CABOMETYX®
(cabozantinib) tablets

What is CABOMETYX?[1]

CABOMETYX is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma (RCC) and for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

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 also 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.

The results of the CELESTIAL trial establish a new role for CABOMETYX, as the first TKI with proven, significant overall survival and progression-free survival benefit in a second-line or later HCC population.

Important Safety Information

The Prescribing Information for CABOMETYX includes Warnings and Precautions for hemorrhage, perforations and fistulas, thrombotic events, hypertension and hypertensive crisis, diarrhea, palmar-plantar erythrodysesthesia, proteinuria, osteonecrosis of the jaw, wound complications, reversible posterior leukoencephalopathy syndrome, and embryo-fetal toxicity.

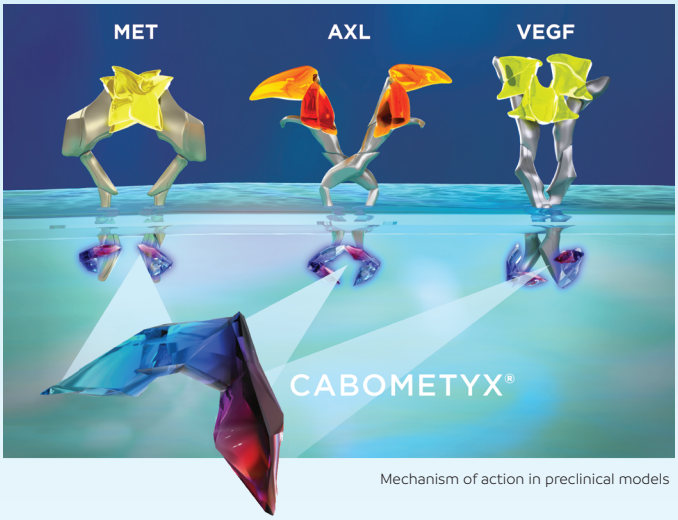
Please see additional Important Safety Information below and the full Prescribing Information for CABOMETYX at https://cabometyx.com/downloads/CABOMETYXUSPI.pdf.

How does CABOMETYX work?[1]

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.

The most commonly reported (≥25%) adverse reactions with CABOMETYX in clinical trials were: diarrhea, fatigue, decreased appetite, palmarplantar erythrodysesthesia, nausea, hypertension, and vomiting.



Mechanism of action in preclinical models

What data support the use of CABOMETYX?[1]

The randomized phase 2 CABOSUN trial comparing CABOMETYX with sunitinib, a current standard of care, in 157 patients with previously untreated advanced RCC demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) with cabozantinib versus sunitinib (the primary endpoint; HR 0.48, 95% CI 0.31-0.74, two-sided P=0.0008).

- Median PFS for cabozantinib was 8.6 months versus 5.3 months for sunitinib.
- CABOSUN was conducted by The Alliance for Clinical Trials in Oncology and sponsored by the National Cancer Institute-Cancer Therapy Evaluation Program under the Cooperative Research and Development Agreement with Exelixis for the development of cabozantinib.

The pivotal phase 3 METEOR trial comparing CABOMETYX with everolimus in 658 patients with advanced RCC who experienced disease progression following treatment with a VEGFR-TKI demonstrated a PFS (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 (HR=0.58, 95% CI 0.45-0.74, P<0.0001).

- CABOMETYX demonstrated a statistically significant and clinically meaningful increase in overall survival (a secondary endpoint; HR=0.66, 95% CI 0.53-0.83, P=0.0003).
- Median overall survival was 21.4 months for CABOMETYX versus 16.5 months for everolimus.

The pivotal phase 3 CELESTIAL trial comparing CABOMETYX with placebo in 707 patients with advanced HCC who received prior sorafenib demonstrated a statistically significant and clinically meaningful improvement in overall survival (the primary endpoint; HR 0.76, 95 percent CI 0.63-0.92; p=0.0049).

- At the planned second interim analysis, median overall survival was 10.2 months with cabozantinib versus 8.0 months with placebo.
- Median PFS (the secondary endpoint) was more than doubled, at 5.2 months with cabozantinib and 1.9 months with placebo (HR 0.44, 95 percent CI 0.36-0.52; p<0.0001).

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1. CABOMETYX® (cabozantinib) Prescribing Information. Available at https://cabometyx.com/downloads/cabometyxuspi.pdf.

IMPORTANT SAFETY INFORMATION

Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas: Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of perforations and fistulas, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a fistula that cannot be appropriately managed or a GI perforation.

Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic event requiring medical intervention.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension occurred in 36% (17% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Diarrhea: Diarrhea occurred in 63% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 44% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Proteinuria: Proteinuria occurred in 7% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

Osteonecrosis of the Jaw (ONJ): ONJ occurred in <1% of CABOMETYX patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain, or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 28 days prior to scheduled dental surgery or invasive dental procedures. Withhold CABOMETYX for development of ONJ until complete resolution.

Wound Complications: Wound complications were reported with CABOMETYX. Stop CABOMETYX at least 28 days prior to scheduled surgery. Resume CABOMETYX after surgery based on clinical judgment of adequate wound healing. Withhold CABOMETYX in patients with dehiscence or wound healing complications requiring medical intervention.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, can occur with CABOMETYX. 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 and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX and advise them to use effective contraception during treatment and for 4 months after the last dose.

ADVERSE REACTIONS

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

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

Strong CYP3A4 Inducers: If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John's wort.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

Hepatic Impairment: In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

Please see accompanying full Prescribing Information https://cabometyx.com/downloads/CABOMETYXUSPI.pdf.

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