

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 ($\geq 25\%$) 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 ($\geq 25\%$) 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*

WARNING: PERFORATIONS AND FISTULAS and HEMORRHAGE

1	INDICATIONS AND USAGE
2	DOSAGE AND ADMINISTRATION
2.1	Recommended Dose
2.2	Dosage Adjustments
3	DOSAGE FORMS AND STRENGTHS
4	CONTRAINDICATIONS
5	WARNINGS AND PRECAUTIONS
5.1	Perforations and Fistulas
5.2	Hemorrhage
5.3	Thrombotic Events
5.4	Wound Complications
5.5	Hypertension
5.6	Osteonecrosis of the Jaw
5.7	Palmar-Plantar Erythrodysesthesia Syndrome
5.8	Proteinuria
5.9	Reversible Posterior Leukoencephalopathy Syndrome
5.10	Drug Interactions
5.11	Hepatic Impairment
5.12	Embryo-fetal Toxicity
6	ADVERSE REACTIONS
6.1	Clinical Trial Experience

7	DRUG INTERACTIONS
7.1	Effect of CYP3A4 Inhibitors
7.2	Effect of CYP3A4 Inducers
8	USE IN SPECIFIC POPULATIONS
8.1	Pregnancy
8.2	Nursing Mothers
8.3	Pediatric Use
8.4	Geriatric Use
8.5	Females and Males of Reproductive Potential
8.6	Hepatic Impairment
8.7	Renal Impairment
10	OVERDOSAGE
11	DESCRIPTION
12	CLINICAL PHARMACOLOGY
12.1	Mechanism of Action
12.3	Pharmacokinetics
12.6	Cardiac Electrophysiology
13	NONCLINICAL TOXICOLOGY
13.1	Carcinogenesis, Mutagenesis, Impairment of Fertility
14	CLINICAL STUDIES
16	HOW SUPPLIED/STORAGE AND HANDLING
17	PATIENT COUNSELING INFORMATION

*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 (\geq 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.

5.10 Drug Interactions

Avoid administration of COMETRIQ with agents that are strong CYP3A4 inducers or inhibitors [*see [Dosage and Administration \(2.1\)](#) and [Drug Interactions \(7.1, 7.2\)](#)*].

5.11 Hepatic Impairment

COMETRIQ is not recommended for use in patients with moderate or severe hepatic impairment [*see [Use in Specific Populations \(8.6\)](#)*].

5.12 Embryo-fetal Toxicity

COMETRIQ can cause fetal harm when administered to a pregnant woman. Cabozantinib was embryo-lethal 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 [*See [Use in Specific Populations \(8.1\)](#)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the label:

- Perforations and Fistula [*see [Boxed Warning, Warnings and Precautions \(5.1\)](#)*]
- Hemorrhage [*see [Boxed Warning, Warnings and Precautions \(5.2\)](#)*]
- Thromboembolic Events [*see [Warnings and Precautions \(5.3\)](#)*]
- Wound Complications [*see [Warnings and Precautions \(5.4\)](#)*]
- Hypertension [*see [Warnings and Precautions \(5.5\)](#)*]
- Osteonecrosis of the Jaw [*see [Warnings and Precautions \(5.6\)](#)*]
- Palmar-plantar erythrodysesthesia syndrome [*see [Warnings and Precautions \(5.7\)](#)*]
- Proteinuria [*see [Warnings and Precautions \(5.8\)](#)*]
- Reversible Posterior Leukoencephalopathy Syndrome [*see [Warnings and Precautions \(5.9\)](#)*]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of COMETRIQ was evaluated in 330 patients with progressive metastatic medullary thyroid cancer randomized to receive 140 mg COMETRIQ (n = 214) or placebo (n = 109) administered daily until disease progression or intolerable toxicity in a randomized, double-blind, controlled trial. [*See [Clinical Studies \(14\)](#)*]. The data described below reflect a median exposure to COMETRIQ for 204 days. The population exposed to COMETRIQ was 70% male, 90% white, and had a median age of 55 years.

