COMETRIQ™ (cabozantinib) oral capsule

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.

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Description:

Cometriq (cabozantinib) capsule is a kinase inhibitor indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC). Cabozantinib is also available as a tablet, under the brand name of Cabometyx®, which is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy. These dosage forms are not interchangeable due to differences in the pharmacokinetics of each formulation.

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.

Definitions:

Drug related events:

Ineffective / failure
Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance
Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual’s outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals' body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

Allergic reaction / hypersensitivity – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

Intolerance – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

Contraindication
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental
Non-adherence
Individual does not follow prescribed regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record.

Precertification:
Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

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.

Criteria:
See “Resources” section for FDA-approved dosage.

- Precertification for Cometriq (cabozantinib) oral capsule requires completion of the specific request form in its entirety. 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 will be returned.

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Cometriq (cabozantinib) is considered medically necessary when ALL of the following criteria are met:
  1. Individual is 18 years of age or older
  2. Individual has medical record documentation of a confirmed diagnosis of progressive, metastatic medullary thyroid cancer
  3. ALL of the following baseline tests have been completed before initiation of treatment:
     - Blood pressure
     - Oral examination
  4. Absence of ALL of the following exclusions:
     - Individual who has or is at risk for severe hemorrhage
     - Severe hepatic impairment (Child-Pugh Class C)
     - Severe renal impairment (CrCl of < 30 mL/min/1.73 sq m)
COMETRIQ™ (cabozantinib) oral capsule (cont.)

- Woman of child bearing age who is pregnant or likely to become pregnant, unless is using effective contraception
- Woman who is breast feeding an infant or child
- Fistulas that cannot be adequately managed or perforations
- Thrombotic Events: myocardial infarction, cerebral infarction, or other serious arterial thromboembolic events
- Malignant hypertension, hypertensive crisis or severe hypertension that cannot be controlled with anti-hypertensive therapy
- Reversible Posterior leukoencephalopathy syndrome (RPLS)
- Nephrotic syndrome
- Osteonecrosis of the jaw
- Simultaneous use with grapefruit or grapefruit juice
- Substituting Cometriq (cabozantinib) capsules for Cabometyx (cabozantinib) tablets
- Simultaneous use of Cometriq (cabozantinib) capsules with Cabometyx (cabozantinib) tablets

OR

- A non-FDA approved use for the treatment of cancer of Cometriq (cabozantinib) is considered medically necessary when ONE of the following criteria are met:

  1. A non-FDA approved use for the treatment of cancer is recognized as safe and effective for the requested type of cancer, that is listed and supported by in ONE of the nationally recognized compendia or guidelines:
     - American Hospital Formulary Service
     - National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium
     - Thomson Micromedex compendium DrugDex
     - Elsevier Gold Standard’s Clinical Pharmacology compendium
     - American Society of Clinical Oncologist (ASCO) treatment guidelines
     - Other authoritative reference as identified by the Secretary of the United States Department of Human Health Services

  2. A non-FDA approved use for the treatment of cancer that is established from clinical trial(s) that have been published in peer reviewed professional medical journal(s) that has been submitted by the prescriber if ALL of the following apply:
     - At least two articles from major peer reviewed professional medical journals have recognized, based on scientific or medical criteria, the drug's safety and effectiveness for treatment of the indication for which the drug has been prescribed
     - No article from a major peer reviewed professional medical journal has concluded, based on scientific or medical criteria, that the drug is unsafe or ineffective or that the drug’s safety and effectiveness cannot be determined for the treatment of the indication for which the drug has been prescribed
     - The literature meets the uniform requirements for manuscripts submitted to biomedical journals established by the international committee of medical journal editors or is published in a journal specified by the United States department of health and human services as acceptable peer reviewed medical literature pursuant to section 186(t)(2)(B) of the social security act (42 United States Code section 1395x(t)(2)(B))
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- Oncology medications for all other indications not previously listed is considered experimental or investigational based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

Resources:

FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
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<tbody>
<tr>
<td>COMETRIQ is a kinase inhibitor indicated for the treatment of patients</td>
<td>• Recommended Dose: 140 mg orally (one 80-mg and three 20-mg capsules), once</td>
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<tr>
<td>with progressive, metastatic medullary thyroid cancer (MTC).</td>
<td>daily.</td>
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<td></td>
<td>• Instruct patients not to eat for at least 2 hours before and at least 1 hour</td>
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<td></td>
<td>after taking Cometriq.</td>
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