PRIOR AUTHORIZATION POLICY

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

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

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

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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.

Automation: None.

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Coverage of Cabometyx is recommended in those who meet one of the following criteria:

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, and C):
   - **A)** Patient is ≥ 12 years of age; AND
   - **B)** Patient has locally advanced, unresectable, or metastatic disease; AND
   - **C)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has well-differentiated, neuroendocrine tumors; OR
     - **ii.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has ONE of the following tumor types (1, or 2):
         1. Pancreatic neuroendocrine tumors; OR
         2. 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.
       - **b)** 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.

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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 RECOMMENDED FOR APPROVAL
Coverage of Cabometyx is not recommended in the following situations:

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]

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2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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