Adverse reactions which occurred in $\geq 25\%$ of COMETRIQ-treated patients occurring more frequently in the COMETRIQ arm with a between-arm difference of $\geq 5\%$ included, in order of decreasing frequency: 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 ($>25\%$) were increased AST, increased ALT, lymphopenia, increased ALP, hypocalcemia, neutropenia, thrombocytopenia, hypophosphatemia, and hyperbilirubinemia. Grade 3-4 adverse reactions and laboratory abnormalities which occurred in $\geq 5\%$ of COMETRIQ-treated patients occurring more frequently in the COMETRIQ arm with a between-arm difference of $\geq 2\%$ included, in order of decreasing frequency; diarrhea, PPES, lymphopenia, hypocalcemia, fatigue, hypertension, asthenia, increased ALT, decreased weight, stomatitis, and decreased appetite (see Table 1, Table 2).

Fatal adverse reactions occurred in 6% of patients receiving COMETRIQ and resulted from hemorrhage, pneumonia, septicemia, fistulas, cardiac arrest, respiratory failure, and unspecified death. Fatal adverse reactions occurred in 5% of patients receiving placebo and resulted from septicemia, pneumonia, and general deterioration.

The dose was reduced in 79% of patients receiving COMETRIQ compared to 9% of patients receiving placebo. The median number of dosing delays was one in patients receiving COMETRIQ compared to none in patients receiving placebo. Adverse reactions led to study treatment discontinuation in 16% of patients receiving COMETRIQ and in 8% of patients receiving placebo. The most frequent adverse reactions leading to permanent discontinuation in patients treated with COMETRIQ were: hypocalcemia, increased lipase, PPES, diarrhea, fatigue, hypertension, nausea, pancreatitis, tracheal fistula formation and vomiting.

Increased levels of thyroid stimulating hormone (TSH) were observed in 57% of patients receiving COMETRIQ after the first dose compared to 19% of patients receiving placebo (regardless of baseline value). Ninety-two percent (92%) of patients on the COMETRIQ arm had a prior thyroidectomy, and 89% were taking thyroid hormone replacement prior to the first dose.

Table 1				
Per-Patient Incidence of Selected Adverse Reactions in Protocol XL184-301				
Occurring at a Higher Incidence in COMETRIQ-Treated Patients				
[Between Arm Difference of $\geq 5\%$ (All Grades)¹ or $\geq 2\%$ (Grades 3-4)]				
MedDRA System Organ Class/ Preferred Terms	Cabozantinib (n=214)		Placebo (n=109)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
GASTROINTESTINAL DISORDERS				
Diarrhea	63	16	33	2
Stomatitis ²	51	5	6	0
Nausea	43	1	21	0
Oral pain ³	36	2	6	0
Constipation	27	0	6	0
Abdominal pain ⁴	27	3	13	1
Vomiting	24	2	2	1
Dysphagia	13	4	6	1
Dyspepsia	11	0	0	0
Hemorrhoids	9	0	3	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Fatigue	41	9	28	3
Asthenia	21	6	15	1
INVESTIGATIONS				
Decreased weight	48	5	10	0
METABOLISM AND NUTRITION DISORDERS				
Decreased appetite	46	5	16	1
Dehydration	7	2	2	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Arthralgia	14	1	7	0
Muscle spasms	12	0	5	0
Musculoskeletal chest pain	9	1	4	0
NERVOUS SYSTEM DISORDERS				
Dysgeusia	34	0	6	0
Headache	18	0	8	0
Dizziness	14	0	7	0
Paresthesia	7	0	2	0
Peripheral sensory neuropathy	7	0	0	0
Peripheral neuropathy	5	0	0	0
PSYCHIATRIC DISORDERS				
Anxiety	9	0	2	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Dysphonia	20	0	9	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
PPES ⁵	50	13	2	0
Hair color changes/ depigmentation, graying	34	0	1	0

Table 1				
Per-Patient Incidence of Selected Adverse Reactions in Protocol XL184-301				
Occurring at a Higher Incidence in COMETRIQ-Treated Patients				
[Between Arm Difference of $\geq 5\%$ (All Grades)¹ or $\geq 2\%$ (Grades 3-4)]				
MedDRA System Organ Class/ Preferred Terms	Cabozantinib (n=214)		Placebo (n=109)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Rash	19	1	10	0
Dry skin	19	0	3	0
Alopecia	16	0	2	0
Erythema	11	1	2	0
Hyperkeratosis	7	0	0	0
VASCULAR DISORDERS				
Hypertension	33	8	4	0
Hypotension	7	1	0	0
¹ National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 ² Includes the following terms: stomatitis, aphthous stomatitis, mouth ulceration, mucosal inflammation ³ Includes the following terms: oral pain, oropharyngeal pain, glossitis, burning mouth syndrome, glossodynia ⁴ Includes the following terms: abdominal pain, abdominal pain lower, abdominal pain upper, abdominal rigidity, abdominal tenderness, esophageal pain ⁵ Palmar-plantar erythrodysesthesia syndrome				

