CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

203756Orig1s008

Trade Name:	**COMETRIQ**
Generic or Proper Name:	cabozantinib
Sponsor:	**Exelixis, Inc**
Approval Date:	01/31/2020
Indication:	Cometriq is a kinase inhibitor indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC).

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

NDA 203756/S-008

SUPPLEMENT APPROVAL

Exelixis, Inc.
Attention: Lisa Sauer
Vice President, Regulatory Affairs and Quality Assurance
1851 Harbor Bay Parkway
Alameda, CA 94502

Dear Ms. Sauer:

Please refer to your supplemental new drug application (sNDA) dated July 15, 2019, and your amendments dated December 30, 2019 and January 17, 2020, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cometriq (cabozantinib) capsules, 20 mg and 80 mg.

This prior approval supplemental new drug application, submitted in response to our May 20, 2019, Prior Approval Supplement Request letter, provides for

- removal of the Boxed Warnings for PERFORATIONS AND FISTULAS and HEMORRHAGE;
- updates to the WARNINGS AND PRECAUTIONS subsection 5.4, retitled Impaired Wound Healing and addition of a new subsection (5.7), Diarrhea with corresponding revisions to PATIENT COUNSELING INFORMATION (17) and Patient Information;
- revisions to subsections 5.1, 5.2, 5.3, 5.5, 5.6, and 5.8 and to the DOSAGE AND ADMINISTRATION subsection (2.2) Dosage Modifications for Adverse Reactions for consistency and clarity;
- creation of new subsections (2.3, 2.4, 2.5) for consistency with current labeling practices; and
- Editorial changes throughout labeling to conform to current laws, regulations, and guidances.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and the Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call Gina Davis, Senior Regulatory Health Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Acting Associate Director of Medical Policy
Oncology Center for Excellence

ENCLOSURE(S):

- Content of Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PATRICIA KEEGAN
01/31/2020 04:51:05 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

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

RECENT MAJOR CHANGES

Boxed Warning	Removed 01/2020
Warnings and Precautions, Impaired Wound Healing (5.4)	01/2020
Warnings and Precautions, Diarrhea (5.7)	01/2020

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).
- Do NOT substitute COMETRIQ capsules with cabozantinib tablets. (2.1)
- Hepatic Impairment: The recommended starting dose of COMETRIQ is 80 mg in patients with mild or moderate hepatic impairment. (2.1)

DOSAGE FORMS AND STRENGTHS

Capsules: 20 mg and 80 mg (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Perforations and Fistulas: Monitor for symptoms. Discontinue COMETRIQ for Grade 4 fistula or perforation. (5.1)
- Hemorrhage: Do not administer COMETRIQ if recent history of hemorrhage. (5.2)
- Thrombotic Events: Discontinue COMETRIQ for myocardial infarction or serious arterial or venous thromboembolic events. (5.3)
- Impaired Wound Healing: Withhold COMETRIQ for at least 3 weeks before elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of COMETRIQ after resolution of wound healing complications has not been established. (5.4)
- Hypertension and hypertensive crisis: Monitor blood pressure regularly. Interrupt for hypertension that is not adequately controlled with anti-hypertensive therapy. Discontinue COMETRIQ for hypertensive crisis or severe hypertension that cannot be controlled with anti-hypertensive therapy. (5.5)
- Osteonecrosis of the Jaw (ONJ): Withhold COMETRIQ for at least 3 weeks prior to invasive dental procedure and for development of ONJ. (5.6)
- Diarrhea: May be severe. Interrupt COMETRIQ immediately until diarrhea resolves or decreases to Grade 1. Recommend standard antidiarrheal treatments. (5.7)
- Palmar-Plantar Erythrodysesthesia (PPE): Interrupt COMETRIQ until PPE resolves or decreases to Grade 1. (5.8)
- Proteinuria: Monitor urine protein. Discontinue for nephrotic syndrome. (5.9)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Discontinue COMETRIQ. (5.10)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.11, 8.1, 8.3)

ADVERSE REACTIONS

- The most common adverse reactions (≥ 25%) are diarrhea, stomatitis, palmar-plantar erythrodysesthesia (PPE), 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

- Strong CYP3A4 Inhibitors: Reduce the COMETRIQ dosage. (2.2, 7.1)
- Strong CYP3A4 Inducers: Increase the COMETRIQ dosage. (2.2, 7.2)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)

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

Revised: 01/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Do NOT substitute COMETRIQ capsules with cabozantinib tablets.

The recommended daily dose of COMETRIQ is 140 mg once daily without food until disease progression or unacceptable toxicity. Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking COMETRIQ.

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 while taking COMETRIQ.

