EXELIXIS™

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IMPORTANT SAFETY AND PRESCRIBING INFORMATION

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Regarding COMETRIQ™ (cabozantinib) capsules

Dear Healthcare Professional:

COMETRIQ™ was approved by the U.S. Food and Drug Administration on 29 November 2012 and is indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer. This letter is to inform you of important safety and prescribing information contained in the Prescribing Information for COMETRIQ. Please review carefully.

WARNING: PERFORATIONS AND FISTULAS, and HEMORRHAGE

Perforations and Fistulas: Gastrointestinal perforations occurred in 3% and fistula formation in 1% of COMETRIQ-treated patients. Discontinue COMETRIQ for perforation or for fistula formation.

Hemorrhage: Severe, sometimes fatal, hemorrhage including hemoptysis and gastrointestinal hemorrhage occurred in 3% of COMETRIQ-treated patients. Monitor patients for signs and symptoms of bleeding. Do not administer COMETRIQ to patients with severe hemorrhage.

OTHER IMPORTANT SAFETY INFORMATION

Gastrointestinal (GI) perforations and fistulas were reported in 3% and 1% of COMETRIQ-treated patients, respectively. All were serious and 1 GI fistula was fatal (<1%). Non-GI fistulas including tracheal/esophageal were reported in 4% of COMETRIQ-treated patients. Two (1%) of these were fatal. Monitor patients for symptoms of perforations and fistulas. Discontinue COMETRIQ in patients who experience a perforation or a fistula.

Serious and sometimes fatal hemorrhage occurred with COMETRIQ. The incidence of Grade ≥3 hemorrhagic events was higher in COMETRIQ-treated patients compared with placebo (3% vs. 1%). Do not administer COMETRIQ to patients with a recent history of hemorrhage or hemoptysis.

COMETRIQ treatment results in an increased incidence of thrombotic events (venous thromboembolism: 6% vs. 3% and arterial thromboembolism: 2% vs. 0% in COMETRIQ-treated and placebo-treated patients, respectively). Discontinue COMETRIQ in patients who develop an acute myocardial infarction or any other clinically significant arterial thromboembolic complication.

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

COMETRIQ treatment results in an increased incidence of treatment-emergent hypertension with Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (modified JNC criteria) stage

1 or 2 hypertension identified in 61% in COMETRIQ-treated patients compared with 30% of placebo-treated patients in the randomized trial. Monitor blood pressure prior to initiation and regularly during COMETRIQ treatment. Withhold COMETRIQ for hypertension that is not adequately controlled with medical management; when controlled, resume COMETRIQ at a reduced dose. Discontinue COMETRIQ for severe hypertension that cannot be controlled with anti-hypertensive therapy.

Osteonecrosis of the jaw (ONJ) occurred in 1% of COMETRIQ-treated 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 initiation of COMETRIQ and periodically during COMETRIQ therapy. Advise patients regarding good oral hygiene practices. For invasive dental procedures, withhold COMETRIQ treatment for at least 28 days prior to scheduled surgery, if possible.

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

Proteinuria was observed in 4 (2%) patients receiving COMETRIQ, including 1 with nephrotic syndrome, as compared to none of the patients receiving placebo. Monitor urine protein regularly during COMETRIQ treatment. Discontinue COMETRIQ in patients who develop nephrotic syndrome.

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

Avoid administration of COMETRIQ with agents that are strong CYP3A4 inducers or inhibitors.

COMETRIQ is not recommended for use in patients with moderate or severe hepatic impairment.

COMETRIQ 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.

Adverse reactions which occurred in ≥25% of COMETRIQ-treated patients occurring more frequently in the COMETRIQ arm with a between-arm difference of ≥5% included, in order of decreasing frequency: diarrhea, stomatitis, PPES, decreased weight, decreased appetite, nausea, fatigue, oral pain, hair color changes, dysgeusia, hypertension, abdominal pain, and constipation. The most common laboratory abnormalities (>25%) were increased AST, increased ALT, lymphopenia, increased alkaline phosphatase, hypocalcemia, neutropenia, thrombocytopenia, hypophosphatemia, and hyperbilirubinemia.

The dose was reduced in 79% of patients receiving COMETRIQ compared to 9% of patients receiving placebo.

ADVERSE EVENT REPORTING

To report SUSPECTED ADVERSE REACTIONS, contact Exelixis, Inc. at 1-855-500-3935 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

The preceding warnings and precautions do not constitute a comprehensive overview of the safety risks associated with cabozantinib treatment. Please see the enclosed COMETRIQ package insert patient information for more information.

For more information, please call 1-855-292-3935 or visit www.COMETRIQ.com.

Sincerely,

Gisela Schwab, MD
Executive Vice President and Chief Medical Officer
Exelixis, Inc.