HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use COMETRIQ safely and effectively. See full prescribing information for COMETRIQ.
COMETRIQ™ (cabozantinib) capsules, for oral use
Initial U.S. Approval: 2012

WARNING: PERFORATIONS AND FISTULAS, and HEMORRHAGE

See full prescribing information for complete boxed warning.

- **Perforations and Fistulas: Gastrointestinal perforations occurred in 3% and fistula formation in 1% of COMETRIQ-treated patients. Discontinue COMETRIQ in patients with perforation or fistula. (5.1)**
- **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. (5.2)**

INDICATIONS AND USAGE

COMETRIQ is a kinase inhibitor indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC). (1)

DOSAGE AND ADMINISTRATION

- Recommended Dose: 140 mg orally, once daily. (2.1)
- Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking COMETRIQ. (2.1).

DOSAGE FORMS AND STRENGTHS

20 mg and 80 mg capsules. (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Thrombotic Events: Discontinue COMETRIQ for myocardial infarction, cerebral infarction, or other serious arterial thromboembolic events. (5.3)
- Wound Complications: Withhold COMETRIQ for dehiscence or complications requiring medical intervention. (5.4)
- Hypertension: Monitor blood pressure regularly. Discontinue COMETRIQ for hypertensive crisis. (5.5)
- Osteonecrosis of the jaw: Discontinue COMETRIQ. (5.6)
- Palmar-plantar Erythrodysesthesia syndrome (PPES): Interrupt COMETRIQ, decrease dose. (5.7)
- Proteinuria: Monitor urine protein. Discontinue for nephrotic syndrome. (5.8)
- Reversible posterior leukoencephalopathy syndrome (RPLS): Discontinue COMETRIQ. (5.9)
- Embryofetal toxicity: Can cause fetal harm. Advise women of potential risk to a fetus. (5.11, 8.1)

ADVERSE REACTIONS

The most commonly reported adverse drug reactions (≥25%) are diarrhea, stomatitis, palmar-plantar erythrodysesthesia syndrome (PPES), decreased weight, decreased appetite, nausea, fatigue, oral pain, hair color changes, dysgeusia, hypertension, abdominal pain, and constipation. The most common laboratory abnormalities (≥25%) are increased AST, increased ALT, lymphopenia, increased alkaline phosphatase, hypocalcemia, neutropenia, thrombocytopenia, hypophosphatemia, and hyperbilirubinemia. (6.1)

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*.

DRUG INTERACTIONS

Cabozantinib is a CYP3A4 substrate (5.10, 7.1, 7.2). Co-administration of strong CYP3A4 inhibitors can increase cabozantinib exposure (2.1, 5.10, 7.1). Chronic co-administration of strong CYP3A4 inducers can reduce cabozantinib exposure. (2.1, 5.10, 7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 11/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the Full Prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

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 [See *Warnings and Precautions* (5.1)].

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 [See *Warnings and Precautions* (5.2)].

1 INDICATIONS AND USAGE

COMETRIQ is indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC).

2 DOSAGE AND ADMINISTRATION

1.1. Recommended Dose

The recommended daily dose of COMETRIQ is 140 mg (one 80-mg and three 20-mg capsules). Do not administer COMETRIQ with food. Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking COMETRIQ. Continue treatment until disease progression or unacceptable toxicity occurs.

Swallow COMETRIQ capsules whole. Do not open COMETRIQ capsules.

Do not take a missed dose within 12 hours of the next dose.

Do not ingest foods (e.g., grapefruit, grapefruit juice) or nutritional supplements that are known to inhibit cytochrome P450 during COMETRIQ.

2.2 Dosage Adjustments

For Adverse Reactions

Withhold COMETRIQ for NCI CTCAE 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 (i.e., return to baseline or resolution to Grade 1), reduce the dose as follows:

- If previously receiving 140 mg daily dose, resume treatment at 100 mg daily (one 80-mg and one 20-mg capsule)

- If previously receiving 100 mg daily dose, resume treatment at 60 mg daily (three 20-mg capsules)
- If previously receiving 60 mg daily dose, resume at 60 mg if tolerated, otherwise, discontinue COMETRIQ

Permanently discontinue COMETRIQ 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

In Patients with Hepatic Impairment

COMETRIQ is not recommended for use in patients with moderate and severe hepatic impairment [*see Warnings and Precautions (5.11) and Use in Specific Populations (8.6)*].

In Patients Taking CYP3A4 Inhibitors

Avoid the use of concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) in patients receiving COMETRIQ *[see Warnings and Precautions (5.10) and Drug Interactions (7.1)]*.

For patients who require treatment with a strong CYP3A4 inhibitor, reduce the daily COMETRIQ dose by 40 mg (for example, from 140 mg to 100 mg daily or from 100 mg to 60 mg daily). Resume the dose that was used prior to initiating the CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor.

In Patients Taking Strong CYP3A4 Inducers

Avoid the chronic use of concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) if alternative therapy is available *[see Warnings and Precautions (5.10) and Drug Interactions (7.2)]*.

Do not ingest foods or nutritional supplements (e.g., St. John's Wort (Hypericum perforatum)) that are known to induce cytochrome P450 activity.

For patients who require treatment with a strong CYP3A4 inducer, increase the daily COMETRIQ dose by 40 mg (for example, from 140 mg to 180 mg daily or from 100 mg to 140

mg daily) as tolerated. Resume the dose that was used prior to initiating the CYP3A4 inducer 2 to 3 days after discontinuation of the strong inducer. The daily dose of COMETRIQ should not exceed 180 mg.

3 DOSAGE FORMS AND STRENGTHS

COMETRIQ 20-mg gelatin capsules are grey with "XL184 20mg" printed in black on the body of the capsule.

COMETRIQ 80-mg gelatin capsules are Swedish orange with "XL184 80mg" printed in black on the body of the capsule.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Perforations and Fistulas

Gastrointestinal (GI) perforations and fistulas were reported in 3% and 1% of COMETRIQ-treated patients, respectively. All were serious and one 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.

5.2 Hemorrhage

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.

5.3 Thrombotic Events

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.

5.4 Wound Complications

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.

5.5 Hypertension

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.

5.6 Osteonecrosis of the Jaw

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.

5.7 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 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.

5.8 Proteinuria

Proteinuria was observed in 4 (2%) of patients receiving COMETRIQ, including one 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.

5.9 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. 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.

DOCKET ALARM

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