2.2 Dosage Modifications for Adverse Reactions

Withhold COMETRIQ for NCI CTCAE Grade 4 hematologic adverse reactions, Grade 3 or greater non-hematologic adverse reactions, intolerable Grade 2 adverse reactions, or osteonecrosis of the jaw.

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
- 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 COMETRIQ

Permanently discontinue COMETRIQ for any of the following:

- development of gastrointestinal (GI) perforation or Grade 4 fistula
- severe hemorrhage
- acute myocardial infarction or arterial or venous thromboembolic events that require medical intervention
- nephrotic syndrome
- severe hypertension that cannot be controlled with anti-hypertensive therapy or hypertensive crisis

- reversible posterior leukoencephalopathy syndrome

2.3 Dosage Modifications For Coadministration With Strong CYP3A4 Inhibitors

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 *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

2.4 Dosage Modifications For Coadministration With Strong CYP3A4 Inducers

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 *[see Drug Interactions (7.2), Clinical Pharmacology (12.3)]*.

2.5 Dosage Modifications for Patients with Hepatic Impairment

The recommended starting dose of COMETRIQ for patients with mild to moderate hepatic impairment is 80 mg *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Capsules:

- 20-mg gelatin capsules, grey with “XL184 20mg” printed in black on the body of the capsule.
- 80-mg gelatin capsules, 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, including fatal cases, were reported in 3% and 1% of COMETRIQ-treated patients (N=214), respectively. Non-GI fistulas including tracheal/esophageal, including fatal cases, were reported in 4% of COMETRIQ-treated patients.

Monitor patients for symptoms of perforations and fistulas, including abscess and sepsis. Discontinue COMETRIQ in patients who experience a Grade 4 fistula or a GI perforation *[see Dosage and Administration (2.2)]*.

5.2 Hemorrhage

Severe and fatal hemorrhage occurred with COMETRIQ. The incidence of Grade ≥ 3 hemorrhagic events was higher in COMETRIQ-treated patients compared with placebo (3% vs. 1%).

Discontinue COMETRIQ for Grade 3 or 4 hemorrhage *[see Dosage and Administration (2.2)]*. Do not administer COMETRIQ to patients with a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

5.3 Thrombotic Events

COMETRIQ increased the 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 arterial or venous thromboembolic events that require medical intervention *[see Dosage and Administration (2.2)]*.

5.4 Impaired Wound Healing

Wound complications have been reported with COMETRIQ. Withhold COMETRIQ for at least 3 weeks prior to elective surgery. Do not administer COMETRIQ for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of COMETRIQ after resolution of wound healing complications has not been established..

5.5 Hypertension and Hypertensive Crisis

COMETRIQ can increase the 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 *[see Adverse Reactions (6.1)]*.

Do not initiate COMETRIQ in patients with uncontrolled hypertension. Monitor blood pressure 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 and for hypertensive crisis *[see Dosage and Administration (2.2)]*.

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. Withhold COMETRIQ treatment for at least 3 weeks prior to scheduled dental surgery, or invasive dental procedures, if possible. Withhold COMETRIQ for development of ONJ until complete resolution *[see Dosage and Administration (2.2)]*.

5.7 Diarrhea

Diarrhea occurred in 63% of patients treated with COMETRIQ. Grade 3-4 diarrhea occurred in 16% of patients treated with COMETRIQ *[see Adverse Reactions (6.1)]*.

Withhold COMETRIQ until improvement to Grade 1 and resume COMETRIQ at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

5.8 Palmar-Plantar Erythrodysesthesia

Palmar-plantar erythrodysesthesia (PPE) occurred in 50% of patients treated with COMETRIQ, including 13% Grade 3 *[see Adverse Reactions (6.1)]*.

Withhold COMETRIQ until improvement to Grade 1 and resume COMETRIQ at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

5.9 Proteinuria

Proteinuria was observed in 2% of patients receiving COMETRIQ, including one with nephrotic syndrome. Monitor urine protein regularly during COMETRIQ treatment. Discontinue COMETRIQ in patients who develop nephrotic syndrome.

5.10 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 *[see Dosage and Administration (2.2)]*.