Table 2				
Percent-Patient Incidence of Laboratory Abnormalities Occurring at a Higher Incidence in COMETRIQ-Treated Patients in Protocol XL184-301				
[Between Arm Difference of \geq 5% (All Grades) or \geq 2% (Grades 3-4)]				
Adverse Event	COMETRIQ (n=214)		Placebo (n=109)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Chemistries				
Increased AST	86	3	35	2
Increased ALT	86	6	41	2
Increased ALP	52	3	35	3
Hypocalcemia	52	12	27	3
Hypophosphatemia	28	3	10	1
Hyperbilirubinemia	25	2	14	5
Hypomagnesemia	19	1	4	0
Hypokalemia	18	4	9	3
Hyponatremia	10	2	5	0
Hematologic				
Lymphopenia	53	16	51	11
Neutropenia	35	3	15	2
Thrombocytopenia	35	0	4	3
ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase				

Nearly all COMETRIQ-treated patients (96% vs. 84% placebo) experienced elevated blood pressure and there was a doubling in the incidence of overt hypertension in COMETRIQ-treated patients over placebo-treated patients (61% vs. 30%) according to modified Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) staging criteria. No patients developed malignant hypertension.

Hypertension, JNC ¹ Stage	COMETRIQ N = 211 ³ (%)	Placebo N = 107 ³ (%)
Normal: Grade 0: Systolic < 120 mmHg and Diastolic < 80 mmHg	4	15
Pre-hypertension: Systolic ≥ 120 mmHg or Diastolic ≥ 80 mmHg	34	54
Stage 1: Systolic ≥ 140 mmHg or Diastolic ≥ 90 mmHg	46	25
Stage 2: Systolic ≥ 160 mmHg or Diastolic ≥ 100 mmHg	15	5
Malignant: Diastolic ≥ 120 mmHg	0	0

¹Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, JAMA 2003; 289:2560. Criteria applied were modified, as multiple readings were not available per timepoint, and therefore not averaged.
²Subjects classified by highest category based on all recorded blood pressure readings beginning after the first dose through 30 days after last dose.
³Subjects with at least two blood pressure measurements after the first dose

7 DRUG INTERACTIONS

7.1 Effect of CYP3A4 Inhibitors

Administration of a strong CYP3A4 inhibitor, ketoconazole (400 mg daily for 27 days) to healthy subjects increased single-dose plasma cabozantinib exposure (AUC_{0-inf}) by 38%. Avoid taking a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) when taking COMETRIQ [see [Dosage and Administration \(2.1\)](#) and [Warnings and Precautions \(5.10\)](#)].

7.2 Effect of CYP3A4 Inducers

Administration of a strong CYP3A4 inducer, rifampin (600 mg daily for 31 days) to healthy subjects decreased single-dose plasma cabozantinib exposure (AUC_{0-inf}) by 77%. Avoid chronic co-administration of strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, St. John's Wort) with COMETRIQ [see [Dosage and Administration \(2.1\)](#) and [Warnings and Precautions \(5.10\)](#)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Risk Summary

Based on its mechanism of action, 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.

Animal Data

In an embryo-fetal development study in which pregnant rats were administered daily doses of cabozantinib during organogenesis, increased loss of pregnancy compared to controls was observed at doses as low as 0.03 mg/kg (less than 1% of the human exposure by AUC at the recommended dose). Findings included delayed ossifications and skeletal variations at doses equal to or greater than 0.01 mg/kg/day (approximately 0.03% of the human exposure by AUC at the recommended dose).

In pregnant rabbits administered cabozantinib daily during organogenesis there were findings of visceral malformations and variations including reduced spleen size and missing lung lobe at 3 mg/kg (approximately 11% of the human exposure by AUC at the recommended dose).

8.2 Nursing Mothers

It is unknown whether cabozantinib or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from COMETRIQ, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.3 Pediatric Use

The safety and effectiveness of COMETRIQ in pediatric patients have not been studied.

