Clinical Policy Title:	bevacizumab
Policy Number:	RxA.665
Drug(s) Applied:	Avastin ®, Zirabev ®, Mvasi ®
Original Policy Date:	01/25/2021
Last Review Date:	03/09/2021
Line of Business Policy Applies to:	All lines of business

Background

Bevacizumab (Avastin®) and its biosimilars, bevacizumab-bvzr (Zirabev ®) and bevacizumab-awwb (Mvasi®) are vascular endothelial growth factor (VEGF) inhibitors.

Bevacizumab and its biosimilars are indicated for:

- Metastatic colorectal cancer
  - In combination with intravenous fluorouracil-based chemotherapy, as first- or second- line treatment.
  - In combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab-containing regimen, as second line treatment.
  - Limitations of use: Avastin®, Zirabev®, Mvasi® are not indicated for adjuvant treatment of colon cancer.
- Non-Squamous Non–Small Cell Lung Cancer
  - In combination with carboplatin and paclitaxel, as first-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic non–squamous non–small cell lung cancer (NSCLC),
- Recurrent Glioblastoma
  - For treatment of recurrent glioblastoma (GBM) in adults.
- Renal Cell Carcinoma
  - In combination with interferon alfa, for the treatment of metastatic renal cell carcinoma (mRCC),
- Cervical Cancer
  - In combination with paclitaxel and cisplatin or paclitaxel and topotecan, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.

Bevacizumab is also indicated:

- Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
  - In combination with carboplatin and paclitaxel, followed by Avastin as a single agent, for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection.
  - In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan, for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens.

- In combination with carboplatin and paclitaxel, or with carboplatin and gemcitabine, followed by Avastin as a single agent, for the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

- Hepatocellular Carcinoma
  - In combination with atezolizumab, for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen***	**Maximum Dose**
bevacizumab (Avastin®); bevacizumab-bvzr (Zirabev®); bevacizumab-awwb (Mvasi ®)	Colorectal cancer, metastatic	In combination with bolus-IFL: 5 mg/kg given as IV infusion every 2 weeks In combination with FOLFOX4: 10 mg/kg given as IV infusion every 2 weeks In combination with fluoropyrimidine-, irinotecan-, or fluoropyrimidine-oxaliplatin-based chemotherapy after progression on a first-line bevacizumab-containing regimen: 5 mg/kg given as IV infusion every 2 weeks or 7.5 mg/kg given as IV infusion every 3 weeks	10 mg/kg
	Non-Squamous NSCLC	In combination with carboplatin and paclitaxel: 15 mg/kg given as IV infusion every 3 weeks.	15 mg/kg
	Recurrent GBM	10mg/kg given as IV infusion over 90 minutes, every 2 weeks	10 mg/kg
	mRCC	In combination with interferon-alfa: 10 mg/kg every 2 weeks	
	Cervical cancer; persistent, recurrent, or metastatic	In combination with paclitaxel and cisplatin, or paclitaxel and topotecan: 15 mg/kg given as IV infusion every 3 weeks	15 mg/kg
bevacizumab (Avastin ®)	Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer, Stage III or IV, following initial surgical resection	In combination with carboplatin and paclitaxel: 15 mg/kg every 3 weeks for up to 6 cycles, followed by 15 mg/kg every 3 weeks as a single agent, for a total of up to 22 cycles	

bevacizumab (Avastin ®)	Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer, Platinum-resistant recurrent	In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan given every week: 10 mg/kg every 2 weeks In combination with topotecan given every 3 weeks: 15 mg/kg every 3 weeks In combination with carboplatin and paclitaxel: 15mg/kg every 3 weeks for 6-8 cycles, followed by 15 mg/kg every 3 weeks as a single agent In combination with carboplatin and gemcitabine: 15 mg/kg every 3 weeks for 6-10 cycles, followed by 15 mg/kg every 3 weeks as a single agent	10 – 15 mg/kg
	Hepatocellular carcinoma	Following administration of 1,200mg of atezolizumab: 15 mg/kg every 3 weeks	15 mg/kg

*First infusion is administered over 90 minutes. Second infusion is administered over 60 minutes, if first is tolerated. All subsequent infusions are administered over 30 minutes if the second infusion over 60 minutes was tolerated.

