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5.21.079

Section:	Prescription Drugs	**Effective Date:**	April 1, 2025
Subsection:	Antineoplastic Agents	**Original Policy Date:**	May 13, 2016
Subject:	Cabometyx	**Page:**	1 of 6

Last Review Date: March 7, 2025

Cabometyx

Description

Cabometyx (cabozantinib)

Background
Cabometyx (cabozantinib) inhibits the tyrosine kinase activity of MET, VEGFR-1, -2, and -3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2. These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, drug resistance, and maintenance of the tumor microenvironment (1).

Regulatory Status
FDA-approved indications: Cabometyx is a kinase inhibitor indicated for the treatment of: (1)

1. Patients with advanced renal cell carcinoma (RCC)
2. Patients with advanced renal cell carcinoma, as a first-line treatment in combination with nivolumab
3. Patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib
4. Adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior VEGF-targeted therapy and who are radioactive iodine-refractory or ineligible

Off-Label Use: (2-3)

1. Non-small cell lung cancer

Cabometyx should be used with caution in patients at increased risk for thrombotic events, hemorrhagic events, gastrointestinal perforation, and fistulas. Discontinue Cabometyx in patients who develop an acute myocardial infarction or any other arterial thromboembolic complication. Cabometyx should be stopped in patients with a hypertensive crisis or severe hypertension that cannot be controlled with anti-hypertensive therapy. Withhold Cabometyx in patients who develop intolerable Grade 2 or Grade 3 palmar-plantar erythrodysesthesia (hand-foot syndrome), until improvement to Grade 1 occurs (1).

Cabometyx should be stopped at least 21 days prior to scheduled surgery, including dental surgery. Permanently discontinue Cabometyx if reversible posterior leukoencephalopathy syndrome (RPLS) occurs. Cabometyx is not recommended for use in patients with severe hepatic impairment (1).

Cabometyx can cause fetal harm when administered to a pregnant woman. Female patients of reproductive potential should be advised to use effective contraception during treatment with Cabometyx and for 4 months after the last dose (1).

The safety and effectiveness of Cabometyx in pediatric patients less than 18 years of age with RCC, HCC, and NSCLC have not been established. The safety and effectiveness of Cabometyx in pediatric patients less than 12 years of age with DTC have not been established (1).

Related policies
Augtyro, Cometriq, Fotivda

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Cabometyx may be considered **medically necessary** if the conditions indicated below are met.

Cabometyx may be considered **investigational** for all other indications.

Prior-Approval Requirements

Diagnoses

Patient must have **ONE** of the following:

1. Advanced renal cell carcinoma (RCC)
    a. 18 years of age or older
2. Hepatocellular carcinoma (HCC) previously treated with Nexavar (sorafenib)
    a. 18 years of age or older
3. Locally advanced or metastatic differentiated thyroid cancer (DTC)
    a. 12 years of age or older
    b. Disease has progressed following prior VEGF-targeted therapy
    c. Radioactive iodine-refractory or ineligible
4. Non-small cell lung cancer
    a. 18 years of age or older

AND ALL of the following:

a. **NO** recent history of severe hemorrhage
b. Prescriber agrees to discontinue if the patient has uncontrolled GI perforations or fistulas
c. Prescriber agrees to withhold the medication if intolerable palmar-plantar erythrodysesthesia (hand-foot syndrome) Grade 2 or 3 occurs, until improvement to Grade 1
d. **NO** uncontrolled severe hypertension
e. Prescriber agrees to discontinue if the patient develops reversible posterior leukoencephalopathy syndrome or nephrotic syndrome
f. Prescriber agrees to discontinue if the patient develops an acute myocardial infarction or any other venous or arterial thromboembolic complication
g. Females of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Cabometyx and for 4 months after the last dose

Prior – Approval *Renewal* Requirements

Diagnoses

Patient must have **ONE** of the following:

1. Advanced renal cell carcinoma (RCC)
    a. 18 years of age or older
2. Hepatocellular carcinoma (HCC)
    a. 18 years of age or older

3. Locally advanced or metastatic differentiated thyroid cancer (DTC)
    a. 12 years of age or older
4. Non-small cell lung cancer
    a. 18 years of age or older