8.4 Geriatric Use

Clinical studies of COMETRIQ did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients

8.5 Females and Males of Reproductive Potential

Contraception

Use effective contraception during treatment with COMETRIQ and up to 4 months after completion of therapy.

Infertility

There are no data on the effect of COMETRIQ on human fertility. Cabozantinib impaired male and female fertility in animal studies [see [Nonclinical Toxicology \(13.1\)](#)].

8.6 Hepatic Impairment

Cabozantinib pharmacokinetics has not been studied in patients with hepatic impairment. There are limited data in patients with liver impairment (serum bilirubin greater than 1.5 times the upper limit of normal). COMETRIQ is not recommended for use in patients with moderate or

severe hepatic impairment, as safety and efficacy have not been established [see [Dosage and Administration \(2.1\)](#) and [Warnings and Precautions \(5.11\)](#)].

8.7 Renal Impairment

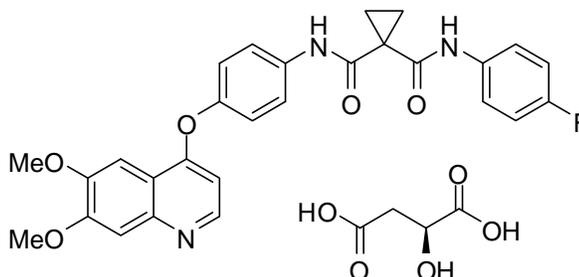
No dose adjustment is recommended for patients with mild or moderate renal impairment. There is no experience with COMETRIQ in patients with severe renal impairment.

10 OVERDOSAGE

One case of overdose was reported in a patient who inadvertently took twice the intended dose (200 mg daily) for nine days. The patient suffered Grade 3 memory impairment, Grade 3 mental status changes, Grade 3 cognitive disturbance, Grade 2 weight loss, and Grade 1 increase in BUN. The extent of recovery was not documented.

11 DESCRIPTION

COMETRIQ is the (*S*)-malate salt of cabozantinib. Cabozantinib (*S*)-malate is described chemically as *N*-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (*2S*)-hydroxybutanedioate. The molecular formula is $C_{28}H_{24}FN_3O_5 \cdot C_4H_6O_5$ and the molecular weight is 635.6 Daltons as malate salt. The chemical structure of cabozantinib (*S*)-malate salt is:



Cabozantinib (*S*)-malate salt is a white to off-white solid that is practically insoluble in aqueous media.

COMETRIQ (cabozantinib) capsules are supplied as printed hard gelatin capsules containing cabozantinib (*S*)-malate equivalent to 20 mg or 80 mg cabozantinib and the following inactive ingredients: silicified microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, fumed silica, and stearic acid.

The grey gelatin capsule shells contain black iron oxide and titanium dioxide and the Swedish orange gelatin capsule shells contain red iron oxide, and titanium dioxide. The printing ink contains shellac glaze, black iron oxide, *N*-butyl alcohol, isopropyl alcohol, propylene glycol, and ammonium hydroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

In vitro biochemical and/or cellular assays have shown that cabozantinib inhibits the tyrosine kinase activity of RET, MET, VEGFR-1, -2 and -3, KIT, 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.

12.3 Pharmacokinetics

A population pharmacokinetic analysis of cabozantinib was performed using data collected from 289 patients with solid tumors including MTC following oral administration of 140 mg daily doses. The predicted effective half-life is approximately 55 hours, the oral volume of distribution (V/F) is approximately 349 L, and the clearance (CL/F) at steady-state is estimated to be 4.4 L/hr.

Absorption and Distribution

Following oral administration of COMETRIQ, median time to peak cabozantinib plasma concentrations (T_{max}) ranged from 2 to 5 hours post-dose. Repeat daily dosing of COMETRIQ at 140 mg for 19 days resulted in 4- to 5-fold mean cabozantinib accumulation (based on AUC) compared to a single dose administration; steady state was achieved by Day 15. Cabozantinib is highly protein bound in human plasma ($\geq 99.7\%$).

A high-fat meal increased C_{max} and AUC values by 41% and 57%, respectively relative to fasted conditions in healthy subjects administered a single 140 mg oral COMETRIQ dose.

