metachronous metastases that converted to resectable disease after primary treatment;
  - For unresectable metachronous metastases that remain unresectable after primary treatment;
- As the preferred anti-angiogenic therapy* as primary treatment, in combination with irinotecan or FOLFIRI in patients with unresectable metachronous metastases and previous adjuvant FOLFOX or CapeOX within the past 12 months (category 2A);
- As subsequent therapy after first progression of unresectable advanced or metastatic disease in combination with chemotherapy (category 2A).

The NCCN clinical practice guidelines on **central nervous system (CNS) cancers** (version 1.2020 – March 10, 2020) recommend bevacizumab as a preferred single-agent therapy for recurrent anaplastic gliomas (category 2A).[8] Anaplastic gliomas includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (A), and other rare anaplastic gliomas. Bevacizumab is also recommended as a preferred single-agent therapy for recurrent glioblastoma (category 2A) and in combination with chemotherapy (carmustine or lomustine, TMZ, carboplatin) [category 2B]. The NCCN guidelines recommend that bevacizumab be considered as a single-agent treatment for recurrence therapy in adults with *intracranial and spinal ependymoma* (excluding subependymoma) [category 2A]. It is also recommended for meningiomas either as monotherapy (category 2A) or in combination with Afinitor (everolimus tablets) [category 2B]. Patients with good performance status who have evidence of radiographic progression may benefit from continuing bevacizumab alone to prevent rapid neurologic deterioration. In patients with glioblastoma or anaplastic gliomas, Bevacizumab plus chemotherapy can be considered in patients who have failed bevacizumab monotherapy.

The NCCN clinical practice guidelines on **NSCLC** (version 3.2020 – February 11, 2020)[6,9] recommend bevacizumab therapy in combination with carboplatin and paclitaxel (category 1), carboplatin and Alimta (category 2A), cisplatin and Alimta (category 2A) for recurrence or metastases in patients with performance status 0 to 1 for tumors of non-squamous cell histology (i.e., adenocarcinoma (with mixed subtypes), large cell carcinoma) and no history of recent hemoptysis for the following uses:

1) initial systemic therapy if *EGFR*, *ALK*, *ROS1*, *BRAF* negative or unknown, and PD-L1 < 50 or unknown;
2) first-line or subsequent therapy for *BRAF V600E*-mutation positive tumors;
3) First-line treatment for EGFR mutation-positive tumors when used in combination with erlotinib (category 2B);
4) subsequent therapy for sensitizing *EGFR* mutation-positive tumors after prior targeted therapy (e.g., erlotinib, Tagrisso® [osimertinib tablets]);
5) subsequent therapy for *ALK* rearrangement-positive tumors after previous targeted therapy (e.g., Xalkori® [crizotinib capsules], Alecensa® [alectinib capsule]);
6) subsequent therapy for *ROS1* rearrangement-positive tumors and prior Xalkori or Zykadia therapy;
7) First-line or subsequent therapy for PD-L1 expression-positive (≥ 50%) tumors and.

Bevacizumab is also recommended in the NCCN guidelines as *continuation maintenance* therapy if given first line with chemotherapy for recurrence or metastasis.[9] This is in patients who achieve tumor response or stable disease following initial cytotoxic therapy.

The NCCN clinical practice guidelines on **ovarian cancer** including fallopian tube or primary peritoneal cancer (version 1.2020 – March 11, 2020) recommendations for bevacizumab treatment of <u>*epithelial*</u> ovarian cancer/fallopian tube cancer/primary peritoneal cancer are as follows:[10]

- Therapy for persistent disease or recurrence for one of the following (category 2A):
  - As preferred therapy if *platinum-sensitive*, in combination with chemotherapy.