AND ALL of the following:

a. **NO** disease progression or unacceptable toxicity
b. Females of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Cabometyx and for 4 months after the last dose

AND NONE of the following:

a. Severe hemorrhage
b. Unmanaged gastrointestinal perforations or fistulas
c. Palmar-plantar erythrodysesthesia (hand-foot syndrome) Grade 2 or 3
d. Uncontrolled severe hypertension
e. Reversible posterior leukoencephalopathy syndrome
f. Acute myocardial infarction or any other venous or arterial thromboembolic complication
g. Nephrotic syndrome

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity

Strength	Quantity
20 mg	90 tablets per 90 days **OR**
40 mg	90 tablets per 90 days **OR**
60 mg	90 tablets per 90 days

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary
Cabometyx (cabozantinib) is a kinase inhibitor indicated for the treatment of advanced renal cell carcinoma, hepatocellular carcinoma, differentiated thyroid cancer, and has an off-label use for non-small cell lung cancer. Cabometyx should not be used in patients with reversible posterior leukoencephalopathy syndrome (RPLS). Cabometyx should be used with caution in patients at increased risk for thrombotic events, hemorrhagic events, gastrointestinal perforation, and fistulas. Cabometyx should be stopped in patients with hypertensive crisis, severe diarrhea, or palmar-plantar erythrodysesthesia (PPE) (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Cabometyx while maintaining optimal therapeutic outcomes.

References
1. Cabometyx [package insert]. Alameda, CA: Exelixis, Inc.; September 2023.
2. NCCN Drugs & Biologics Compendium®. Cabozantinib 2025. National Comprehensive Cancer Network, Inc. Accessed on January 14, 2025.
3. NCCN Clinical Practice Guidelines in Oncology® Non-Small Cell Lung Cancer (Version 3.2025). National Comprehensive Cancer Network, Inc. January 2025. Accessed on January 14, 2025.

Policy History

Date	Action
May 2016	Addition to PA
June 2016	Annual review Addition of physician agrees to discontinue if the patient has unmanaged GI perforations or fistulas; physician agrees to discontinue if palmar-plantar erythrodysesthesia Grade 2 or 3 occurs; physician agrees to discontinue if the patient has uncontrolled hypertension
October 2016	Change of physician agrees to discontinue if palmar-plantar erythrodysesthesia Grade 2 or 3 occurs to withhold the medication until patient improves to Grade 1
December 2016	Annual review
February 2017	Addition of quantity limits
March 2017	Annual review
June 2017	Annual review
September 2017	Annual review

November 2017	Addition of severe to hemorrhage requirement and the removal of hemoptysis. Addition of hypertensive crisis or severe hypertension that cannot be controlled with anti-hypertensive therapy and the removal of uncontrolled hypertension Addition of physician agrees to discontinue if the patient develops reversible posterior leukoencephalopathy syndrome and physician agrees to discontinue if the patient develops an acute myocardial infarction or any other arterial thromboembolic complication per FEP
January 2018	Addition of Non-small cell lung cancer Removal of the requirement of patient has received prior anti-angiogenic therapy from renal cell carcinoma
March 2018	Annual review
January 2019	Addition of new indication: hepatocellular carcinoma
March 2019	Annual review and reference update. Revised requirements to no uncontrolled severe hypertension, prescriber will discontinue if patient develops nephrotic syndrome, and no venous or arterial thromboembolic complication per SME
June 2020	Annual review and reference update
March 2021	Annual editorial review and reference update
June 2021	Annual review and reference update
October 2021	Addition of indication: locally advanced or metastatic differentiated thyroid cancer (DTC). Added requirement for females of reproductive potential to be advised to use effective contraception. Also added renewal requirement of no disease progression or unacceptable toxicity
December 2021	Annual review and reference update
March 2022	Annual review and reference update
March 2023	Annual review and reference update. Changed policy number to 5.21.079
March 2024	Annual review and reference update
March 2025	Annual editorial review and reference update. Changed word “physician” to “prescriber” in requirements

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 7, 2025 and is effective on April 1, 2025.