PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Cabometyx Prior Authorization Policy
- Cabometyx® (cabozantinib tablets – Exelixis)

REVIEW DATE: 03/12/2025; selected revision 04/09/2025

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Cabometyx, a kinase inhibitor, is indicated for the following uses:[1]

- **Differentiated thyroid cancer**, for the treatment of locally advanced or metastatic disease that has progressed following prior vascular endothelial growth factor receptor (VEGFR)-targeted therapy in patients ≥ 12 years of age who are radioactive iodine-refractory or ineligible.
- **Hepatocellular carcinoma,** for the treatment of patients who have been previously treated with sorafenib.
- **Neuroendocrine tumors,** for the treatment of previously treated, unresectable, locally advanced or metastatic, well-differentiated **pancreatic** neuroendocrine tumors (pNET) in adults and pediatric patients ≥ 12 years of age.
- **Neuroendocrine tumors,** for the treatment of previously treated, unresectable, locally advanced or metastatic, well-differentiated **extra-**

pancreatic neuroendocrine tumors (epNET) in adult and pediatric patients ≥ 12 years of age.
- **Renal cell carcinoma**, advanced, as monotherapy or in combination with Opdivo® (nivolumab intravenous infusion) as first-line treatment.

Guidelines

Cabometyx is discussed in the National Comprehensive Cancer Network (NCCN) guidelines:[2]

- **Bone cancer:** NCCN guidelines (version 2.2025 – February 28, 2025) recommend Cabometyx as one of the "other recommended regimens" for second-line (relapsed/refractory or metastatic disease) for Ewing sarcoma and osteosarcoma (category 2A).[3]
- **Gastrointestinal stromal tumors:** NCCN guidelines (version 2.2024 – July 31, 2024) recommend Cabometyx as one of the options after progression on approved therapies as "useful in certain circumstances" (category 2A).[2,4] The approved therapies are imatinib and Ayvakit® (avapritinib tablets; for *PDGFRA* mutation) as first-line therapy; sunitinib or Sprycel® (dasatinib tablets; for *PDGFRA* exon 18 mutations that are insensitive to imatinib (including the *PDGFRA D842V* mutation) as second-line therapy; Stivarga® (regorafenib tablets) as third-line therapy; and Qinlock® (ripretinib tablets) as fourth-line therapy.[4]
- **Hepatocellular carcinoma:** NCCN guidelines (version 4.2024 – January 10, 2025) recommend Cabometyx (Child-Pugh Class A only; Category 1) as a subsequent therapy option, along with many other agents.[5]
- **Kidney cancer:** NCCN guidelines (version 3.2025 – January 9, 2025) state that the "preferred regimens" for first-line therapy in favorable risk patients with relapsed or Stage IV renal cell carcinoma (RCC) with predominant clear cell histology are: Inlyta® (axitinib tablets) + Keytruda® (pembrolizumab intravenous infusion), Cabometyx + Opdivo, Lenvima® (lenvatinib capsules) + Keytruda (all category 1). Cabometyx (category 2B) is one of the "other recommended regimens" in this setting.[6] For patients in the poor/intermediate risk grouping, the "preferred regimens" are Inlyta + Keytruda; Cabometyx + Opdivo; Yervoy (ipilimumab intravenous infusion) + Opdivo; Lenvima + Keytruda (all category 1); Cabometyx monotherapy is also recommended (category 2A). Subsequent therapy is categorized based on prior immune-oncology (IO) therapy status. There are no preferred regimens. Cabometyx is listed under "other recommended regimens" for both IO therapy naïve and with prior IO therapy; Cabometyx + Opdivo is also an option (both category 2A) under "Useful in Certain Circumstances". For patients with non-clear cell histology RCC, Cabometyx, enrollment in clinical trials Lenvima + Keytruda, Opdivo, and Opdivo + Cabometyx are noted as preferred therapies (category 2A, preferred),.
- **Neuroendocrine and adrenal tumors:** NCCN guidelines (version 1.2025 – March 27, 2025) recommend Cabometyx for neuroendocrine tumors of the gastrointestinal tract (well-differentiated grade 1/2), lung, and thymus.[14] It is a category 1 recommendation if prior treatment with everolimus or category 2A if progression on other systemic therapy. It is also a category 1 recommended therapy for pancreatic neuroendocrine tumors, if prior