Metabolism and Elimination

Cabozantinib is a substrate of CYP3A4 *in vitro*. Inhibition of CYP3A4 reduced the formation of the XL184 *N*-oxide metabolite by $>80\%$. Inhibition of CYP2C9 had a minimal effect on cabozantinib metabolite formation (i.e., a $<20\%$ reduction). Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation.

Within a 48-day collection period after a single dose of ^{14}C -cabozantinib in healthy subjects, approximately 81% of the total administered radioactivity was recovered with 54% in feces and 27% in urine.

Specific Populations

Renal Impairment: No formal pharmacokinetic study of cabozantinib has been conducted in patients with renal impairment. The results of a population pharmacokinetic analysis suggested that mild to moderate renal impairment (creatinine clearance value ≥ 30 mL/min) does not have a clinically relevant effect on the clearance of cabozantinib.

Hepatic Impairment: The pharmacokinetics of cabozantinib has not been studied in patients with hepatic impairment [see [Dosage and Administration \(2.1\)](#), [Warnings and Precautions \(5.11\)](#) and [Use in Specific Populations \(8.6\)](#)].

Pediatric Population: The pharmacokinetics of cabozantinib has not been studied in the pediatric population [see [Use in Specific Populations \(8.3\)](#)].

Effects of Age, Gender and Race: A population PK analysis did not identify clinically relevant differences in clearance of cabozantinib between females and males or between Whites (89%) and non-Whites (11%). Cabozantinib pharmacokinetics was not affected by age (20-86 years).

Drug Interactions

CYP Enzyme Inhibition and Induction: Cabozantinib is a noncompetitive inhibitor of CYP2C8 ($K_{i,app} = 4.6$ μ M), a mixed-type inhibitor of both CYP2C9 ($K_{i,app} = 10.4$ μ M) and CYP2C19 ($K_{i,app} = 28.8$ μ M), and a weak competitive inhibitor of CYP3A4 (estimated $K_{i,app} = 282$ μ M) in human liver microsomal (HLM) preparations. IC_{50} values >20 μ M were observed for CYP1A2, CYP2D6, and CYP3A4 isozymes in both recombinant and HLM assay systems.

Cabozantinib is an inducer of CYP1A1 mRNA in human hepatocyte incubations (i.e., 75-100% of CYP1A1 positive control β -naphthoflavone induction), but not of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 mRNA or isozyme-associated enzyme activities.

Cabozantinib at steady-state plasma concentrations (≥ 100 mg/day daily for a minimum of 21 days) showed no effect on single-dose rosiglitazone (a CYP2C8 substrate) plasma exposure (C_{max} and AUC) in patients with solid tumors.

P-glycoprotein Inhibition: Cabozantinib is an inhibitor ($IC_{50} = 7.0$ μ M), but not a substrate, of P-gp transport activities in a bi-directional assay system using MDCK-MDR1 cells. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp.

12.6 Cardiac Electrophysiology

The effect of orally administered COMETRIQ 140 mg on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled study in patients with MTC. A mean increase in QTcF of 10 - 15 ms was observed at 4 weeks after initiating COMETRIQ. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No COMETRIQ-treated patients had a QTcF > 500 ms [see [Clinical Studies \(14\)](#)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies examining the carcinogenic potential of cabozantinib have not been conducted.

Cabozantinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay and was not clastogenic in both the *in vitro* cytogenetic assay using human lymphocytes or in the *in vivo* mouse micronucleus assay.

Based on nonclinical findings, male and female fertility may be impaired by treatment with COMETRIQ. In a fertility study in which cabozantinib was administered to male and female rats at doses of 1, 2.5, and 5 mg/kg/day, male fertility was significantly compromised at doses equal to or greater than 2.5 mg/kg/day (approximately equal to the human exposure by AUC at the recommended dose), with a decrease in sperm counts and reproductive organ weights. In females, fertility was significantly reduced at doses equal to or greater than 1 mg/kg/day (approximately 50% of the human exposure by AUC at the recommended dose) with a significant decrease in the number of live embryos and a significant increase in pre- and post-implantation losses.

Observations of effects on reproductive tract tissues in general toxicology studies were supportive of effects noted in the dedicated fertility study and included hypospermia and absence of corpora lutea in male and female dogs in a 6-month repeat dose study at exposures equal to 6% and 3%, respectively, the human exposure by AUC at the recommended dose. In addition, female rats administered 5 mg/kg/day for 14 days (approximately equal to the human exposure by AUC at the recommended dose) exhibited ovarian necrosis.