Dosage Forms

- Avastin ®: Single-dose vial 100mg/4mL (4 mL), 400mg/16mL (16mL)
- Zirabev ®: Single-dose vial 100mg/4mL (4mL), 400mg/16mL (16mL)
- Mvasi ®: Single-dose vial 100mg/4mL (4mL), 400mg/16mL (16mL)

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the provisions of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Colorectal cancer (must meet all):

1. Member has a diagnosis of metastatic colorectal cancer;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. Member must meet one or more of the following (a or b):
   a. Bevacizumab is being used as a first line treatment, when added to IV 5-fluorouracil based chemotherapy (e.g. IFL, FOLFOX4 etc);
   b. As a second line treatment when added to irinotecan-fluoropyrimidine- or oxaliplatin-fluoropyrimidine-based chemotherapy after disease has progressed on first line therapy containing bevacizumab;
5. Bevacizumab is not being used as adjuvant therapy;
6. For requests other than Zirabev®: Member must have tried and failed Zirabev®, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
7. Dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration:
Commercial: 6 months
Medicaid: 6 months

B. Non- squamous non-small cell lung cancer (must meet all):
1. Member has a diagnosis of non-squamous non-small cell lung cancer;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. Bevacizumab is used as first line treatment in combination with carboplatin and paclitaxel;
5. For requests other than Zirabev®: Member must have tried and failed Zirabev®, at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration:
Commercial: 6 months
Medicaid: 6 months

C. Glioblastoma (must meet all):
1. Member has a diagnosis of recurrent glioblastoma;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. Member must meet one of the following (a or b):
   a. Bevacizumab is being used as a single agent;
   b. Bevacizumab is used in combination with carmustine, lomustine, or temozolomide if monotherapy with bevacizumab has failed;
5. For requests other than Zirabev®: Member must have tried and failed Zirabev®, at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration:
Commercial: 6 months
Medicaid: 6 months

D. Cervical cancer (must meet all):
1. Member has a diagnosis of persistent, recurrent, or metastatic cervical cancer;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. Member must meet one of the following (a or b):
   a. Bevacizumab is being used as first-line or second-line therapy in combination with paclitaxel and cisplatin or paclitaxel and topotecan;
   b. Bevacizumab is being used first-line or second-line therapy in combination with paclitaxel and carboplatin (off-label use);
5. For requests other than Zirabev®: Member must have tried and failed Zirabev® at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration:
Commercial: 6 months
Medicaid: 6 months

E. Ovarian, Fallopian Tube or Peritoneal cancer (must meet all):

1. Request is for Avastin®;
2. Member has a diagnosis of one of the following (a or b):
   a. Stage III or IV ovarian, fallopian tube or peritoneal cancer following initial resection; or
   b. Recurrent disease, platinum resistant or platinum sensitive;
3. Prescribed by or in consultation with an oncologist;
4. Member is 18 years of age or older;
5. Member must meet one of the following (a, b, c, d, or e):
   a. For Stage III or IV disease, bevacizumab is being prescribed in combination with carboplatin and paclitaxel;
   b. For recurrent disease-platinum resistant, bevacizumab is being prescribed with paclitaxel, pegylated liposomal doxorubicin, or topotecan;
   c. For recurrent disease-platinum sensitive, bevacizumab is being prescribed in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine;
   d. Bevacizumab is being used as a single agent following combination therapy indicated above for stage III or IV disease;
   e. Bevacizumab is being used as a single agent following combination therapy indicated above for recurrent disease-platinum sensitive;
6. Dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration:
Commercial: 6 months
Medicaid: 6 months

F. Hepatocellular carcinoma (must meet all):

1. Request is for Avastin®;
2. Member has a diagnosis of unresectable or metastatic hepatocellular carcinoma;
3. Prescribed by or in consultation with an oncologist;
4. Member is 18 years of age or older;
5. Member has not received prior systemic therapy;
6. Bevacizumab is being prescribed in combination with atezolizumab;
7. Dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration:
Commercial: 6 months
Medicaid: 6 months

