Pharmacy Policy Bulletin: J-0888 Anti-Angiogenesis and VEGF Kinase Inhibitors - Commercial and Healthcare Reform	
Number: J-0888	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial** **Prior Authorization (1.):** **1.** Miscellaneous Specialty Drugs Oral = Yes with Prior Authorization **Quantity Limits (1., 2., 3., or 4.):** **1.** Rx Mgmt Quantity Limits = Safety/ Specialty **2.** Rx Mgmt Quantity Limits = Safety/Specialty + Dose Opt **3.** Rx Mgmt Quantity Limits = Safety/Specialty + Dose Opt + Watchful **4.** Rx Mgmt Performance = MRxC = Yes **Healthcare Reform:** Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-0888-020	**Original Date:** 06/04/2003
Effective Date: 07/18/2025	**Review Date:** 06/25/2025

Drugs Product(s):	• Cabometyx (cabozantinib) • Cometriq (cabozantinib) • Fotivda (tivozanib) • Fruzaqla (fruquintinib) • Inlyta (axitinib) • Lenvima (lenvatinib) • Nexavar (sorafenib) • Stivarga (regorafenib) • Sutent (sunitinib) • Votrient (pazopanib)

FDA-Approved Indication(s):	• Cabometyx (cabozantinib)
	  ○ Treatment of patients with advanced renal cell carcinoma (RCC).
	  ○ Treatment of patients with advanced RCC as a first-line treatment in combination with nivolumab.
	  ○ Treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib.

	○ Treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible. ○ Treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumors (pNET). ○ Treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated extra-pancreatic neuroendocrine tumors (epNET). • Cometriq (cabozantinib) ○ Treatment of patients with progressive, metastatic medullary thyroid cancer (MTC). • Fotivda (tivozanib) ○ Treatment of adult patients with relapsed or refractory advanced RCC following two or more prior systemic therapies. • Fruzaqla (fruquintinib) ○ Treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (VEGF) therapy, and, if RAS wild-type and medically appropriate, an anti-epidermal growth factor receptor (EGFR) therapy. • Inlyta (axitinib) ○ In combination with avelumab, for the first-line treatment of patients with advanced RCC. ○ In combination with pembrolizumab, for the first-line treatment of patients with advanced RCC. ○ As a single agent, for the treatment of advanced RCC after failure of one prior systemic therapy. • Lenvima (lenvatinib) ○ Treatment of adult patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer. ○ In combination with pembrolizumab, for the first-line treatment of adult patients with advanced RCC. ○ In combination with everolimus, for the treatment of adult patients with advanced RCC following one prior anti-angiogenic therapy. ○ First-line treatment of patients with unresectable hepatocellular carcinoma. ○ In combination with pembrolizumab, for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR), as determined by an FDA-approved test, or not microsatellite instability-high (MSI-H), who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. • Nexavar (sorafenib) ○ Treatment of unresectable hepatocellular carcinoma. ○ Treatment of advanced RCC. ○ Treatment of locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment. • Stivarga (regorafenib) ○ Treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and if RAS wild type, an anti-EGFR therapy.

	○ Treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib and sunitinib. ○ Treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib. • Sutent (sunitinib) ○ Treatment of adult patients with GIST after disease progression on or intolerance to imatinib. ○ Treatment of adult patients with advanced RCC. ○ Adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy. ○ Treatment of progressive, well-differentiated pancreatic neuroendocrine tumors (pNET) in adult patients with unresectable locally advanced or metastatic disease. • Votrient (pazopanib) ○ Treatment of adults with advanced RCC. ○ Treatment of adults with advanced soft tissue sarcoma who have received prior chemotherapy.