  - As preferred therapy if *platinum-resistant,* in combination with chemotherapy; or
  - As preferred targeted therapy as a single agent for both platinum-sensitive and platinum-resistant disease.
- Maintenance therapy for *platinum-sensitive* persistent disease or recurrence following response.
- Consider as neoadjuvant chemotherapy in combination with paclitaxel and carboplatin for bulky Stage II to IV disease or poor surgical candidates (category 2A). Bevacizumab can also be used with this combination (paclitaxel and carboplatin) for primary adjuvant treatment in stage I to IV disease.
- Bevacizumab is also recommended (mostly in combination with chemotherapy, but sometimes as single agent) for treatment of Other Less Common Histopathologies such as carcinosarcoma, clear-cell carcinoma, mucinous carcinoma, serous/endometrioid epithelial carcinoma, and malignant sex cord stromal tumors either either for adjuvant therapy or for treatment of systemic disease.

For **kidney cancer**, bevacizumab's efficacy was established using Roferon®-A (interferon alfa-2a injection)[11] which is no longer available. Subsequently, bevacizumab was studied in combination with Intron A.[12] The NCCN clinical practice guidelines on **kidney cancer** (version 3.2019 – February 6, 2019) recommend bevacizumab as therapy for relapse or Stage IV disease as follows[13]: as a single-agent subsequent therapy for predominant clear cell histology as "useful under certain circumstances" (category 2B); as single-agent systemic therapy for non-clear cell histology, useful under certain circumstances (category 2A); and 4) in combination with erlotinib (for selected patients with advanced papillary renal cell carcinoma including hereditary leiomyomatosis and renal cell cancer) or everolimus /Afinitor® Disperz™ (everolimus tablets for oral suspension) (category 2A).

The NCCN clinical practice guidelines on **breast cancer** (version 3.2020 – March 6, 2020) recommend bevacizumab in combination with paclitaxel as "useful in certain circumstances" for recurrent or metastatic (stage IV) HER2-negative disease and endocrine therapy refractory (category 2A).[14] The guidelines note that sequential single agents are preferred options, but chemotherapy cmbinations may be used in select patients with high tumor burden, rapidly progressing disease, and visceral crisis. Regarding bevacizumab, the guidelines state that randomized trials in metastatic breast cancer document that adding bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival or quality of life.

The NCCN clinical practice guidelines on **malignant pleural mesothelioma** (version 1.2020 – November 27, 2019) recommend bevacizumab in combination with cisplatin and Alimta (category 1) or with carboplatin and Alimta (category 2A) followed by single-agent maintenance bevacizumab as treatment for 1) unresectable clinical Stage I to III disease and tumors of epithelial histology, or 2) clinical Stage IV disease, tumors of sarcomatoid or mixed histology, or medically inoperable tumors in patients with performance status 0 to 2.[2]

The NCCN Compendium for bevacizumab recommends its use in endometrial carcinoma as a single agent or in combination with other chemotherapy upon progression on prior chemotherapy (category 2A).[6] It is also recommended for small bowel adenocarcinoma in combination with other chemotherapy for initial therapy (category 2A). For soft tissue sarcoma, bevacizumab is recommended for use in combination with temozolomide for the treatment of solitary fibrous tumor and hemangiopericytoma. It is also recommended as single agent therapy for angiosarcoma (category 2A for both). For vulvar cancer, bevacizumab can be used in combination with chemotherapy (e.g., cisplatin and paclitaxel) in various therapy settings (locally advanced unresectable disease, metastatic disease, lymph node recurrence).

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of bevacizumab in patients with conditions other than ophthalmic. The intent of this policy is to provide recommendations 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 (AEs) and long-term efficacy, approval requires bevacizumab to be prescribed by or in consultation with a physician who specializes in the condition being treated.

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. Cervical Cancer. Approve for 1 year if the patient meets the following criteria (A and B):
- **A)** The medication is prescribed by or in consultation with an oncologist; AND
- **B)** The patient has recurrent or metastatic cervical cancer.

Dosing. Approve the following dose:
- **A)** Each bevacizumab dose is 15 mg per kg intravenous infusion; AND
- **B)** Bevacizumab is administered not more frequently than once every 3 weeks.

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2. Colon or Rectal Cancer. Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
- **A)** Bevacizumab is prescribed by or in consultation with an oncologist; AND
- **B)** The patient has advanced or metastatic colon or rectal cancer [Stage IV]; AND
- **C)** Bevacizumab is used in combination with a chemotherapy regimen.
  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); AND
- **D)** Bevacizumab is not being used for adjuvant treatment of colon cancer.

