# Clinical Policy: Cabozantinib (Cabometyx, Cometriq)

Reference Number: CP.PHAR.111
Effective Date: 06.01.13
Last Review Date: 05.22
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

**See Important Reminder at the end of this policy for important regulatory and legal information.**

## Description

Cabozantinib (Cabometyx®, Cometriq®) is a kinase inhibitor.

## FDA Approved Indication(s)

Cabometyx is indicated for the treatment of:

- Patients with advanced renal cell carcinoma (RCC)
- Patients with advanced renal cell carcinoma, as a first-line treatment in combination with nivolumab
- Patients with hepatocellular carcinoma (HCC) who have been previously 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.

Cometriq is indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC).

## Policy/Criteria

*Provider must submit documentation (including such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

It is the policy of health plans affiliated with Centene Corporation® that Cabometyx and Cometriq are **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria**

**A. Renal Cell Carcinoma** (must meet all)**:**

1. Request is for Cabometyx;
2. Diagnosis of relapsed or stage IV (unresectable or metastatic) RCC;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. For Cabometyx request, member must use cabozantinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
6. Request meets one of the following (a, b, c, or d):*
   a. Dose does not exceed 60 mg (1 tablet) per day (monotherapy);
   b. Dose does not exceed 40 mg (1 tablet) per day (combination with Opdivo);
   c. Dose does not exceed 80 mg (2 tablets) per day and documentation that member is concurrently taking a strong CYP3A4 inducer (*see Appendix D*);

d. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**
**Medicaid/HIM –** 6 months
**Commercial –** 12 months or duration of request, whichever is less

**B. Hepatocellular Carcinoma** (must meet all)**:**

1. Request is for Cabometyx;
2. Diagnosis of HCC;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. For Cabometyx request, member must use cabozantinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
6. Confirmation of Child-Pugh class A status;
7. Request meets one of the following (a, b, or c):*
   a. Dose does not exceed 60 mg (1 tablet) per day;
   b. Dose does not exceed 80 mg (2 tablets) per day and documentation that member is concurrently taking a strong CYP3A4 inducer (*see Appendix D*);
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**
**Medicaid/HIM –** 6 months
**Commercial –** 12 months or duration of request, whichever is less

**C. Thyroid Carcinoma** (must meet all)**:**

1. Diagnosis of one of the following (a or b):
   a. Recurrent, unresectable, progressive, or metastatic medullary thyroid carcinoma (MTC);
   b. Differentiated thyroid carcinoma (DTC; i.e., follicular, Hurthle cell, or papillary thyroid carcinoma);
2. Prescribed by or in consultation with an oncologist;
3. Request is for one of the following (a or b):
   a. If MTC, request is for Cometriq;
   b. If DTC, request is for either Cabometyx or Cometriq;
4. Member meets one of the following (a or b):
   a. For Cabometyx request, age ≥ 12 years;
   b. For Cometriq request, age ≥ 18 years
5. For Cabometyx or Cometriq requests, member must use cabozantinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
6. If DTC, failure of Lenvima® or Nexavar®* unless contraindicated or clinically significant adverse effects are experienced;

   **Prior authorization may be required.*
7. Request meets one of the following (a, b, or c):*
   a. For Cabometyx, one of the following:
      i. BSA is ≥ 1.2 $m^2$ and dose does not exceed 60 mg (1 tablet) per day;

ii. BSA is < 1.2 $m^2$ and dose does not exceed 40 mg (1 tablet) per day;
iii. Dose does not exceed 80 mg (2 tablets) per day and documentation that member is concurrently taking a strong CYP3A4 inducer (*see Appendix D*);

b. For Cometriq, one of the following:
i. Dose does not exceed 140 mg (1 capsule) per day;
ii. Dose does not exceed 180 mg (3 capsules) per day and documentation that member is concurrently taking a strong CYP3A4 inducer (*see Appendix D*);

c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**
**Medicaid/HIM –** 6 months
**Commercial –** 12 months or duration of request, whichever is less