5.11 Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, COMETRIQ can cause fetal harm when administered to a pregnant woman. Cabozantinib administration to pregnant animals during organogenesis resulted in embryolethality at exposures below those occurring clinically at the recommended dose, and in increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with COMETRIQ and for 4 months after the last dose *[see Use in Specific Populations (8.1), (8.3), and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed elsewhere in the labeling:

- Perforations and Fistula *[see Warnings and Precautions (5.1)]*
- Hemorrhage *[see Warnings and Precautions (5.2)]*
- Thromboembolic Events *[see Warnings and Precautions (5.3)]*
- Impaired Wound Healing *[see Warnings and Precautions (5.4)]*
- Hypertension and Hypertensive Crisis *[see Warnings and Precautions (5.5)]*
- Osteonecrosis of the Jaw *[see Warnings and Precautions (5.6)]*
- Diarrhea *[see Warnings and Precautions (5.7)]*
- Palmar-Plantar Erythrodysesthesia *[see Warnings and Precautions (5.8)]*
- Proteinuria *[see Warnings and Precautions (5.9)]*
- Reversible Posterior Leukoencephalopathy Syndrome *[see Warnings and Precautions (5.10)]*

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 (Study 1) *[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.

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 COMETRIQ dose was reduced in 79% of patients receiving COMETRIQ and in 9% of patients receiving placebo. The median number of dosing delays was one in patients receiving COMETRIQ and in no patients receiving placebo. Adverse reactions led to study treatment discontinuation in 16% of patients receiving COMETRIQ. The most frequent adverse reactions leading to permanent discontinuation of COMETRIQ were: hypocalcemia, increased lipase, PPE, 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.

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, palmar-plantar erythrodysesthesia (PPE), 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 ≥ 5% of COMETRIQ-treated patients occurring more frequently in the COMETRIQ arm with a between-arm difference of ≥ 2% included, in order of decreasing frequency; diarrhea, PPES, lymphopenia, hypocalcemia, fatigue, hypertension, asthenia, increased ALT, decreased weight, stomatitis, and decreased appetite (Table 1 and Table 2 summarize the adverse reactions and laboratory abnormalities reported in Study 1).

Table 1. Selected Adverse Reactions Occurring at a Higher Incidence in COMETRIQ-Treated Patients (Study 1)
[Between Arm Difference of ≥ 5% (All Grades)[1] or ≥ 2% (Grade 3-4)]

System Organ Class/ Preferred Terms	COMETRIQ (n=214)		Placebo (n=109)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 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
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
PPE[5]	50	13	2	0
Hair color changes/ depigmentation, graying	34	0	1	0
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
INVESTIGATIONS				
Decreased weight	48	5	10	0
METABOLISM AND NUTRITION DISORDERS				
Decreased appetite	46	5	16	1
Dehydration	7	2	2	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Fatigue	41	9	28	3

Table 1. Selected Adverse Reactions Occurring at a Higher Incidence in COMETRIQ-Treated Patients (Study 1)
[Between Arm Difference of ≥ 5% (All Grades)[1] or ≥ 2% (Grade 3-4)]

System Organ Class/ Preferred Terms	COMETRIQ (n=214)		Placebo (n=109)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Asthenia	21	6	15	1
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
VASCULAR DISORDERS				
Hypertension	33	8	4	0
Hypotension	7	1	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Dysphonia	20	0	9	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Arthralgia	14	1	7	0
Muscle spasms	12	0	5	0
Musculoskeletal chest pain	9	1	4	0
PSYCHIATRIC DISORDERS				
Anxiety	9	0	2	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

Table 2. Laboratory Abnormalities Occurring at a Higher Incidence in COMETRIQ-Treated Patients (Study 1) [Between Arm Difference of ≥ 5% (All Grades) or ≥ 2% (Grade 3-4)]				
Test	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.

Table 3. Per-Patient Incidence of Hypertension (Study 1)		
Hypertension, JNC[1] Stage[2]	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
[1]Joint 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. [2]Patients classified by highest category based on all recorded blood pressure readings beginning after the first dose through 30 days after last dose. [3]Patients with at least two blood pressure measurements after the first dose		

Other clinically important adverse reactions (all grades) that were reported in clinical trials include: hepatitis cholestatic (<1%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of COMETRIQ. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hematology: A case of supratherapeutic international normalized ratio (INR) and epistaxis during concomitant use of warfarin

7 DRUG INTERACTIONS

7.1 Effect of CYP3A4 Inhibitors

Administration of a strong CYP3A4 inhibitor, ketoconazole to healthy subjects increased single-dose plasma cabozantinib exposure by 38%. Avoid taking a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) while taking COMETRIQ or reduce the dosage of COMETRIQ if concomitant use with strong CYP3A4 inhibitors cannot be avoided *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3)]*.

Avoid ingestion of foods (e.g., grapefruit, grapefruit juice) or nutritional supplements that are known to inhibit cytochrome P450 while taking COMETRIQ.