Background:	• Cabozantinib is an oral, multi-tyrosine kinase inhibitor that works by blocking abnormal tyrosine kinase proteins, such as MET, VEGFR-1, -2, -3, RET, KIT, TRKB, FLT-3, AXL, and TIE-2. These receptor kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, and maintenance of the tumor microenvironment. ○ It is recommended to avoid use of concomitant CYP3A4 inducers, such as rifampin, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital, or St. John's Wort with Cabometyx. If concomitant use cannot be avoided, the dose of Cabometyx should be increased by 20 mg, not to exceed a daily dose of 80 mg. ○ Cabometyx tablets cannot be substituted with cabozantinib capsules. • Fotivda (tivozanib) is a self-administered oral VEGFR TKI specifically indicated for 3L or later aRCC. Fotivda inhibits phosphorylation of VEGFR-1, VEGFR-2, and VEGFR-3 to halt downstream angiogenesis, cancerous cell proliferation, and cancerous cell survival. In clinical trials, prior systemic therapies included VEGFR TKIs other than tivozanib and checkpoint inhibitors. • Fruzaqla (fruquintinib) is an anti-VEGF oral kinase inhibitor that inhibits VEGF-mediated endothelial cell proliferation and tubular formation by blocking VEGF receptors -1, -2 and -3, which in turn inhibits tumor growth. ○ It is recommended to avoid use of concomitant strong or moderate CYP3A4 inducers with Fruzaqla. If concomitant use cannot be avoided with moderate CYP3A4 inducers, continue to administer Fruzaqla at the recommended dosage. • Inlyta (axitinib) has been shown to inhibit receptor tyrosine kinases including vascular endothelial growth factors (VEGFR)-1, VEGFR-2, and VEGFR-3 at therapeutic plasma concentrations. These receptors are implicated in pathologic angiogenesis, tumor growth, and cancer progression. VEGF-mediated endothelial cell proliferation and survival were inhibited by axitinib in vitro and in mouse models. Inlyta was shown to inhibit tumor growth and phosphorylation of VEGFR-2 in tumor xenograft mouse models. • Lenvima (lenvatinib) is a receptor tyrosine kinase (RTK) inhibitor that inhibits activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR) and VEGFR3 (FLT4). • Nexavar (sorafenib) is a multi-kinase inhibitor. It inhibits Raf-1 kinase and the receptor kinases of vascular endothelial growth factor (VEGFR-2, VEGFR-3),

platelet-derived growth factor receptor (PDGFR)-β, c-KIT, FLT-3, and RET, which are involved in proliferation and angiogenesis.

- Stivarga (regorafenib) is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment.
- Sutent (sunitinib) inhibits multiple receptor tyrosine kinases (RTKs), some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer.
- Votrient (pazopanib) is a multi-target tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α and -β, and c-Kit tyrosine kinases, some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer.
- Prescribing Considerations:
    - Kinase inhibitors should be prescribed under the supervision of a hematologist/oncologist.
    - For the first line treatment of advanced RCC, Bavencio (avelumab) is indicated for use with Inlyta. Inlyta is also indicated as monotherapy for advanced RCC after one prior systemic therapy.

Chemotherapy Class	Examples of Medications
Fluoropyrimidine	capecitabine, floxuridine, fluorouracil
Platinum	oxaliplatin, carboplatin, cisplatin
Anti-VEGF	bevacizumab, ramucirumab, ziv-aflibercept
Anti-EGFR	cetuximab, panitumumab
Taxane	paclitaxel, docetaxel
HER2/neu	trastuzumab
Antiangiogenic	bevacizumab, axitinib, pazopanib

    - For the mCRC indication, additional non-specific ICD-10 diagnosis codes related to this disease state include Z80.0 (family history of malignant neoplasm of digestive organs) and Z85.0 (personal history of malignant neoplasm of digestive organs).

Approval Criteria

I. Initial Authorization

A. Cabometyx (cabozantinib)

1. Renal Cell Carcinoma (RCC)

When a benefit, coverage of Cabometyx may be approved when all of the following criteria are met **(a. and b.)**:

a. The member is 18 years of age or older.

b. The member meets one (1) of the following criteria **(i. or ii.)**:

i. The member has a diagnosis of advanced RCC (ICD-10: C64).

ii. The member has a diagnosis of advanced RCC and is using Cabometyx as a first-line treatment in combination with nivolumab.

2. Hepatocellular Carcinoma

When a benefit, coverage of Cabometyx may be approved when all of the following criteria are met **(a., b., and c.)**:

a. The member is 18 years of age or older.
b. The member has a diagnosis of hepatocellular carcinoma (ICD-10: C22).
c. The member has been previously treated with sorafenib.

