# CABOMETYX®
## (cabozantinib) tablets

## What is CABOMETYX?[1,2]

CABOMETYX is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

CABOMETYX is the first and only TKI to demonstrate superior efficacy versus sunitinib in patients with first-line advanced RCC who were intermediate- or poor-risk per the International Metastatic Renal Cell Carcinoma Database Consortium criteria, as demonstrated in the randomized, phase 2 CABOSUN study.

CABOMETYX is the first single agent therapy to demonstrate in a large, randomized phase 3 trial (METEOR) improved overall survival, progression-free survival and objective response rate in patients with advanced kidney cancer after prior anti-angiogenic therapy. CABOMETYX is currently the most widely used oral therapy for advanced RCC after prior antiangiogenic therapy.

## Important Safety Information

The Prescribing Information for CABOMETYX includes Warnings and Precautions for hemorrhage, GI perforations and fistulas, thrombotic events, hypertension and hypertensive crisis, diarrhea, palmar-plantar erythrodysesthesia, reversible posterior leukoencephalopathy syndrome, and embryo-fetal toxicity.

Please see additional Important Safety Information below and the full Prescribing Information for CABOMETYX at https://cabometyx.com/downloads/CABOMETYXUSPI.pdf.

## How does CABOMETYX work?[1,2]

CABOMETYX belongs to a class of drugs called tyrosine kinase inhibitors (TKIs). Tyrosine kinases are protein receptors on cells that are activated by the addition of a phosphate group. This addition leads to activation of many cellular processes through signaling cascades. TKIs inhibit this phosphate addition.

- In preclinical studies, CABOMETYX affects tyrosine kinases including MET, AXL and vascular endothelial growth factor receptor (VEGFR) -1, -2 and -3.
- These receptor tyrosine kinases are involved in normal cellular function and tumor angiogenesis, invasiveness, metastasis and drug resistance.

## What is RCC?

RCC is the most common type of kidney cancer[4]

RCC accounts for 4% of all new cancer cases in the United States[5]

It is estimated that over 65,000 new cases are diagnosed and approximately 15,000 people will die from RCC in the United States annually[6]

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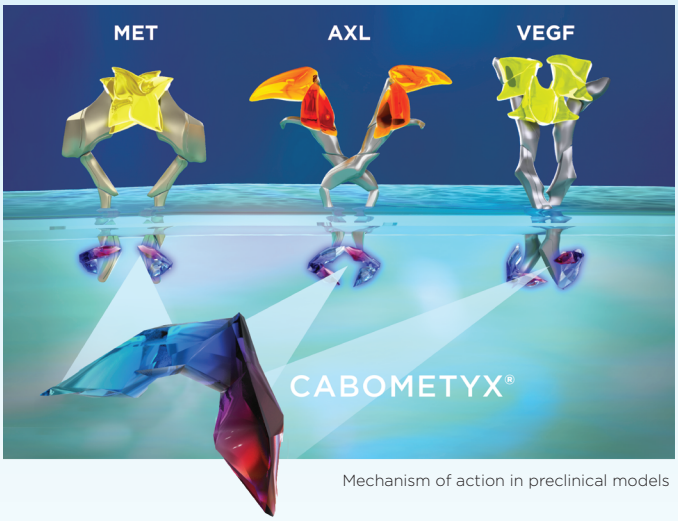


Mechanism of action in preclinical models

## What data support the use of CABOMETYX in patients with advanced RCC?[1]

The randomized phase 2 CABOSUN trial compared CABOMETYX with sunitinib, a current standard of care, in 157 patients with previously untreated advanced RCC.

- CABOSUN demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (the primary endpoint).
  - According to a retrospective blinded independent radiology review committee analysis of the data, CABOMETYX was associated with a significant 52 percent reduced risk of disease progression or death compared with sunitinib (HR 0.48, 95% CI 0.31-0.74, two-sided P=0.0008).
  - Median progression-free survival for cabozantinib was 8.6 months versus 5.3 months for sunitinib, corresponding to a 3.3 month (62 percent) improvement.
- The CABOSUN study was conducted by The Alliance for Clinical Trials in Oncology and was sponsored by the National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP) under the Cooperative Research and Development Agreement with Exelixis for the development of cabozantinib.

The phase 3 pivotal METEOR trial compared CABOMETYX with everolimus in 658 patients with advanced RCC who experienced disease progression following treatment with a VEGFR-TKI.

