cabozantin (Cabometyx®, Cometriq®)
EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO010

Description
Cabozantinib (Cabometyx, Cometriq) is an orally administered tyrosine kinase inhibitor of RET, MET, VEGFR1/2/3, KIT, TRKB, FLT3, and TIE2.

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit*
cabozantinib (Cabometyx®)	20 mg tablet	Advanced and metastatic renal cell carcinoma (aRCC) Progressive or metastatic Hepatocellular (Liver) carcinoma (HCC), in patients previously treated with sorafenib Advanced or metastatic differentiated thyroid carcinoma (DTC) in patients previously treated with vascular endothelial growth factor (VEGF) targeted therapy	30 tablets/30 days
	40 mg tablet		30 tablets/30 days
	60 mg tablet		30 tablets/30 days
cabozantinib (Cometriq®)	60 mg per day blister cards	Progressive or metastatic medullary thyroid carcinoma	84 capsules/28 days
	100 mg per day blister cards		56 capsules/28 days
	140 mg per day blister cards		112 capsules/28 days

**Quantity limits are based on recommended daily dose of cabozantinib for each indication; QL exceptions allowed only for dose reductions*

Initial Criteria

I. **Cabozantinib (Cabometyx)** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by, or in consultation with, an oncologist; **AND**
   B. The member has a diagnosis of one of the following:
      1. **Differentiated Thyroid carcinoma (DTC); AND**

i. Member is 12 years of age or older; **AND**
ii. Disease is locally advanced or metastatic (stage III or IV); **AND**
iii. Member has one of the following subtypes of DTC:
    a. Papillary thyroid carcinoma; **OR**
    b. Follicular thyroid carcinoma; **OR**
    c. Hürthle cell thyroid carcinoma; **AND**
iv. The disease is refractory to radioactive iodine (RAI) treatment, or the member is not eligible for radioactive iodine treatment; **AND**
v. Member has been previously treated with at least one vascular endothelial growth factor (VEGF) targeted therapy (e.g., Lenvatinib [Lenvima], sorafenib [Nexavar], etc.); **AND**
vi. Cabozantinib (Cabometyx) is prescribed as monotherapy; **OR**

2. **Renal cell carcinoma (RCC); AND**
    i. Member is 18 years of age or older; **AND**
    ii. Disease is advanced or metastatic (stage III or IV); **AND**
    iii. Cabozantinib (Cabometyx) is prescribed as monotherapy; **OR**
        a. Prescribed in combination with nivolumab (Opdivo); **OR**
3. **Hepatocellular (Liver) carcinoma (HCC); AND**
    i. Member is 18 years of age or older; **AND**
    ii. Disease is progressive or advanced stage or greater (stage III or IV); **AND**
    iii. Member has been previously treated with a guideline-recommended first-line systemic therapy (e.g., atezolizumab with bevacizumab, tremelimumab-acti with durvalumab, sorafenib, Lenvatinib, durvalumab alone, pembrolizumab); **AND**
    iv. Provider attests the member has Child-Pugh class A liver function; **AND**
    v. Cabozantinib (Cabometyx) is prescribed as monotherapy

II. **Cabozantinib (Cometriq)** may be considered medically necessary when the following criteria below are met:
A. Member is 18 years of age or older; **AND**
B. Treatment is prescribed by, or in consultation with, an oncologist; **AND**
C. Member has a diagnosis of **medullary thyroid carcinoma (MTC)**; **AND**
    1. Disease is locally recurrent progressive or metastatic (stage III or IV); **AND**
    2. Cabozantinib (Cometriq) is prescribed as monotherapy; [cabozantinib (Cabometyx) should not be used for medullary thyroid carcinoma (MTC)].