3. Differentiated Thyroid Cancer

When a benefit, coverage of Cabometyx may be approved when all of the following criteria are met **(a. through d.):**

a. The member is 12 years of age or older.
b. The member has a diagnosis of locally advanced or metastatic differentiated thyroid cancer (ICD-10: C73).
c. The member has experienced disease progression following prior VEGFR-targeted therapy.
d. The member meets one (1) of the following criteria **(i. or ii.):**
  i. The member is radioactive iodine-refractory.
  ii. The member is ineligible for radioactive iodine therapy.

4. Pancreatic Neuroendocrine Tumors (pNET)

When a benefit, coverage of Cabometyx may be approved when all of the following criteria are met **(a., b., and c.)**:

a. The member is 12 years of age or older.
b. The member has a diagnosis of unresectable, locally advanced or metastatic, well-differentiated pNET (ICD-10: C25.4).
c. The member has been previously treated for pNET.

5. Extra-Pancreatic Neuroendocrine Tumors (epNET)

When a benefit, coverage of Cabometyx may be approved when all of the following criteria are met **(a., b., and c.)**:

a. The member is 12 years of age or older.
b. The member has a diagnosis of unresectable, locally advanced or metastatic, well-differentiated epNET (ICD-10: C7A.8).
c. The member has been previously treated for epNET.

6. Quantity Limits

When a benefit, additional quantities of Cabometyx 40 mg, up to 2 tablets per day, may be approved when the following criterion is met **(a.)**:

a. The member is taking a strong CYP3A4 inducer.

B. Cometriq (cabozantinib)

When a benefit, coverage of Cometriq may be approved when all of the following criteria are met **(1. and 2.)**:

1. The member is 18 years of age or older.
2. The member has a diagnosis of progressive, metastatic medullary thyroid cancer (ICD-10: C73).

C. Fotivda (tivozanib)

When a benefit, coverage of Fotivda may be approved when all of the following criteria are met **(1., 2., and 3.)**:

1. The member is 18 years of age or older.
2. The member has a diagnosis of relapsed or refractory advanced renal cell carcinoma (ICD-10: C64).
3. The member has received at least two prior systemic therapies.

D. Fruzaqla (fruquintinib)

When a benefit, coverage of Fruzaqla may be approved when all of the following criteria are met **(1. through 5.)**:

1. The member is 18 years of age or older.
2. The member has a diagnosis of metastatic colorectal cancer (ICD-10: C17, C18, C19, C78).
3. The member has received previous treatment with a fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.
4. The member has received previous treatment with an anti-VEGF therapy.
5. If the member is RAS wild-type, the member meets one (1) of the following **(a. or b.)**:
   a. The member has received previous therapy with an anti-EGFR therapy.
   b. The prescriber attests that treatment with an anti-EGFR therapy would not be medically appropriate.

E. Inlyta (axitinib)

When a benefit, coverage of Inlyta may be approved when all of the following criteria are met **(1., 2., and 3.)**:

1. The member is 18 years of age or older.
2. The member has a diagnosis of advanced renal cell carcinoma (RCC) (ICD-10: C64).
3. The member meets one (1) of the following criteria **(a. or b.)**:
   a. The member is using Inlyta as first-line treatment for advanced RCC and meets one (1) of the following criteria **(i. or ii.)**:
      i. The member is using Inlyta in combination with avelumab.
      ii. The member is using Inlyta in combination with pembrolizumab.
   b. The member is using Inlyta as a single agent and has experienced therapeutic failure of one (1) prior systemic therapy.

F. Lenvima (lenvatinib)

1. Thyroid Cancer

When a benefit, coverage of Lenvima may be approved when all of the following criteria are met **(a. and b.)**:

a. The member is 18 years of age or older.
b. The member has a diagnosis of differentiated thyroid cancer (ICD-10: C73) meeting all of the following criteria **(i., ii., and iii.):**
   i. Disease is classified as locally recurrent or metastatic.
   ii. Disease is classified as progressive.
   iii. Disease is classified as radioactive-iodine refractory.

2. Renal Cell Carcinoma (RCC)

a. Combination with Keytruda (pembrolizumab)

When a benefit, coverage of Lenvima may be approved when all of the following criteria are met **(i. through iv.):**

i. The member is 18 years of age or older.
ii. The member has a diagnosis of advanced RCC (ICD-10: C64).
iii. The member is using Lenvima in combination with pembrolizumab.
iv. The member is using Lenvima and pembrolizumab as first-line treatment.

b. Combination with everolimus

When a benefit, coverage of Lenvima may be approved when all of the following criteria are met **(i. through iv.)**:

i. The member is 18 years of age or older.
ii. The member has a diagnosis of advanced RCC (ICD-10: C64).
iii. The member will be using Lenvima in combination with everolimus.
iv. The member has experienced therapeutic failure or intolerance to one (1) prior anti-angiogenic therapy.