G. Breast cancer (off-label) (must meet all):

1. Member has diagnosis of recurrent or stage IV HER2-negative disease that is hormone receptor-negative or hormone receptor-positive with visceral crisis or is refractory to endocrine therapy;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. Bevacizumab is being prescribed as first-line therapy in combination with paclitaxel;
5. Bevacizumab is being prescribed as second-line therapy in combination with other chemotherapy or in combination with capecitabine in patients previously treated with an anthracycline and a taxane;

6. For requests other than Zirabev®: Member must have tried and failed Zirabev® at maximally indicated doses or clinically significant adverse effects are experienced;
7. Dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration:
Commercial: 6 months
Medicaid: 6 months

H. Central nervous system cancers (off-label) (must meet all):
1. Member has a diagnosis of one of the following:
   a. Metastatic spine tumor;
   b. Meningioma;
   c. Adult low-grade infiltrative supratentorial astrocytoma/oligodendroglioma;
   d. Anaplastic glioma;
   e. Adult intracranial and spinal ependymoma, limited and extensive brain metastases;
   f. Adult medulloblastoma;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. For requests other than Zirabev®: Member must have tried and failed Zirabev® at maximally indicated doses or clinically significant adverse effects are experienced;
5. Dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration:
Commercial: 6 months
Medicaid: 6 months

I. Pleural mesothelioma (off-label) (must meet all):
1. Member has a diagnosis of malignant pleural mesothelioma;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. Bevacizumab is being prescribed in combination with pemetrexed and cisplatin;
5. For requests other than Zirabev®: Member must have tried and failed Zirabev® at maximally indicated doses or clinically significant adverse effects are experienced;
6. Dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration:
Commercial: 6 months
Medicaid: 6 months

J. Age-related macular degeneration (off-label) (must meet all):
1. Member has a diagnosis of macular degeneration;
2. Prescribed by or in consultation with an ophthalmologist;
3. Member is 50 years of age or older;
4. For requests other than Zirabev®: Member must have tried and failed Zirabev® at maximally indicated doses or clinically significant adverse effects are experienced;
5. Dosing is supported by evidence based-guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration:
Commercial: 6 months
Medicaid: 6 months

K. Diabetic macular edema (off-label) (must meet all):
1. Member has a diagnosis of diabetic macular edema;
2. Prescribed by or in consultation with an ophthalmologist;
3. Member is 18 years of age or older;
4. For requests other than Zirabev®: Member must have tried and failed Zirabev® at maximally indicated doses or clinically significant adverse effects are experienced;
5. Dosing is supported by evidence based-guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration:
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. All indications listed in section I (must meet all):
1. Member is currently receiving the medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is positively responding to therapy (e.g. tumour regression, absence of disease progression etc);
3. If request is for a dose increase, dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration:
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
ASCO: American Society of Clinical Oncology
CNS: Central Nervous System
FDA: Food and Drug Administration
FOLFOX: chemotherapy regimen containing leucovorin, fluorouracil, oxaliplatin
HER2: Human Epidermal Growth Factor Receptor 2
IFL: Irinotecan, Fluorouracil, Leucovorin-containing chemotherapy
IV: Intravenous/Intravenously
NCCN: National Comprehensive Cancer Network
NSCLC: Non-Small Cell Lung Cancer
VEGF: Vascular Endothelial Growth Factor

APPENDIX B: Therapeutic Alternatives
Not applicable

APPENDIX C: Contraindications/Boxed Warnings
- Contraindication(s):
  - None

- Boxed Warning(s):
  - None

APPENDIX D: General Information

- Bevacizumab should not be administered for at least 28 days prior to elective surgery. In addition, bevacizumab should not be administered for at least 28 days following surgery and until adequate wound healing.
- Bevacizumab is associated with potentially severe infusion related reactions; a reduced infusion rate, interruption of therapy, or discontinuation of therapy may be necessary.
- Most common adverse reactions are headache, hypertension, rhinitis, proteinuria, nosebleeds, dry skin, back pain and exfoliative dermatitis.

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Review/Revision History	Review/Revised Date	P&T Approval Date
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