BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

CABOMETYX® (cabozantinib) oral
COMETRIQ™ (cabozantinib) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for CABOMETYX (cabozantinib)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by an Oncologist, Nephrologist, Pulmonologist, Endocrinologist, or Gastroenterologist, or in consultation with one of these specialists

Indication
- Advanced renal cell carcinoma (RCC)

PHARMACY COVERAGE GUIDELINE

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- Advanced renal cell carcinoma (RCC) as first line treatment in combination with nivolumab
- Hepatocellular carcinoma (HCC) previously treated with sorafenib
- Locally advanced or metastatic differentiated thyroid cancer (DTC) that progressed after vascular endothelial growth factor receptor (vascular endothelial growth factor receptor) targeted therapy and is radioactive iodine refractory or ineligible
- Previously treated, unresectable, locally advanced or metastatic, well differentiated pancreatic neuroendocrine tumors (pNET)
- Previously treated, unresectable, locally advanced or metastatic, well differentiated extra pancreatic neuroendocrine tumors (pNET)
- Other oncologic direct treatment uses listed in National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

Age Requirement

- **Renal cell carcinomas:** 18 years or older
- **Hepatocellular carcinoma:** 18 years or older
- **Differentiated thyroid cancer:** 12 years or older
- **Pancreatic neuroendocrine tumors:** 12 years or older

Baseline Clinical Evaluation

- Oral examination by medical provider or dentist to assess risk for osteonecrosis of the jaw, with preventative care as needed
- Negative pregnancy test (if applicable)
- Thyroid function test
- Eastern Cooperative Oncology Group Performance (ECOG) score of 0 to 2 or Karnofsky Performance Score of greater than or equal to 70

Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- **NONE** of the following:
  - Recent history of severe hemorrhage (e.g., hemoptysis, hematemesis, melena)
  - GI fistula or perforation
  - Severe hepatic impairment (Child Pugh Class C)
  - Severe renal impairment (eGFR less than 29 mL/min/1.73 m² or requiring dialysis)
  - Uncontrolled hypertension
  - Substitution of Cometriq (cabozantinib) capsules for Cabometyx (cabozantinib) tablets
  - No simultaneous use of Cabometyx (cabozantinib) tablets with Cometriq (cabozantinib) capsules

PHARMACY COVERAGE GUIDELINE

CABOMETYX® (cabozantinib) oral
COMETRIQ™ (cabozantinib) oral
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Documentation Requirements
- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (oral exam, pregnancy test, thyroid function, performance score)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration
- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy)
Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualifications
- Continues to be seen by or in consultation with an Oncologist, Nephrologist, Pulmonologist, Endocrinologist, or Gastroenterologist

Clinical Response
- No evidence of disease progression or unacceptable toxicity

Adherence
- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria
- Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety
- No significant adverse drug effects such as:
  - Severe or life threatening hemorrhage
  - GI perforation or life threatening fistula
  - Thrombotic events (e.g., myocardial infarction, cerebral infarction)
  - Hypertensive crisis or severe hypertension uncontrolled by therapy
  - Severe hepatotoxicity or adrenal insufficiency when used with nivolumab
  - Proteinuria or nephrotic syndrome
  - Osteonecrosis of jaw
  - Reversible posterior leukoencephalopathy syndrome
  - Hypocalcemia not resolved with dose adjustment
- No substitution of Cometriq (cabozantinib) capsules for Cabometyx (cabozantinib) tablets
- No simultaneous use of Cabometyx (cabozantinib) tablets with Cometriq (cabozantinib) capsules

PHARMACY COVERAGE GUIDELINE

CABOMETYX® (cabozantinib) oral
COMETRIQ™ (cabozantinib) oral
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Documentation Requirements
- Chart notes
- Supporting clinical documentation with evidence of improvement
- Lab values confirming safe use

Continuation Therapy Criteria Approval Duration
- 12 months OR end of plan year

Medical Necessity Requirements for COMETRIQ (cabozantinib)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by an Endocrinologist, Pulmonologist, or Oncologist, or in consultation with one of these specialists