7.2 Effect of CYP3A4 Inducers

Administration of a strong CYP3A4 inducer, rifampin to healthy subjects decreased single-dose plasma cabozantinib exposure by 77%. Avoid chronic co-administration of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, St. John's Wort) with COMETRIQ or increase the dosage of COMETRIQ if concomitant use with strong CYP3A4 inducers cannot be avoided *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3)]*.

7.3 Effect of MRP2 Inhibitors

Concomitant administration of MRP2 inhibitors may increase the exposure to cabozantinib. Monitor patients for increased toxicity when MRP2 inhibitors (e.g., abacavir, adefovir, cidofovir, furosemide, lamivudine, nevirapine, ritonavir, probenecid, saquinavir, and tenofovir) are co-administered with COMETRIQ *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, COMETRIQ can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data in pregnant women to inform the drug-associated risk. In animal developmental and reproductive toxicology studies administration of cabozantinib to pregnant rats and rabbits during organogenesis resulted in embryofetal lethality and structural anomalies at exposures that were below those occurring clinically at the recommended dose *(see* Data*)*. Advise pregnant women or women of childbearing potential of the potential hazard to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study in pregnant rats, daily oral administration of cabozantinib throughout organogenesis caused increased embryo-fetal lethality compared to controls at a dose of 0.03 mg/kg (less than 1% of the human exposure by AUC at the 140 mg dose). Findings included delayed ossifications and skeletal variations at a dose of 0.01 mg/kg/day (approximately 0.03% of the human exposure by AUC at the 140 mg dose).

In pregnant rabbits, daily oral administration of cabozantinib throughout organogenesis resulted in 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 140 mg dose).

In a pre- and postnatal study in rats, cabozantinib was administered orally from gestation day 10 through postnatal day 20. Cabozantinib did not produce adverse maternal toxicity or affect pregnancy, parturition or lactation of female rats, and did not affect the survival, growth or postnatal development of the offspring at doses up to 0.3 mg/kg/day (approximately 0.02 times the recommended clinical dose of 140 mg based on body surface area).

8.2 Lactation

Risk Summary

There is no information regarding the presence of cabozantinib or its metabolites in human milk, or their effects on the breastfed infant, or milk production. Because of the potential for serious adverse reactions in a breastfed infant from COMETRIQ, advise a lactating woman not to breastfeed during treatment with COMETRIQ and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating COMETRIQ *[see Use in Specific Populations (8.1)]*.

Contraception

COMETRIQ can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with COMETRIQ and for 4 months after the final dose.

Infertility

Females and Males

Based on findings in animals, COMETRIQ may impair fertility in females and males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

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

Juvenile Animal Toxicity Data

Juvenile rats were administered cabozantinib daily at doses of 1 or 2 mg/kg/day from Postnatal Day 12 (comparable to less than 2 years in humans) through Postnatal Day 35 or 70. Mortalities occurred at doses equal and greater than 1 mg/kg/day (approximately 0.07 times the clinical dose of 140 mg/day based on body surface area). Hypoactivity was observed at both doses tested on Postnatal Day 22. Targets were generally similar to those seen in adult animals, occurred at both doses, and included the kidney (nephropathy, glomerulonephritis), reproductive organs, gastrointestinal tract (cystic dilatation and hyperplasia in Brunner's gland and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and whitening as well as effects on bones including reduced bone mineral content and density, physeal hypertrophy, and decreased cortical bone also occurred at all dose levels. Recovery was not assessed at the 2 mg/kg dose level (approximately 0.14 times the clinical dose of 140 mg based on body surface area) due to high levels of mortality. At the low dose level, effects on bone parameters were partially resolved but effects on the kidney and epididymis/testis persisted after treatment ceased.

8.5 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.

8.6 Hepatic Impairment

Increased exposure to cabozantinib has been observed in patients with mild to moderate hepatic impairment. Reduce the starting dose of COMETRIQ in patients with mild (Child-Pugh score

(C-P) A) or moderate (C-P B) hepatic impairment. COMETRIQ is not recommended for use in patients with severe hepatic impairment *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

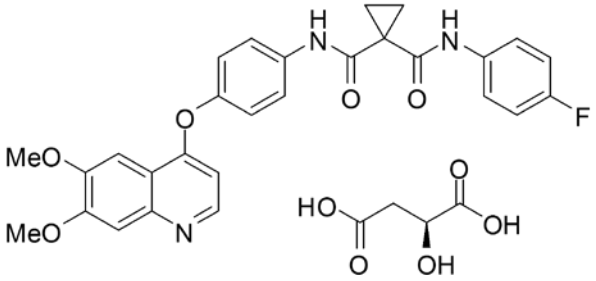
Dosage adjustment is not required in patients with mild or moderate renal impairment. There is no experience with COMETRIQ in patients with severe renal impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

One case of overdosage 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, a kinase inhibitor. Cabozantinib (*S*)-malate is described chemically as *N*-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2*S*)-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 for oral use 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, ROS1, TYRO3, MER, and TIE-2. These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, drug resistance, and maintenance of the tumor microenvironment.