14 CLINICAL STUDIES

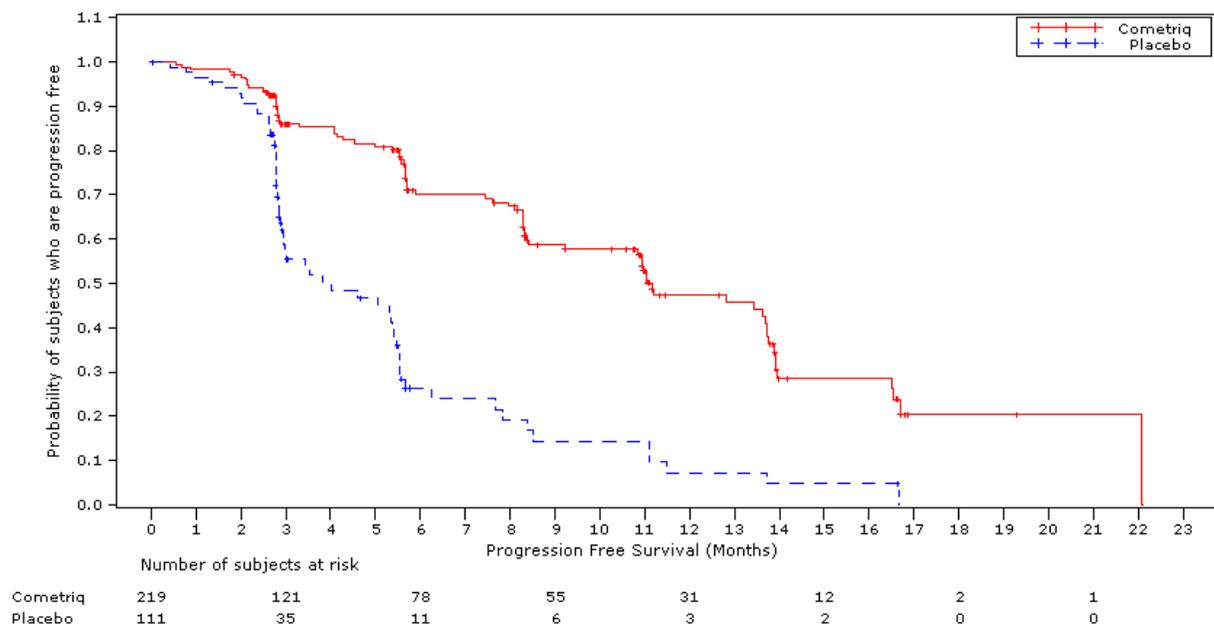
The safety and efficacy of COMETRIQ was assessed in an international, multi-center, randomized, double-blind, controlled trial (Study 1) of 330 patients with metastatic medullary thyroid carcinoma (MTC). Patients were required to have evidence of actively progressive disease within 14 months prior to study entry confirmed by an Independent Radiology Review Committee (IRRC) masked to treatment assignment (89%) or the treating physician (11%). Patients were randomized (2:1) to receive COMETRIQ 140 mg (n = 219) or placebo (n = 111) orally once daily, without food, until disease progression determined by the treating physician or until intolerable toxicity. Randomization was stratified by age (≤ 65 years vs. > 65 years) and prior use of a tyrosine kinase inhibitor (TKI) (yes vs. no). No cross-over was allowed at the time of progression. The main efficacy outcome measures of progression-free survival (PFS), objective response (OR), and response duration were based on IRRC-confirmed events using modified RECIST criteria.

Of 330 patients randomized, 67% were male, the median age was 55 years, 23% were 65 years or older, 89% were white, 54% had a baseline ECOG performance status of 0, 92% had undergone a thyroidectomy, and 48% were reported to be *RET* mutation positive according to research-use assays. Twenty-five percent (25%) had two or more prior systemic therapies and 21% had been previously treated with a TKI.

A statistically significant prolongation in PFS was demonstrated among COMETRIQ-treated patients 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 COMETRIQ and placebo arms, respectively.

Partial responses were observed only among patients in the COMETRIQ 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 COMETRIQ. There was no statistically significant difference in overall survival between the treatment arms at the planned interim analysis.