Indication
- Progressive or metastatic medullary thyroid cancer (MTC)
- Other oncologic direct treatment uses listed in National Comprehensive Cancer Network (National Comprehensive Cancer Network) Guidelines with Categories of Evidence and Consensus of 1 and 2A

Age Requirement
- 18 years of age or older

Baseline Clinical Evaluation
- Oral examination by medical provider or dentist to assess risk for osteonecrosis of the jaw, with preventative care as needed
- Negative pregnancy test (if applicable)
- Eastern Cooperative Oncology Group (ECOG) Performance score of 0–2 or Karnofsky Performance Score of greater than or equal to 70

Brand Specific Criteria
- Have failure, contraindication or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety
- **NONE** of the following:
  - Recent history of severe hemorrhage (e.g., hemoptysis, hematemesis, melena)

- GI fistula or perforation
- Severe hepatic impairment (Child Pugh Class C)
- Severe renal impairment (eGFR less than 29 mL/min/1.73 m² or requiring dialysis)
- Uncontrolled hypertension
- Substitution of Cabometyx (cabozantinib) tablets for Cometriq (cabozantinib) capsules
- Simultaneous use of Cometriq (cabozantinib) capsules with Cabometyx (cabozantinib) tablets

Documentation Requirements

- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (oral exam, pregnancy test, performance score)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy)

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualifications

- Continues to be seen by or in consultation with an Endocrinologist, Pulmonologist, or Oncologist

Clinical Response

- No evidence of disease progression or unacceptable toxicity

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No significant adverse drug effects such as:
  - Severe or life threatening hemorrhage
  - Gastrointestinal perforation or life threatening fistula
  - Thrombotic events (e.g., myocardial infarction, cerebral infarction)
  - Hypertensive crisis or severe hypertension uncontrolled by therapy
  - Proteinuria or nephrotic syndrome
  - Osteonecrosis of jaw

  - Reversible posterior leukoencephalopathy syndrome
  - Hypocalcemia not resolved with dose adjustment
- No substitution of Cabometyx (cabozantinib) tablets for Cometriq (cabozantinib) capsules
- No simultaneous use of Cometriq (cabozantinib) capsules with Cabometyx (cabozantinib) tablets

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement
- Lab values confirming safe use

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications

2. Off-Label Use of Cancer Medications

Description:

Cabometyx (cabozantinib) tablet is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma (RCC), patients with advanced renal cell carcinoma (RCC) as first-line treatment in combination with nivolumab, hepatocellular carcinoma (HCC) who have previously been treated with sorafenib, 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. Cabometyx (cabozantinib) is indicated for the 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). Cabometyx (cabozantinib) is indicated for the 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).

Cabozantinib is also available as a capsule, under the brand name of Cometriq®, which is indicated for treatment of patients with progressive, metastatic medullary thyroid cancer (MTC). These dosage forms are not interchangeable due to differences in the pharmacokinetics of each formulation.

Renal Cell Carcinoma (RCC) is a common type of kidney cancer with three major sub-types: i) clear cell renal carcinoma (the most common RCC), ii) papillary renal cell carcinoma (second most common), and iii)

chromophobe renal cell carcinoma (third most common). There are other rare types of renal cell carcinoma that make up less than 1% of the RCC.

RCC has a high mortality rate but if it is detected early, it is potentially curable by surgery. In localized disease, partial nephrectomy for small tumors and radical nephrectomy for large tumors continue to be the gold-standard treatments. Cytoreductive nephrectomy is often indicated before the start of systemic treatment in patients with metastatic disease as part of integrated management strategy.
Other oral agents used for RCC that affect VEGF development of blood vessels in cancer cells include Afinitor (everolimus), Inlyta (axatinib), Lenvima (lenvatinib), Nexavar (sorafenib), Sutent (sunatinib), and Votrient (pazopanib). Avastin (bevacizumab), given by an intravenous injection in combination with interferon alpha, also affects VEGF blood vessel development in cancer cells.