Dosing: Approve one of the following dosing regimens (A, B, or C):
- **A)** Bevacizumab dose of 5 mg per kg administered intravenously not more frequently than once every 2 weeks; OR
- **B)** Bevacizumab dose of 10 mg per kg administered intravenously not more frequently than once every 2 weeks; OR
- **C)** Bevacizumab dose of 7.5 mg per kg administered intravenously not more frequently than once every 3 weeks.

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3. Central Nervous System Tumors – Glioblastoma (glioblastoma multiforme [GBM], Grade IV astrocytoma), Anaplastic Gliomas, Meningiomas, Intracranial and Spinal Ependymoma

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(Excludes Subependymoma) in Adults. Approve for 1 year if the patient meets the following criteria (A and B):
A) The medication is prescribed by or in consultation with an oncologist; AND
B) The patient has tried at least one other therapy.
Note: Examples of other therapies are temozolomide capsules or injection, radiotherapy.

Dosing. Approve the following dose:
A) Each bevacizumab dose is 10 mg per kg intravenous infusion; AND
B) Bevacizumab is administered not more frequently than once every 2 weeks.

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4. Hepatocellular Carcinoma (HCC). Approve for 1 year if the patient meets the following criteria (A, B, and C):
A) Bevacizumab is prescribed by or in consultation with an oncologist; AND
B) The medication is used in combination with Tecentriq (atezolizumab injection); AND
C) The patient has not received prior systemic therapy.

Dosing. Approve the following dose:
A) Each bevacizumab dose is 15 mg per kg intravenous infusion; AND
B) Bevacizumab is administered not more frequently than once every 3 weeks.

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5. Non-Small Cell Lung Cancer (NSCLC). Approve for 1 year if the patient meets the following criteria (A and B):
A) Bevacizumab is prescribed by or in consultation with an oncologist; AND
B) The patient has advanced or metastatic non-squamous NSCLC (i.e., adenocarcinoma, large cell, or NSCLC not otherwise specified) and meets ONE of the following criteria (i, ii, iii, or iv):
i. The NSCLC tumor is positive for epidermal growth factor receptor (*EGFR*) mutation and bevacizumab is used in combination with erlotinib for first-line treatment; OR
ii. If the NSCLC tumor is positive for any one of the targetable mutations (i.e., epidermal growth factor receptor (*EGFR*) mutations, anaplastic lymphoma kinase (*ALK*) fusions, ROS proto-oncogene 1 [*ROS1*]) at least one of the targeted therapy agents has been tried and bevacizumab is used as subsequent therapy; OR
iii. If the NSCLC tumor is *BRAF V600E* mutation-positive, bevacizumab is used as either first-line or subsequent therapy; OR
iv. The NSCLC tumor is negative or unknown for targetable mutations (e.g., *EGFR, ALK, ROS1, BRAF*) and the patient meets ONE of the following criteria (a or b):
a) Bevacizumab is used as initial therapy in combination with platinum chemotherapy (cisplatin or carboplatin); OR
b) Bevacizumab is used as subsequent therapy and is used either as a single agent or in combination with other agents.

Dosing. Approve the following dose:
A) Each bevacizumab dose is 15 mg per kg intravenous infusion; AND
B) Bevacizumab is administered not more frequently than once every 3 weeks.

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6. Ovarian, Fallopian Tube, or Primary Peritoneal Cancer. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

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

A) Each bevacizumab dose of 15 mg per kg intravenous infusion not more frequently than once every 3 weeks; OR
B) Each bevacizumab dose of 10 mg per kg intravenous infusion not more frequently than once every 2 weeks.

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7. Renal Cell Cancer. Approve for 1 year if the patient meets the following criteria (A and B):
A) The medication is prescribed by or in consultation with an oncologist; AND
B) The patient has advanced (e.g., relapsed, metastatic, or Stage IV) renal cell cancer.

Dosing. Approve the following dose:
A) Each bevacizumab dose of 10 mg per kg intravenous infusion; AND
B) Bevacizumab administered not more frequently than once every 2 weeks.[1]

Other Uses with Supportive Evidence

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8. Breast Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
A) Bevacizumab is prescribed by or in consultation with an oncologist; AND
B) The patient has recurrent or metastatic human epidermal growth factor receptor 2 (HER2)-negative breast cancer;[35-36] AND
C) Bevacizumab is used in combination with paclitaxel.