**D. Non-Small Cell Lung Cancer (off-label)** (must meet all)**:**
1. Diagnosis of non-small cell lung cancer (NSCLC) with an RET gene rearrangement;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed as single-agent therapy for recurrent, advanced or metastatic disease;
5. For Cabometyx or Cometriq requests, member must use cabozantinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*

**Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**
**Medicaid/HIM –** 6 months
**Commercial –** 12 months or duration of request, whichever is less

**E. Additional NCCN Recommended Uses (off-label)** (must meet all)**:**
1. Request is for Cabometyx;
2. Diagnosis of one of the following (a, b, or c):
   a. Gastrointestinal stromal tumor (GIST);
   b. Recurrent or metastatic endometrial carcinoma;
   c. Bone cancer identified as one of the following (i or ii):
      i. Ewing sarcoma;
      ii. Osteosarcoma;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. For GIST: Prescribed as single-agent subsequent therapy for unresectable, recurrent, or metastatic disease;
6. For endometrial carcinoma and bone cancer: Prescribed as single-agent second-line therapy;
7. For Cabometyx requests, member must use cabozantinib, if available, unless contraindicated or clinically significant adverse effects are experienced;

8. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*
   **Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**
**Medicaid/HIM –** 6 months
**Commercial –** 12 months or duration of request, whichever is less

**F. Other diagnoses/indications**

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

## II. Continued Therapy

**A. All Indications in Section I** (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Cabometyx or Cometriq for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. For Cabometyx or Cometriq requests, member must use cabozantinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
4. If request is for a dose increase, request meets one of the following (a, b, or c):*
   a. For Cabometyx, one of the following:
      i. Dose does not exceed 60 mg (1 tablet) per day (monotherapy);
      ii. Dose does not exceed 40 mg (1 tablet) per day (combination with Opdivo);
      iii. Dose does not exceed 80 mg (2 tablets) per day and documentation that member is concurrently taking a strong CYP3A4 inducer (*see Appendix D*);
   b. For Cometriq, one of the following:
      i. Dose does not exceed 140 mg (1 capsule) per day;
      ii. Dose does not exceed 180 mg (3 capsules) per day and documentation that member is concurrently taking a strong CYP3A4 inducer (*see Appendix D*);
   c. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**
**Medicaid/HIM –** 12 months
**Commercial –** 12 months or duration of request, whichever is less

**B. Other diagnoses/indications** (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   **Approval duration: Duration of request or 6 months (whichever is less)**; or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

## III. Diagnoses/Indications for which coverage is NOT authorized:

**A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

## IV. Appendices/General Information

*Appendix A: Abbreviation/Acronym Key*

DTC: differentiated thyroid carcinoma
FDA: Food and Drug Administration
GIST: gastrointestinal stromal tumor
HCC: hepatocellular carcinoma
MTC: medullary thyroid cancer
NCCN: National Comprehensive Cancer Network
NSCLC: non-small cell lung cancer
RCC: renal cell carcinoma

*Appendix B: Therapeutic Alternatives*

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.*

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| Nexavar® (sorafenib) | DTC, HCC: 400 mg PO BID | 800 mg/day |
| Lenvima® (lenvatinib) | DTC: 24 mg PO QD | 24 mg/day |

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

*Appendix C: Contraindications/Boxed Warnings*

- Contraindication(s): none reported
- Boxed warning(s): none reported.

*Appendix D: General Information*

- Cometriq capsules are not interchangeable with Cabometyx tablets.
- Examples of strong CYP3A4 inducers:
  - Apalutamide
  - Carbamazepine
  - Enzalutamide
  - Fosphenytoin
  - Lumacaftor
  - Lumacaftor-ivacaftor
  - Mitotane
  - Phenobarbital
  - Phenytoin
  - Primidone
  - Rifampin (rifampicin)