treatment with everolimus, Lutathera® (lutetium Lu 177 dotatate intravenous injection), or sunitinib. Cabometyx is also recommended (category 2A) for well-differentiated Grade 3 neuroendocrine tumors. In this setting it is for the treatment of unresectable locally advanced or metastatic disease with favorable biology (e.g., relatively low Ki-67 [55%], slow growing, positive SSTR-based PET imaging) that has clinically significant tumor burden or evidence of disease progression. Cabometyx is recommended for the treatment of locoregional unresectable or metastatic adrenocortical carcinoma under "Other Recommended Regimens" (category 2A). It is also recommended for locally unresectable pheochromocytoma/paraganglioma (category 2A).

- **Non-small cell lung cancer:** NCCN guidelines (version 3.2025 – January 14, 2025) recommend Cabometyx as subsequent therapy for *RET* rearrangement positive tumors following progression on first-line therapies, Retevmo® (selpercatinib capsules and tablets) or Gavreto® (pralsetinib capsules). (category 2A).[7]
- **Uterine neoplasms:** NCCN guidelines (version 3.2025 – March 7, 2025) recommend Cabometyx as one of the "Other Recommended Regimens" for second or subsequent line of therapy for recurrent endometrial carcinoma (category 2A).[8]
- **Thyroid carcinoma**: NCCN guidelines (version 5.2024 – January 15, 2025) state that cabozantinib can be considered if patient has progression after Lenvima or sorafenib for the treatment of locally recurrent, advanced, and/or metastatic disease that is not amendable to radioactive iodine therapy. This recommendation is for follicular, oncocytic (formerly Hürthle cell), and papillary cancer subtypes (all category 1).[9] According to NCCN Compendium this refers to the Cometriq formulation of cabozantinib.[2] The prescribing information for Cabometyx has differentiated thyroid cancer as an FDA-approved use.[1]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cabometyx. All approvals are provided for the duration noted below.

- **Cabometyx® (cabozantinib tablets - Exelixis)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indications

1. **Hepatocellular Carcinoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has been previously treated with at least one systemic regimen.
   Note: Examples of a systemic regimen include one of the following drugs: Tecentriq (atezolizumab intravenous infusion), bevacizumab, Imjudo

(tremelimumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), sorafenib, Lenvima (lenvatinib capsules), or Opdivo (nivolumab intravenous infusion).

2. **Neuroendocrine Tumors**. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   A) Patient is ≥ 12 years of age; AND
   B) Patient has locally advanced, unresectable, or metastatic disease; AND
   C) Patient has well-differentiated neuroendocrine tumors; AND
   D) Patient has ONE of the following tumor types (a or b):
      a) Pancreatic neuroendocrine tumors; OR
      b) Extra-pancreatic neuroendocrine tumors; AND
      Note: Examples of tumor sites could be in the small bowel, lung, thymus, rectum, cecum, non-cecum colon, stomach, appendix.
   E) The medication will be used as subsequent therapy.

3. **Renal Cell Carcinoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has relapsed or stage IV disease.

4. **Thyroid Carcinoma, Differentiated.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   A) Patient is ≥ 12 years of age; AND
   B) Patient has differentiated thyroid carcinoma; AND
   Note: Examples of differentiated thyroid carcinoma include papillary, follicular, and oncocytic carcinoma (formerly Hürthle cell carcinoma).
   C) Patient is refractory to radioactive iodine therapy; AND
   D) Patient has tried Lenvima (lenvatinib capsules) or sorafenib.

Other Uses with Supportive Evidence

5. **Adrenal Gland Tumor.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has locoregional unresectable or metastatic adrenocortical carcinoma.

6. **Bone Cancer.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient meets ONE of the following (i or ii):
      i. Patient has Ewing sarcoma; OR
      ii. Patient has osteosarcoma; AND
   B) Patient has tried at least one previous systemic regimen.
   Note: Examples of a systemic regimen include one of the following: vincristine, doxorubicin, cyclophosphamide, topotecan, irinotecan, cisplatin, ifosfamide, Stivarga (regorafenib tablets), sorafenib.

7. **Endometrial Carcinoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried one systemic regimen.
   Note: Examples of a systemic regimen include one of the following: carboplatin, paclitaxel, trastuzumab, docetaxel, doxorubicin, cisplatin, and topotecan.