Dosing. Approve the following dose:
A) Each bevacizumab dose of 10 mg per kg intravenous infusion; AND
B) Bevacizumab administered not more frequently than on Days 1 and 15 of a 28 day cycle.

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9. Endometrial Carcinoma. Approve for 1 year if the patient meets the following criteria (A and B):
A) The medication is prescribed by or in consultation with an oncologist; AND
B) The patient has progressed on prior chemotherapy.
Note: Examples of chemotherapy include carboplatin, cisplatin, paclitaxel, docetaxel, doxorubicin.

Dosing. Approve if the dosing meets following (A and B):
A) Each dose is up to 15 mg/kg intravenous infusion; AND
B) Bevacizumab is administered not more frequently than once every 2 weeks.

Limited dosing is available. Single doses up to 15 mg/kg administered once every 2 or 3 weeks are recommended in the product labeling for approved uses.[1]

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10. 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).

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11. Malignant Pleural Mesothelioma. Approve for 1 year if the patient meets the following criteria (A, B, and C):
A) Bevacizumab is prescribed by or in consultation with an oncologist; AND
B) The patient has unresectable malignant pleural mesothelioma;[48] AND
C) One of the following applies (i or ii):

i. Bevacizumab will be used in combination with a chemotherapy regimen
Note: Examples of chemotherapy are Alimta [pemetrexed injection], cisplatin, carboplatin;[48]
OR

ii. Bevacizumab is being used as a single agent for maintenance therapy after the patient has received combination chemotherapy regimen.
Note: Examples of chemotherapy are Alimta [pemetrexed injection], cisplatin, carboplatin).[48]

Dosing. Approve the following dose:
A) Each bevacizumab dose of 15 mg per kg intravenous infusion; AND
B) Bevacizumab is administered not more frequently than once every 3 weeks.

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12. Small Bowel Adenocarcinoma. Approve for 1 year if the patient meets the following criteria (A and B):
A) The medication is prescribed by or in consultation with an oncologist; AND
B) The medication is used in combination with chemotherapy.
Note: Examples of chemotherapy are fluorouracil, leucovorin, and oxaliplatin (FOLFOX), capecitabine and oxaliplatin (CapeOX), fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI).

Dosing. Approve the following (A and B):
A) Each dose is up to 7.5 mg/kg intravenous infusion; AND
B) Bevacizumab is administered not more frequently than once every 2 weeks.

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13. Soft Tissue Sarcoma – Angiosarcoma and Solitary Fibrous Tumor/Hemangiopericytoma. Approve for 1 year if the medication is prescribed by or in consultation with an oncologist.

Dosing. Approve the following (A and B):
A) Each dose is up to 15 mg/kg intravenous infusion; AND
B) Bevacizumab is administered not more frequently than once every 2 weeks.

Limited dosing is available. Single doses up to 15 mg/kg administered once every 2 or 3 weeks are recommended in the product labeling for approved uses.[1]

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14. Vulvar Cancer (Squamous Cell Carcinoma). Approve for 1 year if the patient meets the following criteria (A and B):
A) The medication is prescribed by or in consultation with an oncologist; AND
B) Bevacizumab is used in combination with a chemotherapy regimen.
Note: Examples of chemotherapy regimen are cisplatin and paclitaxel, carboplatin and paclitaxel.

Dosing. Approve the following dosing:
A) Each dose is up to 15 mg/kg intravenous infusion; AND
B) Bevacizumab is administered not more frequently than once every 2 weeks.