12.2 Pharmacodynamics

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)]*.

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. 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.

Absorption

Following oral administration of COMETRIQ, median time to peak cabozantinib plasma concentrations (T_{max}) ranged from 2 to 5 hours post-dose.

A 19% increase in the C_{max} of the tablet formulation (CABOMETYX™) compared to the capsule formulation (COMETRIQ) was observed following a single 140 mg dose. A less than 10% difference in the AUC was observed between cabozantinib tablet (CABOMETYX) and capsule (COMETRIQ) formulations *[see Dosage and Administration (2.1)]*.

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

Distribution

The oral volume of distribution (V/F) of cabozantinib is approximately 349 L. Cabozantinib is highly protein bound in human plasma (≥ 99.7%).

Elimination

The predicted effective half-life is approximately 55 hours and the clearance (CL/F) at steady-state is estimated to be 4.4 L/hr.

Metabolism

Cabozantinib is a substrate of CYP3A4 *in vitro.*

Excretion

Approximately 81% of the total administered radioactivity was recovered within a 48-day collection period following a single 140 mg dose of an investigational ^{14}C-cabozantinib formulation in healthy subjects. Approximately 54% was recovered in feces and 27% in urine. Unchanged cabozantinib accounted for 43% of the total radioactivity in feces and was not detectable in urine following a 72 hour collection.

Specific Populations

The following patient characteristics did not result in a clinically relevant difference in the pharmacokinetics of cabozantinib: age (20-86 years), sex, race (Whites and non-Whites), or mild to moderate renal impairment (eGFR greater than or equal to 30 mL/min/1.73 m^2 as estimated by MDRD (modification of diet in renal disease equation)). The pharmacokinetics of cabozantinib is unknown in patients with worse than moderate renal impairment (eGFR less than 29 mL/min/1.73m^2) as estimated by MDRD equation or renal impairment requiring dialysis.

Patients with Hepatic Impairment

Following a single oral 60 mg COMETRIQ, mean $AUC_{0\text{-}inf}$ for cabozantinib increased by 81% in subjects with mild (Child-Pugh A) hepatic impairment and 63% in subjects with moderate (Child-Pugh B) hepatic impairment compared to subjects with normal hepatic function *[see Dosage and Administration (2.5), Use in Specific Populations (8.6)]*.

The pharmacokinetics of cabozantinib has not been studied in patients with severe (Child-Pugh C) hepatic impairment *[see Use in Specific Populations (8.6)]*.

Drug Interaction Studies

CYP3A4 Inhibition on Cabozantinib

Administration of a strong CYP3A4 inhibitor, ketoconazole (400 mg daily for 27 days) to healthy subjects increased single-dose plasma cabozantinib exposure ($AUC_{0\text{-}inf}$) by 38%.

CYP3A4 Induction on Cabozantinib

Administration of a strong CYP3A4 inducer, rifampin (600 mg daily for 31 days) to healthy subjects decreased single-dose plasma cabozantinib exposure ($AUC_{0\text{-}inf}$) by 77%.

Cabozantinib on CYP2C8 substrates

No clinically-significant effect on single-dose rosiglitazone (a CYP2C8 substrate) plasma exposure (C_{max} and AUC) was observed when co-administered with cabozantinib at steady-state plasma concentrations (≥ 100 mg/day daily for a minimum of 21 days) in patients with solid tumors.

Gastric pH modifying agents on Cabozantinib

No clinically-significant effect on plasma cabozantinib exposure (AUC) was observed following co-administration of the proton pump inhibitor (PPI) esomeprazole (40 mg daily for 6 days) with a single dose of 100 mg cabozantinib to healthy volunteers.

In vitro Studies

Metabolic Pathways:

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.

Although cabozantinib is an inhibitor of CYP2C8 *in vitro*, a clinical study of this potential interaction concluded that concurrent use did not result in a clinically relevant effect on CYP2C8 substrate exposure. Given this finding, other less sensitive substrates of pathways affected by cabozantinib *in vitro* (i.e., CYP2C9, CYP2C19, and CYP3A4) were not evaluated in a clinical study because, although a clinically relevant exposure effect cannot be ruled out, it is unlikely. Cabozantinib does not inhibit CYP1A2 and CYP2D6 isozymes *in vitro*.

Cabozantinib is an inducer of CYP1A1 mRNA; however, the clinical relevance of this finding is unknown. Cabozantinib does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4.

