PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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CABOMETYX® (cabozantinib) oral
COMETRIQ™ (cabozantinib) oral

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

CABOMETYX® (cabozantinib) oral
COMETRIQ™ (cabozantinib) oral

Cabometyx (cabozantinib)

- **Criteria for initial therapy:** Cabometyx (cabozantinib) oral tablet is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist, Nephrologist, Pulmonologist, or Gastroenterologist depending upon indication or use

2. Individual is 18 years of age or older

3. A confirmed diagnosis of **ONE** of the following:
    a. Advanced renal cell carcinoma (RCC) as single agent therapy or used in combination with Opdivo (nivolumab)

    b. Hepatocellular carcinoma (HCC) in patients previously treated with Nexavar (sorafenib)

    c. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

4. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
    a. Oral examination performed by a medical provider or dentist to determine risk for osteonecrosis of the jaw, individuals with risk factors for ONJ (see Definition section) should receive appropriate preventive dentistry prior to initiation

    b. A negative pregnancy test in a woman of childbearing potential

    c. Eastern Cooperative Oncology Group Performance score of 0-2 or a Karnosky Performance Score of greater than or equal to 70

5. There is no recent history of severe hemorrhage or hemoptysis or melena

6. There is no GI fistula or perforation

7. The individual does not have severe hepatic impairment (Child-Pugh Class C)

8. Individual does not have severe renal impairment (eGFR < 29 mL/min/1.73 m^2 by MDRS or requiring dialysis)

9. Individual does not have uncontrolled hypertension

10. There are no significant interacting drugs

11. **NONE** of the following:
    a. Substitution of Cometriq (cabozantinib) capsules for Cabometyx (cabozantinib) tablets
    b. Simultaneous use of Cabometyx (cabozantinib) tablets with Cometriq (cabozantinib) capsules

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Cabometyx (cabozantinib) oral tablet is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist, Nephrologist, Pulmonologist, or Gastroenterologist depending upon indication or use

2. Individual's condition responded while on therapy
    a. Response is defined as:
        i. No evidence of disease progression
        ii. Documented evidence of efficacy, disease stability and/or improvement

3. Individual has been adherent with the medication

4. Individual has not developed any significant adverse drug effects that may exclude continued use
    a. Significant adverse effect such as:
        i. Severe hemorrhage
        ii. GI perforation or fistula
        iii. Arterial thrombotic events: MI, cerebral infarction, or other serious arterial thromboembolic events
        iv. Reversible posterior leukoencephalopathy syndrome (RPLS)
        v. Malignant hypertension, hypertensive crisis or severe hypertension that cannot be controlled with anti-hypertensive therapy
        vi. Osteonecrosis of jaw
        vii. Proteinuria or nephrotic syndrome
        viii. When used with nivolumab, ALT or AST greater than ten times the upper limit of normal (ULN) or three times ULN with a concurrent total bilirubin two or more times the ULN
        ix. When used with nivolumab, severe adrenal insufficiency

5. There are no significant interacting drugs

6. **NONE** of the following:
    a. Substitution Cometriq (cabozantinib) capsules for Cabometyx (cabozantinib) tablets
    b. Simultaneous use of Cabometyx (cabozantinib) tablets with Cometriq (cabozantinib) capsules

Renewal duration: 12 months

CABOMETYX® (cabozantinib) oral
COMETRIQ™ (cabozantinib) oral

- 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 a Non-Cancer Medications**

  2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

Cometriq (cabozantinib)

- **Criteria for initial therapy:** Cometriq (cabozantinib) oral capsule is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Endocrinologist, Pulmonologist, or Oncologist

  2. Individual is 18 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     a. Medullary thyroid cancer (MTC) that is progressive or metastatic

     b. Papillary, follicular, or Hurthle Cell thyroid carcinoma if other systemic therapies are not available or appropriate for treatment of progressive and/or symptomatic disease

     c. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

  4. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     a. Oral examination performed by a medical provider or dentist to determine risk for osteonecrosis of the jaw, individuals with risk factors for ONJ (see Definition section) should receive appropriate preventive dentistry prior to initiation

     b. A negative pregnancy test in a woman of childbearing potential

     c. Eastern Cooperative Oncology Group Performance score of 0-2 or a Karnosky Performance Score of greater than or equal to 70

  5. There is no recent history of severe hemorrhage or hemoptysis or melena

  6. There is no GI fistula or perforation

  7. The individual does not have severe hepatic impairment (Child-Pugh Class C)

8. Individual does not have severe renal impairment (eGFR < 29 mL/min/1.73 m^2 by MDRS or requiring dialysis)

9. Individual does not have uncontrolled hypertension

10. There are no significant interacting drugs

11. **NONE** of the following:
    a. Substitution of Cabometyx (cabozantinib) tablets for Cometriq (cabozantinib) capsules
    b. Simultaneous use of Cabometyx (cabozantinib) tablets with Cometriq (cabozantinib) capsules

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Cometriq (cabozantinib) oral capsule is considered ***medically necessary*** and will be approved with documentation of **ALL** of the following:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Endocrinologist, Pulmonologist, or Oncologist

2. Individual's condition responded while on therapy
    a. Response is defined as:
        i. No evidence of disease progression
        ii. Documented evidence of efficacy, disease stability and/or improvement

3. Individual has been adherent with the medication

4. Individual has not developed any significant adverse drug effects that may exclude continued use
    a. Significant adverse effect such as:
        i. Severe hemorrhage
        ii. GI perforation or fistula
        iii. Arterial thrombotic events: MI, cerebral infarction, or other serious arterial thromboembolic events
        iv. Reversible Posterior leukoencephalopathy syndrome (RPLS)
        v. Malignant hypertension, hypertensive crisis or severe hypertension that cannot be controlled with anti-hypertensive therapy
        vi. Osteonecrosis of jaw
        vii. Proteinuria or nephrotic syndrome

5. There are no significant interacting drugs

6. **NONE** of the following:
    a. Substitution of Cabometyx (cabozantinib) tablets for Cometriq (cabozantinib) capsules
    b. Simultaneous use of Cabometyx (cabozantinib) tablets with Cometriq (cabozantinib) capsules

Renewal duration: 12 months

CABOMETYX® (cabozantinib) oral
COMETRIQ™ (cabozantinib) oral

- 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:

  3. **Off-Label Use of a Non-Cancer Medications**

  4. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

Description:

Cabometyx (cabozantinib) tablet is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC) who have previously been treated with sorafenib. 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. 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.

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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:

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	

Resources:

Cabometyx (cabozantinib) tablet product information, revised by Exelixis, Inc. 01-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on June 22, 2021.

Cometriq (cabozantinib) capsule product information, revised by Exelixis, Inc. 10-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on June 22, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Hepatobiliary Cancers Version 3.2021 – Updated June 15, 2021. Available at https://www.nccn.org. Accessed on June 22, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Kidney Cancer Version 4.2021 – Updated April 19, 2021. Available at https://www.nccn.org. Accessed on June 22, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Thyroid Carcinoma Version 1.2021 – Updated April 09,2021. Available at https://www.nccn.org. Accessed on June 22, 2021.

National Comprehensive Cancer Network (NCCN) Compendium: Cabometyx. National Comprehensive Cancer Network (NCCN). NCCN Drugs & Biologics Compendium. Available at: http://www.nccn.org. Accessed on June 22, 2021.

National Comprehensive Cancer Network (NCCN) Compendium: Cometriq. National Comprehensive Cancer Network (NCCN). NCCN Drugs & Biologics Compendium. Available at: http://www.nccn.org. Accessed on June 22, 2021.

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.