COMETRIQ™ (cabozantinib) Capsules for Oral Use

Overview:
Cabozantinib is a kinase inhibitor. In vitro assays have shown that cabozantinib inhibits the tyrosine kinase activity of RET, MET, VEGFR-1, -2 and -3, TRKB, FLT-3, AXL, and TIE-2. These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, and maintenance of the tumor microenvironment.

FDA approval of cabozantinib in metastatic medullary thyroid cancer was based on data from the double-blind, randomized, placebo-controlled, phase III EXAM trial. The study enrolled 330 patients with metastatic medullary thyroid cancer and evidence of actively progressive disease within 14 months prior to study entry, confirmed by an Independent Radiology Review Committee (IRRC). Patients were randomized (2:1) to receive cabozantinib (n = 219) or placebo (n = 111) until disease progression as determined by the treating physician or until intolerable toxicity. The primary efficacy outcome measures of progression-free survival (PFS), objective response (OR), and response duration were based on IRRC-confirmed events using modified RECIST criteria.

Patients treated with cabozantinib demonstrated a statistically significant prolongation in PFS compared to those receiving placebo [HR 0.28 (95% CI: 0.19, 0.40); p <0.0001] with median PFS times of 11.2 months and 4.0 months in the cabozantinib and placebo arms, respectively. Partial responses were observed only among patients in the cabozantinib arm (27% vs. 0; p<0.0001). The median duration of objective responses was 14.7 months (95% CI: 11.1, 19.3) for patients treated with cabozantinib.

Indication:
Cabozantinib is a kinase inhibitor indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer.

Dosing & Administration
The recommended daily dose of cabozantinib is 140 mg (one 80-mg and three 20-mg capsules).

Cabozantinib should not be administered with food. Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib. A missed dose should not be taken within 12 hours of the next dose.

Continue treatment until disease progression or unacceptable toxicity occurs.

Withhold cabozantinib for Grade 4 hematologic adverse reactions, Grade 3 or greater non-hematologic adverse reactions or intolerable Grade 2 adverse reactions. Upon resolution/improvement of the adverse reaction reduce the dose as follows:
- If previously receiving 140 mg daily dose, resume treatment at 100 mg daily
- If previously receiving 100 mg daily dose, resume treatment at 60 mg daily
- If previously receiving 60 mg daily dose, resume at 60 mg if tolerated, otherwise, discontinue

Permanently discontinue cabozantinib for any of the following:
- Development of visceral perforation or fistula formation
- Severe hemorrhage
- Serious arterial thromboembolic event (e.g., myocardial infarction, cerebral infarction)
- Nephrotic syndrome
- Malignant hypertension, hypertensive crisis, persistent uncontrolled hypertension despite optimal medical management
- Osteonecrosis of the jaw
- Reversible posterior leukoencephalopathy syndrome

Avoid the use of concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) in patients receiving cabozantinib. For patients who require treatment with a strong CYP3A4 inhibitor, reduce the daily cabozantinib dose by 40 mg. Resume the dose that was used prior to initiating the CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor.

Avoid the chronic use of concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) if alternative therapy is available. Do not ingest foods or nutritional supplements (e.g., St. John’s Wort) that are known to induce cytochrome P450 activity. For patients who require treatment with a strong CYP3A4 inducer, increase the daily cabozantinib dose by 40 mg.
### Common Adverse Effects

The most frequently observed adverse drug reactions (≥30%) in patients receiving cabozantinib are diarrhea, stomatitis, nausea, oral pain, fatigue, decreased weight, decreased appetite, dysgeusia, palmar-plantar erythrodysesthesia syndrome, hair color changes/depigmentation, and hypertension.

See [prescribing information](#) for complete list of adverse effects.

### Warnings & Precautions

Refer to [prescribing information](#) for more detailed information on warnings & precautions.

**Perforations and Fistulas**
Gastrointestinal perforations and fistulas have been reported in patients receiving cabozantinib. Monitor patients for symptoms of perforations and fistulas and discontinue cabozantinib in patients who experience a perforation of fistula.