Limited dosing is available. Single doses up to 15 mg/kg administered once every 2 or 3 weeks are recommended in the product labeling for approved uses.[1]

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Bevacizumab has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

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

REFERENCES

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13. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 – August 5, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 27, 2020.
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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
Annual revision	• Colorectal cancer: First and second-line therapy are defined as initial and subsequent. This aligns with NCCN guidelines wording. Avastin will not be used I combination with Erbitux or Vectibix was removed. The combinations that are approved are listed in the criteria. • NSCLC: For first-line therapy, criteria were added requiring that the patient's tumor has a PD-L1 expression test for Keytruda (pembrolizumab) that is negative (< 50%) or unknown. Follows NCCN guidelines. For continuation maintenance therapy, criteria were removed that stated the tumor is negative for EGFR mutations, ALK fusions, or ROS1 rearrangements and also removed the requirement that Avastin would be used alone or with Alimta. For subsequent therapy, the following were added. Testing has to have been completed for EGFR mutations, ALK fusions, or ROS1 rearrangements and if these are positive targeted therapy must have been tried. This wording is consistent with what we've done for other policies with a non-squamous cell NSCLC indication. Also added that if PD-L1 expression testing is positive (≥ 50%) that Keytruda has been tried OR that PD-L1 expression is unknown. These are following the current NCCN guidelines. Testing for PD-L1 expression for Keytruda (pembrolizumab) was added to Labs/Diagnostics required for first-line or subsequent therapy. • Ovarian, fallopian tube, or primary peritoneal cancer: For platinum-sensitive disease, added that Avastin will be used in combination with carboplatin and paclitaxel. New in the prescribing information. Criteria regarding use of Avastin as a single agent was revised that it's for platinum-sensitive or platinum-resistant disease. This is recommended in the NCCN guidelines and could be with or without prior use of Avastin in combination with chemotherapy. • Myopic choroidal neovascularization: New indication added for this ophthalmic condition. See policy for details.	02/08/2017
Annual revision	• Colorectal Cancer: The criterion, Avastin is not being used for adjuvant therapy, was revised to add "of colon cancer". • Glioblastoma: Anaplastic Gliomas in Adults was added to this indication. • NSCLC: For first-line or initial therapy, testing has been completed for EGFR, ALK, and PD-L1 expression for Keytruda was added. ROS1 testing was deleted. For subsequent therapy, testing for ROS1 was removed. The names of targeted drugs used for EGFR mutations and ALK fusions were removed and replaced with "the patient has received targeted drug therapy for the specific mutation. In Labs/Diagnostics, detection of ROS1 was removed. • Ovarian, Fallopian Tube, or Primary Peritoneal Cancer: Persistent was added to the criterion recurrent (i.e., relapsed or refractory. The criterion, Avastin has not been previously used for persistent disease or recurrence was deleted, since Avastin may be used for maintenance. • Renal Cell Cancer: Another use for Avastin was added as follows: combinations use with Tarceva or Afinitor for non-clear cell histology disease in patients with advanced papillary renal cell carcinoma. • Malignant Pleural Mesothelioma: This indication was added. See policy for details. • Other Cancer-Related Indications: Revised. See policy for details.	02/28/2018
Annual revision	The policy name has been changed to bevacizumab products since the biosimilar, Mvasi, has been added. Avastin has been changed to "bevacizumab" throughout the policy. Consistent with the other policies, the initial/extended approval, duration of therapy, Labs/Diagnostics section have all been deleted. Instead for all indication, the approval duration is in the criteria and the standard approval duration is now 1 year. Under the Dosing section, all dosing have been re-worded to "approve" for the listed dosing. • Colon or Rectal Cancer: Previously used to state "colorectal" cancer. Deleted specific references to "first-line or second-line" or "neoadjuvant"	03/27/2019

