INDICATION
CABOMETYX® (cabozantinib) is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

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.

Please see Important Safety Information on pages 10-11 and full Prescribing Information.
What’s inside

This guide provides strategies and tips on the dosing and administration of CABOMETYX, including appropriate steps to withhold, reduce, or discontinue CABOMETYX if needed. In all circumstances, dose management should be at the discretion of the treating physician. Advise patients to talk to their physician about any adverse reaction (AR) that bothers them or that does not go away. Exelixis® does not provide medical advice specific to any individual patient. For more information about CABOMETYX, please see full Prescribing Information.

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Available in 3 strengths to help you find the right dose for your patients when needed

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Recommended Starting Dose</th>
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<tbody>
<tr>
<td>First reduction</td>
<td>40 mg daily</td>
</tr>
<tr>
<td>Second reduction</td>
<td>20 mg daily</td>
</tr>
</tbody>
</table>

Pharmacokinetics
- The predicted terminal half-life is approximately 99 hours

Dose Exchange Program: Supporting your patients who require a dose modification during CABOMETYX treatment
- Patients who require a dose reduction can receive a onetime free supply to help them transition to a lower dose. Additional restrictions and eligibility rules apply.
- Contact EASE at 1-844-900-EASE (3273) or visit www.EASE.us to obtain a Dose Exchange Program Form

You may need to adjust the CABOMETYX dose based on individual patient safety and tolerability

If ARs occur, consider supportive care and/or adjust the dose

<table>
<thead>
<tr>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withhold</td>
<td>CABOMETYX</td>
</tr>
<tr>
<td>Wait</td>
<td>until improvement or resolution (return to baseline or resolution to Grade 1)</td>
</tr>
<tr>
<td>Restart</td>
<td>For patients who previously received 60 mg or 40 mg: RESTART CABOMETYX at a dose reduced by 20 mg</td>
</tr>
<tr>
<td>Resume</td>
<td>For patients who previously received 20 mg: RESUME CABOMETYX at 20 mg if tolerated; otherwise, DISCONTINUE</td>
</tr>
</tbody>
</table>

Permanently discontinue CABOMETYX for any of the following:
- Development of unmanageable fistula or GI perforation, severe hemorrhage, arterial thromboembolic event, hypertensive crisis or severe hypertension despite optimal medical management, nephrotic syndrome, or reversible posterior leukoencephalopathy syndrome.

GI=gastrointestinal.
Drug interactions

When strong CYP3A4 inhibitors cannot be avoided

REDUCE DOSE BY 20 mg

Reduce the daily dose of CABOMETYX if concomitant use with strong CYP3A4 inhibitors cannot be avoided.

Resume previous dose of CABOMETYX after discontinuing a strong CYP3A4 inhibitor for 2 to 3 days

Examples of strong CYP3A4 inhibitors

Boceprevir, clarithromycin, conivaptan, grapefruit juice,* indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, and voriconazole.

When strong CYP3A4 inducers cannot be avoided

INCREASE DOSE BY 20 mg

Increase the daily dose of CABOMETYX if concomitant use with strong CYP3A4 inducers cannot be avoided.

Resume previous dose of CABOMETYX after discontinuing a strong CYP3A4 inducer for 2 to 3 days

— The daily dose of CABOMETYX should not exceed 80 mg

Examples of strong CYP3A4 inducers

Rifampin, phenytoin, carbamazepine, phenobarbital, rifabutin, rifapentine, and St. John’s Wort.†

*The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation is used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation is used (e.g., low dose, single strength).

†The effect of St. John’s Wort varies widely and is preparation-dependent.

Specific populations

Renal impairment

Dose adjustment is not required in patients with mild to moderate renal impairment

There is no experience with CABOMETYX in patients with severe renal impairment

Hepatic impairment

Reduce the starting dose of CABOMETYX to 40 mg once daily in patients with mild or moderate hepatic impairment

CABOMETYX is not recommended for use in patients with severe hepatic impairment

Pediatrics

The safety and effectiveness of CABOMETYX in pediatric patients have not been established

Geriatrics

No dose modification required

Surgery

For patients undergoing surgery, stop treatment with CABOMETYX at least 28 days prior to scheduled surgery, including dental surgery

Lactation

Advise a lactating woman not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose

Males and females of reproductive potential

CABOMETYX can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose

Based on findings in animals, CABOMETYX may impair fertility in females and males of reproductive potential

Please see Important Safety Information on pages 10-11 and full Prescribing Information.
Recommended administration of CABOMETYX

How to take CABOMETYX

- DO NOT EAT for at least 2 hours before
- Swallow whole
- DO NOT CRUSH
- 8 oz of water
- DO NOT EAT for at least 1 hour after

- Do not substitute CABOMETYX tablets with cabozantinib capsules

Guidance for your patients if they miss a dose

IF THE NEXT SCHEDULED DOSE IS:

<table>
<thead>
<tr>
<th>in less than 12 hours</th>
<th>in 12 hours or more</th>
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<tbody>
<tr>
<td>Do not make up the missed dose</td>
<td>Take the missed dose as soon as possible</td>
</tr>
<tr>
<td>Take the next dose at the usual time</td>
<td>Take the next dose at the usual time</td>
</tr>
</tbody>
</table>

- Do not ingest foods (eg, grapefruit or grapefruit juice) or nutritional supplements that are known to inhibit cytochrome P450 during CABOMETYX treatment

- A high-fat meal increased Cmax and AUC values by 41% and 57%, respectively, relative to fasting conditions in healthy subjects administered a single 140-mg oral dose of cabozantinib capsules

For more information on drug interactions, see page 6.

Storage and handling

- Store CABOMETYX at room temperature: 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F)
- Keep CABOMETYX and all medications out of the reach of children
- CABOMETYX tablets are not scored

<table>
<thead>
<tr>
<th>Strength</th>
<th>NDC</th>
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<tbody>
<tr>
<td>60 mg, 30 tablets</td>
<td>42388-023-26</td>
</tr>
<tr>
<td>40 mg, 30 tablets</td>
<td>42388-025-26</td>
</tr>
<tr>
<td>20 mg, 30 tablets</td>
<td>42388-024-26</td>
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</tbody>
</table>
**Indication**

CABOMETYX® (cabozantinib) is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

**Important Safety Information**

**Warnings and Precautions**

**Hemorrhage:** Severe and fatal hemorrhages have occurred with CABOMETYX. In RCC trials, the incidence of Grade $\geq 3$ 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 $\geq 3$) 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.

**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.

**Adverse Reactions**

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

**Important Safety Information**

**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 findings 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.

Find the right dose for your patients when needed

- Convenient, once-daily oral dosing
- **CABOMETYX is available in 3 strengths**
  - Recommended starting dose: 60 mg daily
  - Dose after first reduction: 40 mg daily
  - Dose after second reduction: 20 mg daily
- You may need to adjust the **CABOMETYX dose** based on individual patient safety and tolerability

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**IMPORTANT SAFETY INFORMATION (cont’d)**

**WARNINGS AND PRECAUTIONS**

**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.

Please see Important Safety Information on pages 10-11 and [full Prescribing Information](#).

Visit [CABOMETYX.com](http://CABOMETYX.com) to learn more