8. **Gastrointestinal Stromal Tumors.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried ALL of the following (i, ii, iii, and iv):
      i. One of imatinib or Ayvakit (avapritinib tablets); AND
      ii. One of sunitinib or Sprycel (dasatinib tablets); AND
      iii. Stivarga (regorafenib tablets); AND
      iv. Qinlock (ripretinib tablets).

9. **Non-Small Cell Lung Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has a *RET* rearrangement positive tumor; AND
   C) Patient has progressed on one of the first-line therapies, Gavreto (pralsetinib capsules) or Retevmo (selpercatinib capsules or tablets).

10. **Pheochromocytoma/Paraganglioma.** Approve for 1 year if the patient meets BOTH of the following (A and B):
    A) Patient is ≥ 18 years of age; AND
    B) Patient has locally unresectable disease.

CONDITIONS NOT COVERED

- **Cabometyx® (cabozantinib tablets - Exelixis)**

is(are) considered not medically necessary for ANY other use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Metastatic Castration-Resistant Prostate Cancer (mCRPC).** Results from the COMET-1 Phase III pivotal study with Cabometyx 60 mg tablets in men with mCRPC are published.[10] Patients included in the study had disease progression after treatment with docetaxel as well as abiraterone acetate and/or Xtandi® (enzalutamide capsules). The study failed to meet its primary endpoint of demonstrating statistically significant increase in overall survival (OS) compared with prednisone. The median OS with Cabometyx was 11.0 months vs. 9.8 months with prednisone, which was not statistically significant. Based on these results, the second Phase III study, COMET-2 has been discontinued.[11] In another small phase 1/2 study (n = 13), treatment with cabozantinib + docetaxel + prednisone

vs. docetaxel + prednisone alone improved the median time to progression and overall survival.[13] There is an ongoing Phase III, randomized, open-label study (CONTACT-02) of cabozantinib + Tecentriq (atezolizumab for intravenous injection) in various tumor types, including CRPC.[12]

REFERENCES

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3. The NCCN Bone Cancer Clinical Practice Guidelines in Oncology (version 2.2025 – February 28, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 10, 2025.
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11. Exelixis. Study of cabozantinib (XL184) versus mitoxantrone plus prednisone in men with previously treated symptomatic castration-resistant prostate cancer (COMET-2). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2025 March 11]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01522443?term=NCT01522443&rank=1.NLM identifier: NCT01522443 (terminated).
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13. Madan RA, Karzai FH, Al Harthy M, et al. Cabozantinib plus docetaxel and prednisone in metastatic castration-resistant prostate cancer. *BJU Int*. 2021;127(4):435-444.
14. The NCCN Neuroendocrine and Adrenal Tumors Clinical Practice Guidelines in Oncology (version 1.2025 – March 27, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed April 7, 2025.

HISTORY

Type of Revision	Summary of Changes	Review Date

Annual Revision	**Bone Cancer:** Clarified criteria to state patient has "tried" at least one previous systemic regimen. Added a Note with examples of systemic therapy regimens.	03/22/2023
Annual Revision	**Thyroid Carcinoma, Differentiated:** For examples of thyroid carcinoma, changed Hürthle cell carcinoma name to "oncocytic carcinoma (formerly Hürthle cell carcinoma)" based on guideline changes.	03/20/2024
Annual Revision	**Neuroendocrine Tumors:** Added new approval condition and criteria. **Non-Small Cell Lung Cancer:** Cabometyx is no longer recommended as first-line therapy for RET rearrangement positive disease. Added criterion that patient has progressed on Gavreto or Retevmo (first-line therapies).	03/12/2025
Selected Revision	**Neuroendocrine Tumors:** Moved indication from Other Uses with Supportive Evidence to FDA-Approved use. Changed age criteria to ≥ 12 years of age based on prescribing information. Removed "lung or thymus tumors and gastrointestinal tract tumors" and replaced it with "extra-pancreatic tumors" based on labeling. **Adrenal Gland Tumor:** New condition of approval and criteria were added under Other Uses with Supportive Evidence. **Pheochromocytoma/Paraganglioma:** New condition of approval and criteria were added under Other Uses with Supportive Evidence.	04/09/2025