	therapy. Instead of referencing specific chemotherapy regimens, in accordance with other policies, listed the chemotherapy options as examples. • Central Nervous System Tumors – Glioblastoma (glioblastoma multiforme [GBM], Grade IV astrocytoma), or Anaplastic Gliomas, Meningiomas, Intracranial and Spinal Ependymoma (Excludes Subependymoma) in Adults: Added "Central Nervous System Tumors" to indication and added intracranial and spinal ependymoma to the list. This was moved from "Other Cancer-Related Indications." • Non-Small Cell Lung Cancer: Criteria were simplified in line with other medical policies with this indication. Bevacizumab is approved for subsequent therapy in combination with chemotherapy if there is a targetable mutation and targeted therapy has been tried. If BRAF V600E positive, then bevacizumab can be used for initial or subsequent therapy. If there are no known targetable mutations, then bevacizumab can be used first line in combination with chemotherapy and/or as single agent for subsequent therapy. • Ovarian, Fallopian Tube, or Primary Peritoenal Cancer: Criteria were simplified to only require the specialist physician. Prior criteria was detailed, but would have approved for any patient who had platinum-sensitive or platinum-resistant disease, or if bevacizumab was used as single-agent or in combination. • Renal Cell Cancer (RCC): Simplified criteria to only require specialist physician and advanced disease. Although prior criteria was detailed, it would have approved bevacizumab for any patient with RCC. • Breast Cancer: Deleted criteria that patient has not received previous chemotherapy for recurrent HER2-negative disease. Also modified criteria to state bevacizumab is used in combination with paclitaxel (as in guidelines). • Diabetic Macular Edema: Noted in indication that it includes patients with diabetic retinopathy with macular edema. • Diabetic Retinopathy in Patients with Diabetic Macular Edema: Deleted this condition since it is covered in above indication for Diabetic Macular Edema. • Malignant Pleural Mesothelioma: Wherever chemotherapy is listed as specific agents previously, it is now listed as an example. • Vulvar Cancer (Squamous Cell Carcinoma): Added new condition and criteria based on NCCN compendium category 2A recommendation. • Patient has been started on Avastin: Deleted this criterion since patients are required to meet indication/criteria/dosing for re-approval. This is in-line with other medical policies.	
Selected revision	The addition of Zirabev™ was added to the product list. Ophthalmic conditions are no longer targeted in this policy. A new indication of **Neovascular and Vascular Ophthalmic Conditions** was created to combine all indication previously listed in the policy. All requests for ophthalmic indications are to approve for 1 year. • **Diabetic Macular Edema (Includes Patients with Diabetic Retinopathy and Diabetic Macular Edema).** Existing criteria and dosing were removed. This indication was placed within the new indication of **Neovascular and Vascular Ophthalmic Conditions.** • **Endometrial Cancer.** Added new condition for approval. Previously, this condition was listed under Other Cancer-Related Indications. • **Macular Edema Following Retinal Vein Occlusion.** Existing criteria and dosing were removed. This indication was placed within the new indication of **Neovascular and Vascular Ophthalmic Conditions.** • **Myopic Choroidal Neovascularization.** Existing criteria and dosing were removed. This indication was placed within the new indication of **Neovascular and Vascular Ophthalmic Conditions.** • **Neovascular (Wet) Age-Related Macular Degeneration.** Existing criteria and dosing were removed. This indication was placed within the new indication of **Neovascular and Vascular Ophthalmic Conditions.**	09/11/2019

	• **Other Neovascular Diseases of the Eye (e.g., neovascular glaucoma, retinopathy of prematurity, sickle cell neovascularization, choroidal neovascular conditions).** Existing criteria and dosing were removed. This indication was placed within the new indication of **Neovascular and Vascular Ophthalmic Conditions.** • **Small Bowel Adenocarcinoma.** Added new condition for approval based on guideline recommendations. • **Soft Tissue Sarcoma.** Added new condition for approval. Previously, this was listed under Other Cancer-Related Indications. • **Other Cancer-Related Indications.** Deleted this indication. Listed out conditions as separate criteria.	
Selected revision	Approval duration for **Neovascular or Vascular Ophthalmic Conditions** was changed from 1 year to 3 years.	11/06/2019
Annual revision	• **Non-Small Cell Lung Cancer.** Added new criteria for bevacizumab use in EGFR mutation-positive NSCLC in combination with erlotinib in first-line setting. • **Vulvar Cancer.** Changed dosing wording to state "not more frequently than once every 2 weeks."	04/01/2020
Selected revision	• Added new FDA-approval indication for hepatocellular carcinoma. For Dosing, added "not more frequently" for interval durations in all conditions.	06/10/2020

NSCLC – Non-small cell lung cancer; EGFR – Epidermal growth factor receptor; ALK – Anaplastic lymphoma kinase; NCCN – National Comprehensive Cancer Network; PD-L1 – Programmed death-ligand 1.