Drug Transporter Systems:

Cabozantinib is an inhibitor, but not a substrate, of P-gp transport activities and has the potential to increase plasma concentrations of co-administered substrates of P-gp. The clinical relevance of this finding is unknown.

Cabozantinib is a substrate of MRP2 *in vitro* and MRP2 inhibitors have the potential to increase plasma concentrations of cabozantinib. The clinical relevance of this finding is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of cabozantinib has been evaluated in two species: rasH2 transgenic mice and Sprague-Dawley rats. In the 2-year rat carcinogenicity study, once daily oral administration of cabozantinib resulted in a statistically significant increase in the incidence of malignant/complex malignant pheochromocytoma in combination with benign pheochromocytoma or in benign pheochromocytoma alone in male rats at a dose of 1 mg/kg (approximately 0.6 times the human exposure by AUC at the recommended 140 mg dose). Cabozantinib was not carcinogenic in a 26-week carcinogenicity study in rasH2 transgenic mice at a slightly higher exposure than the intended human therapeutic exposure.

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

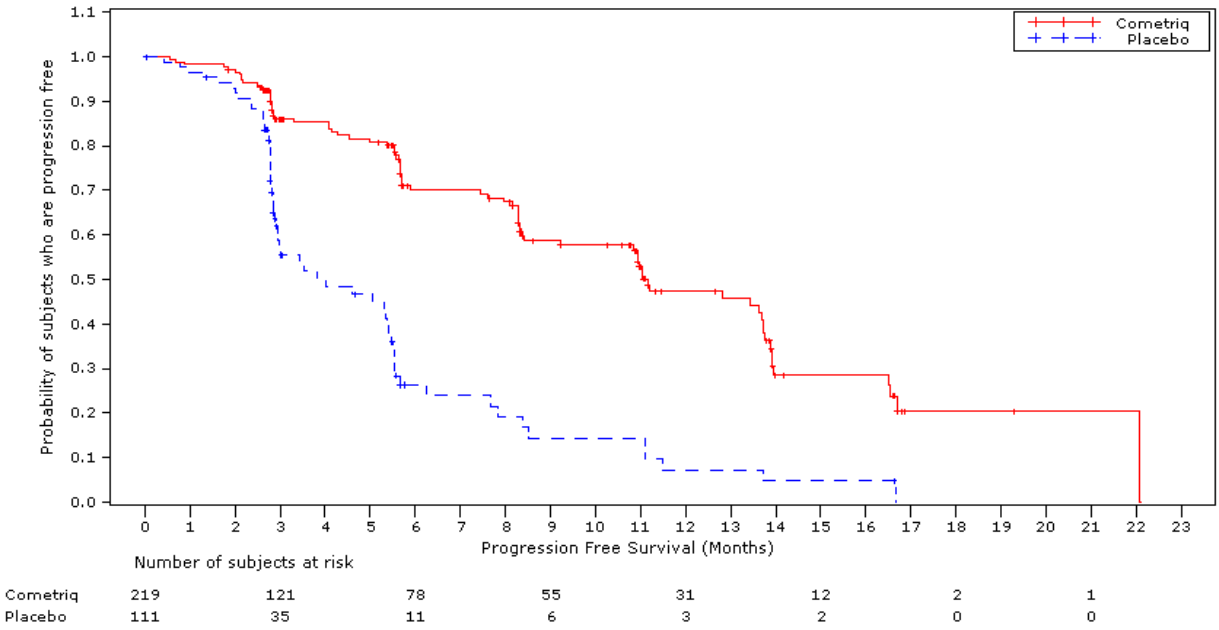
The safety and efficacy of COMETRIQ was assessed in an international, multi-center, randomized, double-blind, controlled trial (Study 1) of 330 patients with metastatic medullary thyroid carcinoma (MTC). Patients were required to have evidence of actively progressive disease within 14 months prior to 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, and 92% had undergone a thyroidectomy. The *RET* mutation status determined by a research-use assay was positive in 51%, negative in 14%, and was unknown in 35%. 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 (median OS: 26.6 months in the COMETRIQ arm vs. 21.1 months in the placebo arm [HR = 0.85 (95% CI: 0.64, 1.12), p = 0.2409]).

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)

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

Advise patients to read the FDA-approved patient labeling (Patient Information).