Thyroid cancer is the most common of the endocrine malignancies. The annual incidence of thyroid cancer varies considerably by geographic area, age and sex. The only recognized environmental risk factor for thyroid carcinoma is exposure to ionizing radiation.

Thyroid cancer can develop from follicular or non-follicular thyroid cells. Medullary thyroid cancer (MTC) arises from non-follicular thyroid cells called calcitonin-producing cells. Thyroid cancers from follicular cells include papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), Hurthle cell cancer (HCC, also known as oxyphil thyroid cancer, a subtype of FTC), and anaplastic thyroid cancer (ATC). PTC and FTC are often referred to as differentiated thyroid cancer (DTC). There are several subtypes of DTC that includes tall cell, columnar and insular thyroid cancers. ATC is an undifferentiated thyroid cancer.

Hepatobiliary cancers are lethal cancers that include carcinomas arising from the liver (hepatocellular carcinoma, HCC), gall bladder, and bile ducts. Risk factors for the development of HCC are cirrhosis and chronic liver disease.

Targeted therapy is a treatment that targets the cancer's specific genes, proteins, or the tissue environment that contributes to cancer growth and survival. This type of treatment attempts to blocks the growth and spread of cancer cells while limiting damage to healthy cells. Anti-angiogenesis therapy is a type of treatment aimed at the process by which cancer cells make new blood vessels. Many of the anti-angiogenesis agents used attack the protein known as vascular endothelial growth factor (VEGF) that controls the formation of new blood vessels. Cabozantinib inhibits the tyrosine kinase activity of MET, VEGFR-1, -2 and -3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2. These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, drug resistance, and maintenance of the tumor microenvironment.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Osteonecrosis of the jaw (ONJ):
According to the American College of Rheumatology, ONJ can be diagnosed on oral examination by the presence of exposed bone that has lasted more than eight weeks.

ONJ risk factors include:

- Invasive dental procedures (e.g. tooth extraction, dental implants, oral surgery)
- Diagnosis of cancer
- Concomitant therapies (e.g. chemotherapy, corticosteroids, angiogenesis inhibitors)
- Poor oral hygiene
- Co-morbid disorders (e.g. periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures)

ECOG Performance status:

Eastern Co-operative Oncology Group (ECOG) Performance Status	
Grade	ECOG description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982	

Karnofsky Performance Scale:

Score	Description	
100	Normal, no complaints, no evidence of disease	Able to carry on normal activity and to work No special care needed
90	Able to carry on normal activity, only minor signs or symptoms of disease present	
80	Normal activity with effort, some signs or symptoms of disease present	
70	Cares for self, but unable to carry on normal activity or do active work	Unable to work but able to live at home and care for most personal needs Various degrees of assistance may be needed
60	Requires occasional assistance from others, but is able to care for most of his/her needs	
50	Requires considerable assistance from others and needs frequent medical care	
40	Disabled, requires special care and assistance	Unable to care for self Requires equivalent of institutional or hospital care
30	Severely disabled, hospitalization indicated, but death not imminent	
20	Very sick, hospitalization indicated, active support treatment is necessary but death not imminent	
10	Moribund, fatal process progressing rapidly	
0	Dead	

NCCN recommendation definitions:

Category 1:
Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A:
Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B:

Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3:

Resources:

Cabometyx (cabozantinib) tablet product information, revised by Exelixis, Inc. 03-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 07, 2025.

Cometriq (cabozantinib) capsule product information, revised by Exelixis, Inc. 08-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 07, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Hepatocellular Carcinoma Version 1.2025 – Updated March 20, 2025. Available at https://www.nccn.org. Accessed May 08, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Kidney Cancer Version 3.2025 – Updated January 09, 2025. Available at https://www.nccn.org. Accessed May 08, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Thyroid Carcinoma Version 1.2025 – Updated March 27, 2025. Available at https://www.nccn.org. Accessed May 08, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Neuroendocrine and Adrenal Tumors Version 1.2025 – Updated March 27, 2025. Available at https://www.nccn.org. Accessed May 08, 2025.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.