- The METEOR trial demonstrated a statistically significant and clinically meaningful increase in overall survival (a secondary endpoint) for patients treated with CABOMETYX compared with everolimus, a current standard of care after first-line treatment.
  - CABOMETYX was associated with a significant 34 percent reduced risk of death compared with everolimus.
  - Median overall survival was 21.4 months for patients receiving CABOMETYX versus 16.5 months for those receiving everolimus (HR=0.66, 95% CI 0.53-0.83, P=0.0003).
- CABOMETYX was associated with a progression-free survival (the primary endpoint) of 7.4 months versus 3.8 months for everolimus, corresponding to a 42 percent reduction in the rate of disease progression or death compared with everolimus (HR=0.58, 95% CI 0.45-0.74, P<0.0001).

The most commonly reported (frequency ≥25 percent) adverse reactions with CABOMETYX are diarrhea, fatigue, nausea, decreased appetite, hypertension, palmar-plantar erythrodysesthesia, weight decreased, vomiting, dysgeusia and stomatitis.

## MEDIA CONTACT

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**1.** CABOMETYX® (cabozantinib) Prescribing Information. Available at https://cabometyx.com/downloads/cabometyxuspi.pdf. **2.** Internal data on file. **3.** Arora, A. & Scholar, E.M. 2005. Role of Tyrosine Kinase Inhibitors in Cancer Therapy. Journal of Pharmacology and Experimental Therapeutics, 315 (3), 971-979. **4.** National Cancer Institute. Kidney Cancer - Patient Version. (http://www.cancer.gov/types/kidney.) Accessed January 2018. **5.** National Cancer Institute. SEER Stat Fact Sheets: Kidney and Renal Pelvis Cancer. (http://seer.cancer.gov/statfacts/html/kidrp.html). Accessed January 2018. **6.** American Cancer Society. Cancer Facts & Figures 2018. (https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf). Accessed January 2018.

# IMPORTANT SAFETY INFORMATION

## WARNINGS AND PRECAUTIONS

- **Hemorrhage:** Severe and fatal hemorrhages have occurred with CABOMETYX. In RCC trials, the incidence of Grade ≥ 3 hemorrhagic events was 3% in CABOMETYX patients. Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.
- **Gastrointestinal (GI) Perforations and Fistulas:** In RCC trials, GI perforations were reported in 1% of CABOMETYX patients. Fatal perforations occurred in patients treated with CABOMETYX. In RCC studies, fistulas were reported in 1% of CABOMETYX patients. Monitor patients for symptoms of perforations and fistulas, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a GI perforation or a fistula that cannot be appropriately managed.
- **Thrombotic Events:** Thrombotic events increased with CABOMETYX. In RCC trials, venous thromboembolism occurred in 9% (including 5% pulmonary embolism) and arterial thromboembolism occurred in 1% of CABOMETYX patients. Fatal thrombotic events occurred in the cabozantinib clinical program. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or any other arterial thromboembolic complication.
- **Hypertension and Hypertensive Crisis:** Treatment-emergent hypertension, including hypertensive crisis, increased with CABOMETYX. In RCC trials, hypertension was reported in 44% (18% Grade ≥3) of CABOMETYX patients. Monitor blood pressure prior to initiation and regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX if there is evidence of hypertensive crisis or for severe hypertension that cannot be controlled with antihypertensive therapy or medical management.
- **Diarrhea:** In RCC trials, diarrhea occurred in 74% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 diarrhea or Grade 3-4 diarrhea that cannot be managed with standard antidiarrheal treatments until improvement to Grade 1; resume CABOMETYX at a reduced dose.
- **Palmar-Plantar Erythrodysesthesia (PPE):** In RCC trials, PPE occurred in 42% of CABOMETYX patients. Grade 3 PPE occurred in 8% of CABOMETYX patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPE or Grade 3 PPE until improvement to Grade 1; resume CABOMETYX at a reduced dose.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in the cabozantinib clinical program. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.
- **Embryo-fetal Toxicity:** CABOMETYX can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during CABOMETYX treatment and for 4 months after the last dose.

## ADVERSE REACTIONS

The most commonly reported (≥25%) adverse reactions were: diarrhea, fatigue, nausea, decreased appetite, hypertension, PPE, weight decreased, vomiting, dysgeusia, and stomatitis.

## DRUG INTERACTIONS

- **Strong CYP3A4 Inhibitors:** If concomitant use with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage.
- **Strong CYP3A4 Inducers:** If concomitant use with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage.

## USE IN SPECIFIC POPULATIONS

- **Lactation:** Advise women not to breastfeed while taking CABOMETYX and for 4 months after the final dose.
- **Hepatic Impairment:** In patients with mild to moderate hepatic impairment, reduce the CABOMETYX dosage. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

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