- Perforations and fistulas: Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during COMETRIQ treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistula have been reported in patients taking COMETRIQ *[see Warnings and Precautions (5.1)]*.
- Hemorrhage: Instruct patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual severe bleeding or hemorrhage *[see Warnings and Precautions (5.2)]*.
- Thrombotic events: Venous and arterial thrombotic events have been reported. Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolus have been reported. Advise patients to contact their health care provider if new onset of dyspnea, chest pain, or localized limb edema occurs *[see Warnings and Precautions (5.3)]*.
- Impaired wound healing: Advise patients that COMETRIQ may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure *[see Warnings and Precautions (5.4)]*.
- Hypertension and hypertensive crisis: Inform patients of the signs and symptoms of hypertension. Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if they experience signs or symptoms of hypertension *[see Warnings and Precautions (5.5)]*.
- Osteonecrosis of the jaw: Advise patients regarding good oral hygiene practices. Advise patients to immediately contact their healthcare provider for signs or symptoms associated with osteonecrosis of the jaw *[see Warnings and Precautions (5.6)]*.
- Diarrhea: Advise patients to notify their healthcare provider at the first signs of poorly formed or loose stool or an increased frequency of bowel movements *[see Warnings and Precautions (5.7)]*.
- Palmar-plantar erythrodysesthesia: Advise patients to contact their healthcare provider for progressive or intolerable rash *[see Warnings and Precautions (5.8)]*.
- Reversible posterior leukoencephalopathy syndrome: Advise patients to immediately contact their health care provider for new onset or worsening neurological function *[see Warnings and Precautions (5.10)]*.

- Embryo-fetal toxicity:
  - Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.11), Use in Specific Populations (8.1)]*.
  - Advise patients of reproductive potential to use effective contraception during treatment with COMETRIQ and for at least 4 months after the final dose *[see Use in Specific Populations (8.3)]*.
- Lactation: Advise women not to breastfeed during treatment with COMETRIQ and for 4 months following the last dose *[see Use in Specific Populations (8.2)]*.
- Drug interactions: Advise patients to inform their healthcare provider of all prescription or nonprescription medications, vitamins or herbal products. Inform patients to avoid grapefruit, grapefruit juice, and St. John's wort *[see Drug Interactions (7.1), (7.2)]*.

Important administration information:

- Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking COMETRIQ. Instruct patients that COMETRIQ capsules should not be opened or crushed and to take COMETRIQ capsules with a full glass (at least 8 ounces) of water.

Manufactured for Exelixis, Inc. Alameda, CA 94502

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

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.

Before you take COMETRIQ, tell your healthcare provider about all of your medical conditions including if you:

- have a recent history of coughing up blood or bleeding or any unusual bleeding
- have an open wound
- have high blood pressure
- plan to have any surgery, a dental procedure, or have had a recent surgery. You should stop taking COMETRIQ at least 3 weeks before planned surgery. See **"What are the possible side effects of COMETRIQ?"**
- have liver problems
- are pregnant or plan to become pregnant. COMETRIQ can harm your unborn baby. If you are able to become pregnant, you should use effective birth control during treatment and for 4 months after the final dose of COMETRIQ. Talk to your healthcare provider about birth control methods that may be right for you. If you become pregnant or think you are pregnant, tell your healthcare provider right away.
- are breastfeeding or plan to breastfeed. It is not known if COMETRIQ passes into your breast milk. Do not breastfeed during treatment and for 4 months after the final dose of COMETRIQ.

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.

How should I take COMETRIQ?

- Take COMETRIQ exactly as your healthcare provider tells you to take it.
- **Do not** take COMETRIQ with food. **Do not** eat for at least 2 hours before and at least 1 hour after taking COMETRIQ.
- Swallow COMETRIQ capsules whole with a full glass (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.

What should I avoid while taking COMETRIQ?

Do not drink grapefruit juice, eat grapefruit or supplements that contain grapefruit during treatment with COMETRIQ.

What are the possible side effects of COMETRIQ?

COMETRIQ may cause serious side effects, including:

- **a tear in your stomach or intestinal wall (perforation) or an abnormal connection between 2 parts of your body (fistula) that may lead to death.** Tell your healthcare provider right away if you get tenderness or pain in your stomach-area (abdomen).
- **bleeding (hemorrhage). COMETRIQ can cause severe bleeding that may lead to death.** Tell your healthcare provider right away if you get any signs of bleeding during treatment with 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

