Clinical Policy: Cabozantinib (Cabometyx, Cometriq)

Reference Number: CP.PHAR.111
Effective Date: 06.01.13
Last Review Date: 02.25
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
- Adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumors (pNET)
- 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 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. For monotherapy, dose does not exceed both of the following (i and ii):
      i. 60 mg per day;
      ii. 1 tablet per day;
   b. For use in combination with Opdivo, dose does not exceed both of the following (i and ii):
      i. 40 mg per day;
      ii. 1 tablet per day;
   c. Documentation that member is concurrently taking a strong CYP3A4 inducer (*see Appendix D*) and dose does not exceed both of the following (i and ii):
      i. 80 mg per day;
      ii. 2 tablets per day;
   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 unresectable, inoperable, or metastatic HCC;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. Prescribed as subsequent-line therapy;
6. Prescribed as a single-agent therapy;
7. For Cabometyx request, member must use cabozantinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
8. Confirmation of Child-Pugh class A status;
9. Request meets one of the following (a, b, or c):*
   a. Dose does not exceed both of the following (i and ii):
      i. 60 mg per day;
      ii. 1 tablet per day;
   b. Documentation that member is concurrently taking a strong CYP3A4 inducer (*see Appendix D*) and dose does not exceed both of the following (i and ii):
      i. 80 mg per day;
      ii. 2 tablets per day;
   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. Locally advanced, unresectable, or metastatic DTC (i.e., follicular, oncocytic [formerly known as 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. Prescribed as single-agent therapy;
6. For Cabometyx or Cometriq requests, member must use cabozantinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. If DTC, both of the following are met (a and b):
   a. Failure of Lenvima® and/or sorafenib* unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required.*
   b. Disease is not amenable (e.g., iodine-refractory or ineligible) to radioactive iodine therapy;
8. Request meets one of the following (a, b, or c):*
   a. For Cabometyx, one of the following (i, ii, or iii):
      i. For weight ≥ 40 kg, dose does not exceed both (1 and 2):
         1) 60 mg per day;
         2) 1 tablet per day;
      ii. For weight < 40 kg, dose does not exceed both (1 and 2):
         1) 40 mg per day;
         2) 1 tablet per day;
      iii. Documentation that member is concurrently taking a strong CYP3A4 inducer (*see Appendix D*) and dose does not exceed both of the following (1 and 2):
         1) 80 mg per day;
         2) 2 tablets per day;
   b. For Cometriq, one of the following:
      i. Dose does not exceed both (1 and 2):
         1) 140 mg per day;
         2) 4 capsules per day;
      ii. Documentation that member is concurrently taking a strong CYP3A4 inducer (*see Appendix D*) and dose does not exceed both (1 and 2):
         1) 180 mg per day;
         2) 3 capsules per day;
   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. Neuroendocrine Tumors (must meet all)**:**
1. Request is for Cabometyx;
2. Diagnosis of one of the following (a or b):
   a. pNET;
   b. epNET (including, but not limited to, tumors from any of the following origins: gastrointestinal tract, lung/thymus, well-differentiated grade 3 disease, adrenocortical carcinoma, pheochromocytoma, paraganglioma);
3. Disease is unresectable, recurrent, locally advanced, or metastatic;
4. Prescribed by or in consultation with an oncologist;
5. Age ≥ 12 years;
6. Prescribed in one of the following ways (a or b):
   a. As a single agent;
   b. For pNET or epNET of the gastrointestinal tract: In combination with either Sandostatin® LAR or lanreotide;
7. For Cabometyx request, member must use cabozantinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
8. Request meets one of the following (a, b, c, or d):*
   a. For weight ≥ 40 kg, dose does not exceed both of the following (i and ii):
      i. 60 mg per day;
      ii. 1 tablet per day;
   b. For weight < 40 kg, dose does not exceed both of the following (i and ii):
      i. 40 mg per day;
      ii. 1 tablet per day;
   c. Documentation that member is concurrently taking a strong CYP3A4 inducer (*see Appendix D*), and dose does not exceed both of the following (i and ii):
      i. 80 mg per day;
      ii. 2 tablets per day;
   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

E. Non-Small Cell Lung Cancer (off-label) (must meet all)**:**
1. Diagnosis of non-small cell lung cancer (NSCLC) that is both of the following (a and b):
   a. Recurrent, advanced, or metastatic;
   b. Positive for RET gene rearrangement;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed as single-agent therapy;
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

F. Additional NCCN Recommended Uses (off-label) (must meet all)**:**
1. Request is for Cabometyx;
2. Diagnosis of one of the following (a, b, c, d, or e):
   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;
   d. Brain metastases;
   e. Soft tissue sarcoma (e.g. alveolar soft part sarcoma, extraskeletal myxoid chondrosarcoma);
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. For GIST: Prescribed for unresectable, recurrent, or metastatic disease as both (a and b):
   a. Single-agent therapy;
   b. Subsequent therapy;
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

G. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business:

CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: 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. For monotherapy, dose does not exceed both of the following (1 and 2):
         1) 60 mg per day;
         2) 1 tablet per day;
      ii. For use in combination with Opdivo, dose does not exceed both of the following (1 and 2):
         1) 40 mg per day;
         2) 1 tablet per day;
      iii. Documentation that member is concurrently taking a strong CYP3A4 inducer (*see Appendix D*) and dose does not exceed both (1 and 2):
         1) 80 mg per day;
         2) 2 tablets per day;
   b. For Cometriq, one of the following:
      i. Dose does not exceed both (1 and 2):
         1) 140 mg per day;
         2) 4 capsules per day;
      ii. Documentation that member is concurrently taking a strong CYP3A4 inducer (*see Appendix D*) and dose does not exceed both (1 and 2):
         1) 180 mg per day;
         2) 3 capsules per day;
   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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: 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
epNET: extra-pancreatic neuroendocrine tumors
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
pNET: pancreatic neuroendocrine tumors
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
sorafenib (Nexavar®)	DTC, HCC: 400 mg PO BID	800 mg/day
Lenvima® (lenvatinib)	DTC: 24 mg PO QD, HCC: 8-12 mg PO QD	24 mg/day
Tecentriq® (atezolizumab) + bevacizumab	HCC: Varies	Varies
tremelimumab-actl + durvalumab	HCC: Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
durvalumab	HCC: Varies	Varies
lenvatinib	HCC: Varies	Varies
sorafenib	HCC: Varies	Varies
tislelizumab-jsgr	HCC: Varies	Varies
pembrolizumab	HCC: Varies	Varies

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
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, pNET, epNET	*HCC, RCC monotherapy* • Monotherapy: 60 mg PO QD • Strong CYP3A4 inhibitors: Reduce the daily cabozantinib dose by 20 mg • Strong CYP3A4 inducers: Increase the daily cabozantinib dose by 20 mg *RCC combination therapy* 40 mg PO QD with Opdivo (nivolumab) 240 mg IV every 2 weeks or 480 mg IV every 4 weeks *DTC, pNET, epNET* • Adults and pediatric patients aged ≥ 12 years with body weight ≥ 40 kg: 60 mg PO QD • Pediatric patients ≥ 12 years with body weight < 40 kg: 40 mg PO QD	80 mg/day
Cabozantinib (Cometriq)	MTC	• 140 mg PO QD • Strong CYP3A4 inhibitors: Reduce the daily cabozantinib dose by 40 mg • 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.; March 2025. Available at: https://www.cabometyxhcp.com/sites/default/files/2021-03/prescribing-information.pdf. Accessed April 10, 2025.
2. Cometriq Prescribing Information. South San Francisco, CA: Exelixis, Inc.; August 2023. Available at: http://www.cometriq.com/downloads/Cometriq_Full_Prescribing_Information.pdf. Accessed October 18, 2024.
3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at www.nccn.org. Accessed April 10, 2025.
4. National Comprehensive Cancer Network. Thyroid Carcinoma Version 4.2024. Available at https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed November 25, 2024.
5. National Comprehensive Cancer Network. Hepatocellular Carcinoma Version 3.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hcc.pdf. Accessed November 25, 2024.
6. National Comprehensive Cancer Network. Kidney Cancer Version 2.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed November 25, 2024.
7. National Comprehensive Cancer Network. Neuroendocrine and Adrenal Tumors Version 1.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed April 21, 2025.

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
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	02.03.21	02.21

Reviews, Revisions, and Approvals	Date	P&T Approval Date
references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.		
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
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
Template changes applied to other diagnoses/indications.	09.30.22	
1Q 2023 annual review: for HCC per NCCN Compendium added requirements for subsequent therapy and as a single agent; for DTC updated criterion for failure of Lenvima AND/or sorafenib, added requirement that disease is not amenable to radioactive iodine therapy, and added that it be prescribed as single-agent therapy per NCCN; for DTC corrected maximum number of Cometriq daily capsules; references reviewed and updated.	10.24.22	02.23
1Q 2024 annual review: Per NCCN: for thyroid carcinomas, revised "Hurthle cell" to "oncocytic" per updated terminology and clarified that DTC is locally advanced, unresectable, or metastatic; for HCC clarified that disease is unresectable, inoperable, or metastatic; references reviewed and updated.	11.05.23	02.24
1Q 2025 annual review: for NCCN recommended uses criteria, added off label indications for brain metastases and soft tissue sarcoma (e.g., alveolar soft part sarcoma, extraskeletal myxoid chondrosarcoma) as supported by NCCN compendium; for HCC, added alternative 1st-line systemic therapy regimens per NCCN in Appendix B; references reviewed and updated.	10.18.24	02.25
RT4: added new neuroendocrine tumors indication and updated DTC dosing for Cabometyx.	04.16.25	

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.