3. Hepatocellular Carcinoma

When a benefit, coverage of Lenvima may be approved when all of the following criteria are met **(a., b., and c.)**:

- **a.** The member is 18 years of age or older.
- **b.** The member has a diagnosis of unresectable hepatocellular carcinoma (ICD-10: C22).
- **c.** The member is using Lenvima as first-line treatment.

4. Endometrial Carcinoma

When a benefit, coverage of Lenvima may be approved when all of the following criteria are met **(a. through g.)**:

- **a.** The member is 18 years of age or older.
- **b.** The member has a diagnosis of endometrial carcinoma (ICD-10: C54, C55).
- **c.** Disease is classified as advanced.
- **d.** The member is using Lenvima in combination with pembrolizumab.
- **e.** The member meets at least one (1) of the following criteria **(i. or ii.):**
  - **i.** Disease is **not** classified as microsatellite instability-high (MSI-H).
  - **ii.** Disease is classified as mismatch repair proficient (pMMR), as determined by an FDA-approved test.
- **f.** The member has experienced disease progression following prior systemic therapy.
- **g.** The prescriber attests that the member is not a candidate for curative surgery or radiation.

G. Nexavar (sorafenib)

1. Renal Cell Carcinoma (RCC)

When a benefit, coverage of Nexavar (sorafenib) may be approved when all of the following criteria are met **(a., b., and c.)**:

- **a.** The member is 18 years of age or older.
- **b.** The member has a diagnosis of advanced RCC (ICD10: C64).
- **c.** If the request is for brand Nexavar, the member has experienced therapeutic failure or intolerance to generic sorafenib.

2. Hepatocellular Carcinoma

When a benefit, coverage of Nexavar (sorafenib) may be approved when all of the following criteria are met **(a., b., and c.)**:

- **a.** The member is 18 years of age or older.
- **b.** The member has a diagnosis of unresectable hepatocellular carcinoma (ICD-10: C22).
- **c.** If the request is for brand Nexavar, the member has experienced therapeutic failure or intolerance to generic sorafenib.

3. Thyroid Carcinoma

When a benefit, coverage of Nexavar (sorafenib) may be approved when all of the following criteria are met **(a. through d.)**:

- **a.** The member is 18 years of age or older.
- **b.** The member has a diagnosis of locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (for example, papillary, follicular or Hurthle cell carcinoma; ICD-10: C73).
- **c.** The member is refractory to iodine treatment.
- **d.** If the request is for brand Nexavar, the member has experienced therapeutic failure or intolerance to generic sorafenib.

H. Stivarga (regorafenib)

1. Colorectal Cancer

When a benefit, coverage of Stivarga may be approved when all of the following criteria are met **(a. through e.)**:

- **a.** The member is 18 years of age or older.

b. The member has a diagnosis of metastatic colorectal cancer (ICD-10: C17, C18, C19, C78).
c. The member has received previous treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.
d. The member has received previous treatment with an anti-VEGF therapy.
e. If the member is *RAS* wild-type, the member has received previous treatment with an anti-EGFR therapy.

2. GIST
When a benefit, coverage of Stivarga may be approved when all of the following criteria are met **(a. through d.)**:
a. The member is 18 years of age or older.
b. The member has a diagnosis of locally advanced, unresectable or metastatic GIST (ICD-10: C49.A).
c. The member has received previous treatment with imatinib.
d. The member has received previous treatment with sunitinib.

3. Hepatocellular Carcinoma
When a benefit, coverage of Stivarga may be approved when all of the following criteria are met **(a., b., and c.)**:
a. The member is 18 years of age or older.
b. The member has a diagnosis of hepatocellular carcinoma (ICD-10: C22).
c. The member has received previous treatment with sorafenib.

I. Sutent (sunitinib)

1. Gastrointestinal Stromal Tumor (GIST)
When a benefit, coverage of Sutent (sunitinib) may be approved when all of the following criteria are met **(a. through d.)**:
a. The member is 18 years of age or older.
b. The member has a diagnosis of GIST (ICD-10: C49.A).
c. The member has experienced therapeutic failure, intolerance or contraindication to imatinib.
d. If the request is for brand Sutent, the member has experienced therapeutic failure or intolerance to generic sunitinib.