## V. Dosage and Administration

| Drug Name | Indication | Dosing Regimen | Maximum Dose |
|---|---|---|---|
| Cabozantinib (Cabometyx) | HCC, RCC, DTC | *HCC, RCC monotherapy*<br>Monotherapy: 60 mg PO QD<br>Strong CYP3A4 inhibitors: Reduce the daily cabozantinib dose by 20 mg<br>Strong CYP3A4 inducers: Increase the daily cabozantinib dose by 20 mg | 80 mg/day |

| Drug Name | Indication | Dosing Regimen | Maximum Dose |
|---|---|---|---|
| | | *RCC combination therapy*<br>40 mg PO QD with Opdivo (nivolumab) 240 mg IV every 2 weeks or 480 mg IV every 4 weeks<br>*DTC*<br>Adults and pediatric patients with BSA ≥ 1.2 $m^2$: 60 mg PO QD<br>Pediatric patients with BSA ≤ 1.2 $m^2$: 40 mg PO QD | |
| Cabozantinib (Cometriq) | MTC | 140 mg PO QD<br>Strong CYP3A4 inhibitors: Reduce the daily cabozantinib dose by 40 mg<br>Strong CYP3A4 inducers: Increase the daily cabozantinib dose by 40 mg | 180 mg/day |

## VI. Product Availability

| Drug Name | Availability |
|---|---|
| Cabometyx | Tablets: 20 mg, 40 mg, 60 mg |
| Cometriq | Capsules: 20 mg, 80 mg |

## VII. References

1. Cabometyx Prescribing Information. South San Francisco, CA: Exelixis, Inc.; September 2021. Available at: https://www.cabometyx.com/downloads/CABOMETYXUSPI.pdf. Accessed November 9, 2021.
2. Cometriq Prescribing Information. South San Francisco, CA: Exelixis, Inc.; October 2020. Available at http://www.cometriq.com/downloads/Cometriq_Full_Prescribing_Information.pdf. Accessed November 9, 2021.
3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at www.nccn.org. Accessed November 9, 2021.
4. National Comprehensive Cancer Network. Thyroid Carcinoma Version 3.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed November 10, 2021.
5. National Comprehensive Cancer Network. Hepatobiliary Cancers Version 5.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed November 9, 2021.

## Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

| HCPCS Codes | Description |
|---|---|
| J8999 | Prescription drug, oral, chemotherapeutic, NOS |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| 1Q18 annual review:<br>Combined Medicaid and commercial policies.<br>Removed safety requirement for hemorrhage and hemoptysis per CPAC safety guidance endorsed by medical affairs<br>For RCC, modified redirection to apply only for clear cell histology, requiring NCCN Category 1 recommended alternatives.<br>Added off-label use for RCC with non-clear cell histology and NSCLC<br>References reviewed and updated. | 11.08.17 | 02.18 |
| Cabometyx's FDA indication for advanced RCC is expanded from second- to first- or second line therapy. Redirection to other therapies and delineation by histology removed.<br>Added specialist.<br>"Progressive" removed from MTC descriptors; recent history of hemorrhage removed.<br>Restriction limiting NSCLC treatment to only Cabometyx rather than including both Cabometyx and Cometriq is removed per NCCN.<br>References reviewed and updated.<br>New policy for HIM | 01.23.18 | 02.18 |
| 1Q 2019 annual review; recurrent or unresectable added to MTC per NCCN; off-label DTC and HCC uses added; references reviewed and updated. | 11.13.18 | 02.19 |
| 1Q 2020 annual review: no significant changes; removed HIM NF disclaimer statements; updated Cabometyx FDA approved indications to include HCC and removed off-label designation; references reviewed and updated. | 10.28.19 | 02.20 |
| 1Q 2021 annual review: oral oncology generic redirection language added; for Cometriq, boxed warning removed; GIST added per NCCN; RT4: added new FDA-approved indication for combination use with nivolumab as first-line treatment for advanced RCC references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated. | 02.03.21 | 02.21 |
| Delineated maximum dose based on drug interactions per prescribing information. | 03.23.21 | |
| 1Q 2022 annual review: RT4: updated DTC indication for Cabometyx; added endometrial carcinoma and bone cancer off-label indications per NCCN; removed criteria for Nexavar failure from HCC as Nexavar is no longer the preferred 1st line systemic therapy and added criterion for Child-Pugh class A status per NCCN; added clarification that NSCLC be recurrent, advanced or metastatic per NCCN; clarified oral oncology generic redirection language to "must use"; references reviewed and updated. | 11.10.21 | 02.22 |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less | 01.20.22 | 05.22 |

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

**Note:**
**For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.