PRIOR AUTHORIZATION POLICY

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

REVIEW DATE: 03/22/2023

INSTRUCTIONS FOR USE

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CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Cabometyx, a kinase inhibitor, is indicated for the following uses:[1]
- **Differentiated thyroid cancer**, for the treatment of patients ≥ 12 years of age with locally advanced or metastatic disease that has progressed following prior vascular endothelial growth factor receptor (VEGFR)-targeted therapy and who are radioactive iodine-refractory or ineligible.
- **Hepatocellular carcinoma,** for the treatment of patients who have been previously treated with sorafenib.
- **Renal cell carcinoma**, advanced, as monotherapy or in combination with Opdivo® (nivolumab intravenous infusion) as first-line treatment.

Guidelines

Cabometyx is discussed in guidelines from the National Comprehensive Cancer Network (NCCN):[2]
- **Bone cancer:** NCCN guidelines (version 2.2023 – September 28, 2022) 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 1.2023 – March 13, 2023) 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 1.2023 – March 10, 2023) 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 4.2023 – January 18, 2023) 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). For patients with non-clear cell histology RCC, sunitinib, Cabometyx, and enrollment in clinical trials are noted as preferred therapies (category 2A, preferred); Keytruda, Opdivo, Opdivo + Cabometyx, and Lenvima + everolimus are other recommended regimens (all category 2A). Many other agents are listed as "useful in certain circumstances".
- **Non-small cell lung cancer:** NCCN guidelines (version 2.2023 – February 17, 2023) recommend Cabometyx for *RET* rearrangement positive tumors (category 2A).[7]
- **Uterine neoplasms:** NCCN guidelines (version 1.2023 – December 22, 2022) 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 3.2022 – November 1, 2022) state that Cabometyx 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, Hürthle cell, and papillary cancer subtypes (all category 1).[9]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Cabometyx. All approvals are provided for 1 year in duration unless otherwise 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 the following criteria (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. **Renal Cell Carcinoma.** Approve for 1 year if the patient meets both of the following criteria (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has relapsed or stage IV disease.

3. **Thyroid Carcinoma, Differentiated.** Approve for 1 year if the patient meets 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 Hürthle cell thyroid carcinoma.
   - **C)** Patient is refractory to radioactive iodine therapy; AND
   - **D)** Patient has tried Lenvima (lenvatinib capsules) or sorafenib.

Other Uses with Supportive Evidence

4. **Bone Cancer.** Approve for 1 year if the patient meets the following criteria (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.

5. **Endometrial Carcinoma.** Approve for 1 year if the patient meets the following criteria (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.

6. **Gastrointestinal Stromal Tumors.** Approve for 1 year if the patient meets the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has tried each 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).

7. **Non-Small Cell Lung Cancer.** Approve for 1 year if the patient meets the following criteria (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has a *RET* rearrangement positive tumor.

CONDITIONS NOT COVERED

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

is(are) considered experimental, investigational or unproven 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

1. Cabometyx® tablets [prescribing information]. San Francisco, CA: Exelixis; September 2021.

2. The NCCN Drugs & Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 13, 2023. Search term: cabozantinib.
3. The NCCN Bone Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – September 28, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 17, 2023.
4. The NCCN Gastrointestinal Stromal Tumors (GISTs) Clinical Practice Guidelines in Oncology (version 1.2023 – March 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 17, 2023.
5. The NCCN Hepatocellular Carcinoma Clinical Practice Guidelines in Oncology (version 1.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 16, 2023.
6. The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – January 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 16, 2023.
7. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – February 17, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 17, 2023.
8. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 1.2023 – December 22, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 16, 2023.
9. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (version 3.2022 – November 1, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 16, 2023.
10. Smith M, De Bono J, Sternberg C, et al. Phase III study of cabozantinib in previously treated metastatic castration-resistant prostate cancer: COMET-1. *J Clin Oncol.* 2016;34:3005-3013.
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 2017 April 18]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01522443?term=NCT01522443&rank=1. NLM identifier: NCT01522443 (terminated).
12. Exelixis. Study of cabozantinib in combination with atezolizumab to subjects with locally advanced or metastatic solid tumors. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2023 March 20]. Available from: https://clinicaltrials.gov/ct2/show/NCT03170960. NLM identifier: NCT03170960.
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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Hepatocellular Carcinoma:** A requirement was added that the patient is ≥ 18 years of age. The requirement that the patient has been treated with "one tyrosine kinase inhibitor therapy" was changed to "one systemic regimen." **Renal Cell Carcinoma:** A requirement was added that the patient is ≥ 18 years of age. **Thyroid Carcinoma**: The word "differentiated" was added to the condition of approval. **Endometrial Carcinoma:** Condition was added to Other Uses with Supportive Evidence section. **Gastrointestinal Stromal Tumors:** A requirement was added that the patient is ≥ 18 years of age. An option of trial of Sprycel (dasatinib tablets) was added to trial of Sutent (sunitinib capsules). **Non-Small Cell Lung Cancer:** A requirement was added that the patient is ≥ 18 years of age.	03/02/2022
Selected Revision	**Hepatocellular Carcinoma:** The duration of approval was changed from 3 years to 1 year. **Renal Cell Carcinoma:** The duration of approval was changed from 3 years to 1 year. **Thyroid Carcinoma, Differentiated**: The duration of approval was changed from 3 years to 1 year. The requirement that the patient has tried a vascular endothelial growth factor receptor (VEGFR)-targeted therapy was revised to "patient has tried Lenvima (lenvatinib capsules) or Nexavar (sorafenib tablets)." **Bone Cancer:** The duration of approval was changed from 3 years to 1 year. **Endometrial Carcinoma:** The duration of approval was changed from 3 years to 1 year. **Gastrointestinal Stromal Tumors:** The duration of approval was changed from 3 years to 1 year. **Non-Small Cell Lung Cancer:** The duration of approval was changed from 3 years to 1 year.	06/22/2022
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