III. Cabozantinib (Cabometyx or Cometriq) is considered investigational when used for all other conditions, including but not limited to:
A. Adrenocortical carcinoma
B. Anaplastic Thyroid Cancer
C. Breast cancer
D. Cervical Cancer
E. Cholangiocarcinoma
F. Colorectal cancer

G. Head and neck cancer
H. Merkel cell carcinoma and skin cancer
I. Multiple myeloma, acute myeloid leukemia
J. Neuroendocrine Tumors
K. Neurofibromas
L. Non-small cell lung cancer
M. Pheochromocytomas and paraganglioma
N. Prostate cancer
O. Salivary gland cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this Health Plan or has been established on therapy from a previous Health Plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this Health Plan; **AND**
III. Provider attests to or provides clinical documentation of response to treatment, such as stabilization of disease or decrease in tumor size or tumor spread; **AND**
IV. A diagnosis of one the following:
    A. **Differentiated Thyroid Carcinoma (DTC)**; **AND**
        1. Cabozantinib (Cabometyx) is prescribed as monotherapy; **OR**
    B. **Renal Cell Carcinoma (RCC); AND**
        1. Cabozantinib (Cabometyx) is prescribed as monotherapy; **OR**
            ii. Cabozantinib (Cabometyx) is prescribed in combination with nivolumab (Opdivo); **OR**
    C. **Hepatocellular Carcinoma (HCC); AND**
        1. Cabozantinib (Cabometyx) is prescribed as monotherapy; **OR**
    D. **Medullary Thyroid Carcinoma (MTC)**; **AND**
            i. Cabozantinib (Cometriq) is prescribed as monotherapy

Supporting Evidence

I. Given the complexities surrounding diagnosis and treatment choices, targeted drug therapies such as multi-kinase inhibitors must be prescribed by, or in consultation with, an oncologist.
II. Cabozantinib (Cabometyx) carries three FDA approved indications and is used in the treatment of advanced renal cell carcinoma (RCC) with, or without, nivolumab (Opdivo), hepatocellular carcinoma (HCC) in patients previously treated with sorafenib, and advanced or metastatic differentiated thyroid carcinoma (DTC) patients previously treated with a vascular endothelial growth factor receptor (VEGFR) targeted therapy. Cabozantinib (Cabometyx) should only be used for these indications due to its specific formulation, dosing, and packaging differences compared to Cabozantinib (Cometriq).
III. Efficacy and safety of cabozantinib (Cometriq) and cabozantinib (Cabometyx) has not been established in patients less than 18 years of age diagnosed with medullary thyroid carcinoma (MTC), RCC, and HCC. Only cabozantinib (Cabometyx) has been approved for ages 12 years and older in DTC.

IV. Multi-kinase inhibitors are considered medically necessary when used as monotherapy. Efficacy and safety have not been studied in combination with other oncology agents with the exception of cabozantinib (Cabometyx) in combination with nivolumab (Opdivo) in the advanced RCC.

V. **Differentiated thyroid carcinoma (DTC)**

a. DTC is categorized into papillary, follicular, or Hürthle cell cancer subtypes and is unrelated to MTC due to differing pathophysiology, evaluation, and treatment strategies than MTC. Additionally, cabozantinib (Cabometyx) has not been studied for the treatment of MTC.

b. Cabozantinib (Cabometyx) is FDA approved in patients twelve years of age or older with locally advanced or metastatic DTC that are RAI-refractory or ineligible and have progressed on a prior VEGFR-targeted therapy (lenvatinib and/or sorafenib). Cabozantinib (Cabometyx) was evaluated for efficacy and safety in the treatment of DTC via a double-blind, placebo-controlled trial (COSMIC-311). Although the COSMIC-311 trial did not meet one of its co-primary endpoints of statistically significant objective response rate in the first 100 randomized patients versus placebo, the other co-primary endpoint, progression-free survival (PFS) in all patients, was met. Cabozantinib (Cabometyx) significantly reduced the risk of disease progression or death in the primary PFS analysis compared to placebo (median 11 months vs. 1.9 months [HR 0.22; 95% CI 0.15-0.31; p<0.0001]).

c. NCCN v3.2021 guidelines for thyroid carcinoma recommend lenvatinib as the first line preferred regimen in advanced or metastatic DTC. Cabozantinib (Cabometyx) received a Category 1 recommendation for patients that had progression on lenvatinib and/or sorafenib for advanced or metastatic DTC.

d. The recommended dose for cabozantinib (Cabometyx) is 60mg once daily for adults with BSA greater than, or equal to, 1.2 m^2 and 40 mg once daily in pediatric patients 12 years of age and older, with BSA less than 1.2m^2.