2. Pancreatic Neuroendocrine Tumors (pNET)
When a benefit, coverage of Sutent (sunitinib) may be approved when all of the following criteria are met **(a., b., and c.)**:
a. The member is 18 years of age or older.
b. The member has a diagnosis of progressive, well-differentiated pNET (ICD-10: C25.4) meeting one (1) of the following criteria **(i. or ii.)**:
i. Disease is classified as locally advanced.
ii. Disease is classified as metastatic.
c. If the request is for brand Sutent, the member has experienced therapeutic failure or intolerance to generic sunitinib.

3. Renal Cell Carcinoma (RCC)
When a benefit, coverage of Sutent (sunitinib) may be approved when all of the following criteria are met **(a., b., and c.):**
a. The member is 18 years of age or older.
b. The member meets one (1) of the following criteria **(i. or ii.)**:
i. The member has a diagnosis of advanced RCC (ICD-10: C64).
ii. The member has undergone nephrectomy and meets all of the following criteria **(A) and B)):**

A) The member is using sunitinib as adjuvant therapy.
B) The member is at high risk of recurrent RCC following nephrectomy.

c. If the request is for brand Sutent, the member has experienced therapeutic failure or intolerance to generic sunitinib.

J. Votrient (pazopanib)

1. Renal Cell Carcinoma (RCC)

When a benefit, coverage of Votrient (pazopanib) may be approved when all of the following criteria are met **(a., b., and c.)**:

a. The member is 18 years of age or older.
b. The member has a diagnosis of advanced RCC (ICD-10: C64).
c. If the request is for brand Votrient, the member has experienced therapeutic failure or intolerance to generic pazopanib.

2. Advanced Soft Tissue Sarcoma

When a benefit, coverage of Votrient (pazopanib) may be approved when all of the following criteria are met **(a. through d.)**:

a. The member is 18 years of age or older.
b. The member has a diagnosis of advanced soft-tissue sarcoma (excluding adipocytic soft tissue sarcoma and GIST; ICD-10: C49.9).
c. The member has failed at least one (1) prior chemotherapy regimen.
d. If the request is for brand Votrient, the member has experienced therapeutic failure or intolerance to generic pazopanib.

II. Reauthorization

When a benefit, reauthorization of a kinase inhibitor may be approved when all of the following criteria are met **(A. and B.)**:

A. The prescriber attests that the member is tolerating therapy and has experienced a therapeutic response defined as either one (1) of the following **(1. or 2.)**:
1. Disease improvement
2. Delayed disease progression

B. If the request is for brand Sutent, brand Nexavar, or brand Votrient, the member has experienced therapeutic failure or intolerance to the AB-rated generic.

III. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

IV. Coverage of oncology medications listed in this policy may be approved on a case-by-case basis per indications supported in the most current NCCN guidelines.

Limitations of Coverage

I. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.

II. For members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

- Commercial and HCR Plans: If approved, up to a 12 month authorization may be granted.

Automatic Approval Criteria

None

Refer to J-699 for previous versions.

References:

1. Bavencio [package insert]. Rockland, MA: EMD Serono Inc. and Pfizer Inc.; November 2024
2. Cabometyx [package insert]. Alameda, CA; Exelixis, Inc.: March 2025.
3. Cometriq [package insert]. Alameda, CA; Exelixis, Inc.: August 2023.
4. Fotivda [package insert]. Boston, Massachusetts: Aveo Pharmaceuticals; August 2024.
5. Fruzaqla [package insert]. Lexington, MA: Takeda Pharmaceuticals U.S.A; November 2023.
6. Inlyta [package insert]. New York, NY: Pfizer Labs; July 2024.
7. Lenvima [package insert]. Woodcliff Lake, NJ: Eisai Inc.; November 2024.
8. Nexavar [package insert]. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc.; August 2023.
9. Stivarga [package insert]. Bayer HealthCare Pharmaceuticals Inc; Whippany, NJ, December 2020.
10. Sutent [package Insert]. New York NY; Pfizer Labs: August 2021.
11. Votrient [package insert]. East Hanover, NJ; Novartis Pharms Corp: January 2024.