Figure 1: Progression-Free Survival



16 HOW SUPPLIED/STORAGE AND HANDLING

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.

COMETRIQ capsules are supplied as follows:

Cartons

- 140 mg daily-dose carton

NDC#42388-011-14

Containing four 140 mg daily-dose blister cards (each blister card contains seven 80-mg and twenty-one 20-mg capsules)

- 100 mg daily-dose carton NDC#42388-012-14

Containing four 100 mg daily-dose blister cards (each blister card contains seven 80-mg and seven 20-mg capsules)

- 60 mg daily-dose carton NDC#42388-013-14

Containing four 60 mg daily-dose blister cards (each blister card contains twenty-one 20-mg capsules)

Bottle containing sixty 20-mg COMETRIQ capsules NDC#42388-014-25

Store COMETRIQ at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use).

Inform patients of the following:

- COMETRIQ often causes diarrhea which may be severe in some cases. Inform patients of the need to contact their healthcare provider if severe diarrhea occurs during treatment with COMETRIQ.
- COMETRIQ often causes palmar plantar erythrodysesthesia syndrome. Advise patients to contact their healthcare provider for progressive or intolerable rash.
- COMETRIQ often causes sores in the mouth, oral pain, changes in taste, nausea or vomiting. Advise patients to contact their healthcare provider if any of these symptoms are severe or prevent patients from eating and drinking.
- COMETRIQ often causes weight loss which may be significant in some cases. Advise patients to report significant weight loss.
- To contact their healthcare provider before any planned surgeries, including dental procedures.
- COMETRIQ may interact with other drugs; advise patients to inform their healthcare provider of all prescription or nonprescription medication or herbal products that they are taking.
- Patients of childbearing potential must use effective contraception during therapy and for at least four months following their last dose of COMETRIQ.
- Breast-feeding mothers must discontinue nursing while receiving COMETRIQ therapy.
- COMETRIQ should **not** be taken with food. Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking COMETRIQ. COMETRIQ capsules should not be opened or crushed but should be taken with a full glass (at least 8 ounces) of water.

This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugsatfda>

- Patients should **not** consume grapefruits or grapefruit juice while taking COMETRIQ treatment.

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PATIENT INFORMATION
COMETRIQ™ (Ko-me-trik)
cabozantinib
capsules

What is the most important information I should know about COMETRIQ?

COMETRIQ can cause serious side effects which can lead to death, including:

Severe bleeding (hemorrhage). Tell your healthcare provider right away if you get any signs of bleeding while taking or after you stop taking COMETRIQ, including:

- coughing up blood or blood clots
- vomiting blood or if your vomit looks like coffee-grounds
- red or black (looks like tar) stools
- menstrual bleeding that is heavier than normal
- any unusual or heavy bleeding

A tear in your stomach or intestinal wall (perforation), or an abnormal connection between 2 parts of your body (fistula). Tell your healthcare provider right away if you get:

- severe pain in your stomach-area (abdomen)
- coughing, gagging, and choking especially when eating or drinking

What is COMETRIQ?

COMETRIQ is a prescription medicine used to treat people with medullary thyroid cancer that has spread to other parts of the body.

It is not known if COMETRIQ is safe and effective in children.

What should I tell my healthcare provider before taking COMETRIQ?

Before you take COMETRIQ, tell your healthcare provider if you:

- have high blood pressure
- have a recent history of coughing up blood or bleeding or any unusual bleeding
- have an open wound
- have had recent surgery or plan to have surgery or a dental procedure
- have liver problems
- have any other medical conditions
- are pregnant or you or your partner plan to become pregnant. COMETRIQ can cause harm to your unborn baby. Talk to your healthcare provider if you are pregnant or if you or your partner plan to become pregnant.
- are a female who is able to become pregnant, or are a male whose female partner is able to become pregnant; you should use effective birth control during

your treatment with COMETRIQ and for at least 4 months after your last dose of COMETRIQ.

- Talk to your healthcare provider about birth control methods to prevent pregnancy while you are taking COMETRIQ.
- Tell your healthcare provider right away if you or your female partner becomes pregnant while taking COMETRIQ.
- are breastfeeding or plan to breastfeed. It is not known if COMETRIQ passes into your breast milk. You and your healthcare provider should decide if you will take COMETRIQ or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription or over-the-counter medicines, vitamins, and herbal supplements. COMETRIQ and certain other medicines may affect each other causing side effects.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take COMETRIQ?