VI. **Renal Cell Carcinoma (RCC)**

a. The NCCN guidelines have been updated to favor the use of multi-TKI in combination with immune checkpoint inhibitors. Cabozantinib (Cabometyx) in combination with nivolumab (Opdivo) joins lenvatinib in combination with pembrolizumab (Keytruda) as a first-line (category 1) treatment for clear-cell advanced RCC.

i. Cabozantinib (Cabometyx) in combination with nivolumab (Opdivo) was studied against sunitinib in a phase 3, randomized, open-label trial (CheckMate-9ER, N=651). PFS was doubled with cabozantinib (Cabometyx) plus nivolumab than with sunitinib (median, 16.6 months vs. 8.3 months; HR 0.51; 95% CI, 0.41 to 064; P<0.0001). Additionally, overall survival (OS) was longer with cabozantinib (Cabometyx) in combination with nivolumab than with sunitinib (HR 0.60; 99% CI, 0.40 to 0.89; P = 0.001).

b. The NCCN guidelines recommend cabozantinib (Cabometyx) monotherapy as second-line (category 1) treatment in clear-cell advanced RCC and in first-line (category 2A) intermediate or poor-risk clear-cell advanced RCC.

i. Cabozantinib (Cabometyx) was evaluated for the treatment of advanced RCC against everolimus in a phase 3 RCT (METEOR study). The open-label trial enrolled 658 patients with clear-cell advanced RCC that have trialed at least one

prior anti-angiogenic therapy. Cabozantinib monotherapy showed a statistically significant improvement in progression-free survival, overall survival, and objective response rate compared to everolimus.

ii. Additionally, cabozantinib (Cabometyx) monotherapy was evaluated for first line treatment for patients with intermediate or poor risk clear-cell advanced RCC against sunitinib in a phase 2, randomized, open-label trial (CABOSUN, N=157). Cabozantinib significantly prolonged PFS compared to sunitinib (median, 8.6 months vs. 5.3 months; HR 0.48; 95% CI, 0.31 to 074; P=0.0008).

VII. **Hepatocellular Carcinoma (HCC)**

a. Cabozantinib (Cabometyx) was evaluated in Child-Pugh class A patients with advanced and progressing hepatocellular carcinoma against a placebo. All patients had been previously treated with sorafenib in this phase III trial and had received a maximum of two previous systemic therapies for advanced hepatocellular carcinoma. Overall survival was statistically significantly longer with cabozantinib compared to placebo. (10.2 months vs. 8 months [HR 0.76; CI 0.63-0.92; p=0.005]).

b. NCCN guideline for HCC was recently updated to include atezolizumab (Tecentriq) and bevacizumab (Avastin) as the preferred first-line therapy (category 1 recommendation). Sorafenib (Nexavar) and lenvatinib (Lenvima) are other recommended monotherapy options for first-line therapy (category 1) in patients with a Child-Pugh Class A score [or class A/ B7 for sorafenib], and those who are treatment naïve in the first-line setting. Incidence of hematological, respiratory, and hepatic adverse reactions is significant with atezolizumab and bevacizumab regimen and in many situations, patients discontinue the regimen due to adverse reactions and transition to multi-TKI agents without having progressed on the first-line therapy. Cabozantinib monotherapy received a NCCN Category 1 recommendation along with regorafenib as subsequent-line therapy for patients with Child-Pugh A liver function following disease progression on or after sorafenib. Additionally, lenvatinib and sorafenib are also recommended as subsequent-line agents with category 2A NCCN recommendations should there be progression on first-line therapy with atezolizumab and bevacizumab. Other than sorafenib or nivolumab, there is no data to define optimal treatment for those who progress after first-line systemic therapy; therefore, treatment with cabozantinib (Cabometyx) for progressive HCC is recommended based on the clinical benefit limited to patients who progressed on sorafenib.

VIII. **Medullary thyroid carcinoma (MTC)**

a. MTC accounts for 1-2% of thyroid cancers in the United States and is characterized as sporadic or hereditary as part of the multiple endocrine neoplasia type 2 (MEN2) syndrome with elevated calcitonin as a hallmark feature. MTC is not a type of DTC and cabozantinib (Cometriq) shall be used for MTC due to its specific formulary, dosing, and packaging differences compared to cabozantinib (Cabometyx). Systemic treatment may be warranted in advanced and metastatic MTC for high volume, symptomatic, or progressive disease.