**Hemorrhage**
Serious and sometimes fatal hemorrhages have occurred in patients treated with cabozantinib. Do not administer cabozantinib to patients with a recent history of hemorrhage or hemoptysis.

**Thrombotic Events**
Cabozantinib treatment may result in an increased incidence of thrombotic events. Discontinue use in patients who develop an acute myocardial infarction or any other clinically significant arterial thromboembolic complication.

**Wound Complications**
Wound complications have been reported with cabozantinib. Stop treatment at least 28 days prior to scheduled surgery. Resume therapy after surgery based on clinical judgment of adequate wound healing. Withhold cabozantinib in patients with dehiscence or wound healing complications requiring medical intervention.

**Hypertension**
Cabozantinib treatment results in an increased incidence of treatment-emergent hypertension. Monitor blood pressure prior to initiation and regularly during treatment. Withhold cabozantinib for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Discontinue cabozantinib for severe hypertension that cannot be controlled with anti-hypertensive therapy.

**Osteonecrosis of the Jaw**
Osteonecrosis of the jaw has been reported in patients receiving cabozantinib. Perform an oral examination prior to initiation of cabozantinib and periodically during therapy. Advise patients regarding good oral hygiene practices. For invasive dental procedures, withhold treatment for at least 28 days prior to scheduled surgery, if possible.

**Palmar-Plantar Erythrodysesthesia Syndrome**
Palmar-plantar erythrodysesthesia syndrome (PPES) occurred in 50% of patients treated with cabozantinib and was severe (≥ Grade 3) in 13% of patients. Withhold cabozantinib in patients who develop intolerable Grade 2 PPES or Grade 3-4 PPES until improvement to Grade 1; resume at a reduced dose.

**Proteinuria**
Proteinuria has been observed in patients receiving cabozantinib. Monitor urine protein regularly during treatment. Discontinue cabozantinib in patients who develop nephrotic syndrome.

**Reversible Posterior Leukoencephalopathy Syndrome**
Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in one (<1%) patient in clinical trials. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue cabozantinib in patients who develop RPLS.

**Drug Interactions**
Avoid administration of cabozantinib with agents that are strong CYP3A4 inducers or inhibitors.
**Hepatic Impairment**
Cabozantinib is not recommended for use in patient with moderate or severe hepatic impairment.

**Embryo-Fetal Toxicity**
Cabozantinib can cause fetal harm when administered to a pregnant woman. Cabozantinib was embryolethal in rats at exposures below the recommended human dose, with increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

**How Supplied**
COMETRIQ 20 mg capsules are supplied as hard gelatin capsules with grey cap and grey body, printed with “XL184 20mg” in black ink and containing cabozantinib (S)-malate salt equivalent to 20 mg cabozantinib.

COMETRIQ 80 mg capsules are supplied as hard gelatin capsules with Swedish orange cap and Swedish orange body, printed with “XL184 80mg” in black ink and containing cabozantinib (S)-malate salt equivalent to 80 mg cabozantinib.

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<th>NDC</th>
<th>Description</th>
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<tbody>
<tr>
<td>42388-011-14</td>
<td>COMETRIQ 140 mg daily-dose carton</td>
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<tr>
<td>42388-012-14</td>
<td>COMETRIQ 100 mg daily-dose carton</td>
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<td>42388-013-14</td>
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<tr>
<td>42388-014-25</td>
<td>COMETRIQ 20 mg capsules – bottle of 60</td>
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Store capsules at 20°C to 25°C (68°F to 77°F) in a dry place and keep the container tightly closed. Excursions permitted from 15°C to 30°C (59°F to 86°F).

Cabozantinib is only available through Diplomat Specialty Pharmacy.
Phone: 1-855-253-3273

**Reimbursement and Patient Access Services**
Exelixis Access Services helps to resolve specific access and reimbursement issues for individual patients. They may be reached at:
Phone: 1-855-253-3273

**References**