- Take COMETRIQ exactly as your healthcare provider tells you to take it.
- Take COMETRIQ on an empty stomach, do not eat for at least 2 hours before and at least 1 hour after taking COMETRIQ.
- Swallow COMETRIQ capsules whole with at least 8 ounces of water. Do not crush or open COMETRIQ capsules.
- If you miss a dose and your next dose is in:
 - less than 12 hours, take your next dose at the normal time. Do not make up the missed dose.
 - 12 hours or more, take the missed dose as soon as you remember. Take your next dose at the normal time.
- Call your healthcare provider right away if you take too much COMETRIQ.

What should I avoid while taking COMETRIQ?

You should not drink grapefruit juice, eat grapefruit or any foods or supplements that contain these products, during treatment with COMETRIQ. They may increase the amount of COMETRIQ in your blood.

What are the possible side effects of COMETRIQ?

COMETRIQ may cause serious side effects, including:

- **See “What is the most important information I should know about COMETRIQ?”**
 - **blood clots, stroke, heart attack, and chest pain.** Get emergency help right away if you get:

- swelling or pain in your arms or legs
 - shortness of breath
 - feel lightheaded or faint
 - sweating more than usual
 - numbness or weakness of your face, arm or leg, especially on one side of your body
 - sudden confusion, trouble speaking or understanding
 - sudden trouble seeing in one or both eyes
 - sudden trouble walking
 - dizziness, loss of balance or coordination
 - a sudden severe headache
-
- **wound healing problems.** If you need to have surgery, tell your healthcare provider that you are taking COMETRIQ. Your healthcare provider should stop your treatment with COMETRIQ at least 28 days before any planned surgery, including dental procedures. Your healthcare provider should tell you when you may start taking COMETRIQ again after surgery.
 - **high blood pressure (hypertension) which may be severe.** Your healthcare provider should check your blood pressure during treatment with COMETRIQ. If needed, your healthcare provider should prescribe medicine for you to treat high blood pressure.
 - **severe jaw bone problems (osteonecrosis).** Symptoms may include: jaw pain, toothache, or sores on your gums. Your healthcare provider should examine your mouth before you start and during treatment with COMETRIQ. Tell your dentist that you are taking COMETRIQ. It is important for you to practice good mouth care during treatment with COMETRIQ.
 - **a skin problem called hand-foot skin reaction.** Symptoms may include: redness, pain, swelling, or blisters on the palms of your hands or soles of your feet.
 - **protein in your urine and possible kidney problems.** Symptoms may include: swelling in your hands, arms, legs or feet.
 - **Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** A condition called reversible posterior leukoencephalopathy syndrome can happen while taking COMETRIQ. Call your healthcare provider right away if you have headaches, seizures, confusion, changes in vision, or problems thinking.

Your healthcare provider may tell you to stop taking COMETRIQ if you have any of the serious side effects listed above.

The most common side effects of COMETRIQ are:

- redness, swelling or pain in your mouth or throat, or mouth sores

- diarrhea
- weight loss
- decreased appetite
- nausea and vomiting
- tiredness and weakness
- change in taste
- hair color turning lighter
- constipation
- voice changes or hoarseness
- change in liver function blood tests
- low levels of calcium in your blood

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of COMETRIQ. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store COMETRIQ?

- Store COMETRIQ at room temperature 68°F to 77°F (20°C to 25°C).

Keep COMETRIQ and all medicines out of the reach of children.

General information about COMETRIQ.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use COMETRIQ for a condition for which it was not prescribed. Do not give COMETRIQ to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about COMETRIQ that is written for health professionals.

For more information, go to www.cometriq.com or call 1-855-292-3935.

What are the ingredients in COMETRIQ?

Active ingredient: cabozantinib (S)-malate

Inactive ingredients:

- **Capsule contents:** silicified microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, fumed silica, and stearic acid
- **Capsule shells:**
- Grey gelatin capsules: black iron oxide and titanium dioxide
- Swedish orange gelatin capsules: red iron oxide and titanium dioxide

This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugsatfda>

- **Printing ink:** shellac glaze, black iron oxide, *N*-butyl alcohol, isopropyl alcohol, propylene glycol, and ammonium hydroxide

This Patient Information has been approved by the U.S. Food and Drug Administration.

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