b. Cabozantinib (Cometriq) is FDA-approved for the treatment of medullary thyroid carcinoma in adult patients with progressive, metastatic disease in the phase III EXAM trial against a placebo. Patients in the trial had either hereditary, sporadic, or metastatic

disease. Fifty nine percent of patients had a RET positive mutation while 40% had unknown RET mutation. Cabozantinib (Cometriq) demonstrated statistically significant median PFS compared to placebo (11.2 months vs. 4 months [HR: 0.28; 95% CI 0.19-0.40; p<0.001]). The follow up analysis, published in 2017, indicated that cabozantinib did not show a statistically significant difference in overall survival compared to placebo for the overall group of 330 patients; however, in an exploratory assessment of overall survival, cabozantinib showed a statistically significant difference in overall survival for the RET M918T mutation population (44.3 months vs 18.9 months [HR 0.60; CI 0.38-.094; p=0.03]). Cabozantinib and vandetanib received a category 1 preferred recommendation for advanced and metastatic medullary thyroid carcinoma in the NCCN v3.2021 guidelines, regardless of RET-mutation status. Additionally, cabozantinib (Cometriq) remains a preferred (category 1) systemic therapy for recurrent, persistent-locoregional or asymptomatic MTC, wherein genomic testing is not a recommended common practice. Selpercatinib and pralsetinib are FDA-approved in RET-mutated MTC and carry a category 2A recommendation for treatment.

Investigational or Not Medically Necessary Uses

I. Cabozantinib (Cabometyx or Cometriq) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Adrenocortical carcinoma
   B. Anaplastic Thyroid Cancer
   C. Breast cancer
   D. Cervical Cancer
   E. Cholangiocarcinoma
   F. Colorectal cancer
   G. Head and neck cancer
   H. Merkel cell carcinoma and skin cancer
   I. Multiple myeloma, acute myeloid leukemia
   J. Neuroendocrine Tumors
   K. Neurofibromas
   L. Non-small cell lung cancer
   M. Pheochromocytomas and paraganglioma
   N. Prostate cancer
   O. Salivary gland cancer

References

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy	Disease State
Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)	Thyroid Carcinoma
	Hepatocellular Carcinoma (HCC)
	Renal Cell Carcinoma (RCC)
	Soft Tissue Sarcoma (STS)
	Endometrial Carcinoma (EC)
selpercatinib (Retevmo™), pralsetinib (Gavreto™)	RET Fusion-Positive Non-Small Cell Lung Cancer
	RET-Mutant Medullary Thyroid Cancer
	RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory
vandetanib (Caprelsa®)	Locally advanced or metastatic medullary thyroid cancer
everolimus (Afinitor®, Afinitor Disperz®)	Advanced Renal cell Carcinoma
	Angiomyolipoma of the kidney, tuberous sclerosis syndrome
	Breast cancer, advanced, HR+, HER2 -, in combination with exemestane after failure with letrozole or anastrozole
	Neuroendocrine tumor, gastrointestinal, lung or pancreatic, unresectable locally advanced or metastatic
	Subependymal giant cell astrocytom
	Partial seizure, adjunct, tuberous sclerosis syndrome
	Subependymal giant cell astrocytoma
axitinib (Inlyta®)	Advance renal cell carcinoma

sunitinib (Sutent®)	Advance renal cell carcinoma
	Gastrointestinal stromal tumor
	Renal cell carcinoma, adjuvant following nephrectomy
	Neuroendocrine pancreatic tumor

Policy Implementation/Update

Action and Summary of Changes	Date
Updated hepatocellular carcinoma criteria to align with recent NCCN guidelines; Cabometyx may be used after any approved first line treatment.	05/2024
Updated policy to separate criteria for Cabometyx and Cometriq. Added criteria for Cabometyx in members 13 years of age and older in DTC. Added criteria for use of Cabometyx in combination with nivolumab in advanced RCC. Added Child-Pugh A liver function status requirement for Cabometyx in HCC given guidelines recommendations. Removed criteria requiring RET-mutation status for MTC. Removal of oncologist requirements upon renewal. Updated supporting evidence and references accordingly. Added anaplastic thyroid cancer, NETS, cervical cancer, NSCLC to E/I. Added Related Policies section.	03/2022
Transitioned criteria to policy format, added hepatocellular carcinoma indication, added age criteria and monotherapy criteria to all indications.	02/2019
Removed step therapy in RCC; Updated renewal language to assess response to therapy	01/2018
Previous Reviews	12/2012