- **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 understandin
  - sudden trouble seeing in one or both eyes
  - sudden trouble walking
  - dizziness, loss of balance or coordination
  - a sudden severe headache
- **wound healing problems.** Wound healing problems have happened in some people who take COMETRIQ. Tell your healthcare provider if you plan to have any surgery before or during treatment with COMETRIQ.
  - You should stop taking COMETRIQ at least 3 weeks before planned surgery.
  - Your healthcare provider should tell you when you may start taking COMETRIQ again after surgery.
- **high blood pressure (hypertension).** Hypertension is common with COMETRIQ and can be severe. Your healthcare provider will check your blood pressure before starting COMETRIQ and during treatment with COMETRIQ. If needed, your healthcare provider may prescribe medicine to treat your 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.
- **diarrhea.** Diarrhea is common with COMETRIQ and can be severe. If needed, your healthcare provider may prescribe medicine to treat your diarrhea. Tell your healthcare provider right away, if you have frequent loose, watery bowel movements.
- **a skin problem called hand-foot skin reaction.** Hand-foot skin reactions are common with COMETRIQ and can be severe. Tell your healthcare provider right away if you have rashes, 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 during treatment with COMETRIQ. Tell your healthcare provider right away if you have headaches, seizures, confusion, changes in vision, or problems thinking.

Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with COMETRIQ if you have certain side effects.

The most common side effects of COMETRIQ are:

- diarrhea
- redness, swelling or pain in your mouth or throat, or mouth sores. Tell your healthcare provider if these symptoms prevent you from eating or drinking.
- weight loss
- decreased appetite
- nausea
- tiredness
- hair color turning lighter
- change in taste
- pain in your abdomen
- constipation
- increased liver function blood tests
- decreased calcium and phosphate blood levels
- decreased white blood cell counts
- decreased platelet counts
- increased bilirubin blood levels

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.

What are the ingredients in COMETRIQ?

Active ingredient: cabozantinib

Inactive ingredients: silicified microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, fumed silica, and stearic acid

Capsule shells: Grey gelatin capsule shells contain black iron oxide and titanium dioxide. 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.

Manufactured for Exelixis, Inc. Alameda, CA 94502

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

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 01/2020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203756Orig1s008

CLINICAL REVIEW(S)

Labeling Supplement (PAS 8) – Clinical Review

Application Type (NDA/BLA)	NDA
Application Number(s)/ supplement number	203756
Received Date	July 31, 2019
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Review Completion Date	January 15, 2020
Division/Office	Division of Oncology 2 / Office of New Drugs
Medical Officer	Sonia Singh
Team Leader	Suzanne Demko
Signatory	Patricia Keegan
Product: Established Name (Trade name)	Cabozantinib (COMETRIQ)
Formulation	Capsules (20 mg and 80 mg) for oral use
Established Pharmacologic Class (EPC)	Kinase inhibitor
Applicant	Exelixis, Inc.
Recommended Regulatory Action	Approval of this labeling supplement

1. Executive Summary:

Cabozantinib is a kinase inhibitor with anti-VEGFR, VEGFR2, and VEGFR3 activity. Agents that antagonize the VEGF pathway present safety risks to patients due to impaired wound healing from inhibition of angiogenesis which manifests clinically as a higher incidence of wound dehiscence, intestinal perforations and fistulas.

In an effort to provide consistent communication regarding adverse reactions related to inhibition of VEGF signaling, FDA requested Exelixis, and other commercial sponsors of similar agents, to submit draft labeling proposing changes to update the Warnings and Precautions subsection detailing potential wound healing complications.

Exelixis's proposal to withhold Cometriq for at least three weeks prior to elective surgery based on the drug's half-life ($t_{1/2}$ = 55 hours; 12 days is approximately 5 half-lives) and to withhold for at least two weeks after surgery and until adequate wound healing is acceptable. Although Exelixis' search of the cabozantinib global safety database yielded clinical data on wound healing complications that is too limited to support a formal recommendation on withholding Cometriq post-operatively, the two-week suspension period was selected based on normal wound healing physiology. VEGF is crucial for angiogenesis during the proliferation phase that spans approximately 3-10 days after injury; as such, it is during this timeframe that VEGF inhibition may have the most harmful effect on wound healing.

Based on review of preclinical and clinical data for multiple drug products with VEGF inhibition, FDA agrees that labeling should instruct prescribers to withhold these agents for at least 5 half-lives (or at least 28 days for antibodies with half-lives of 2 weeks or longer) prior to scheduled surgical procedures and for at least 2 weeks following surgery and until adequate wound healing.

Exelixis also proposed the following label changes: removal of the boxed warning for "Perforations and Fistulas, and Hemorrhage," addition of "Perforations and Fistulas" and "Hemorrhage" to the Warnings and Precautions section, and addition of "Diarrhea" as a Warning and Precaution. The proposed text is consistent with the Cabometyx label.

2. Regulatory Background

Cometriq is a multi-kinase inhibitor of VEGFR, VEGFR2, VEGFR3, MET and RET. Cometriq is approved for the treatment of patients with progressive, metastatic medullary thyroid cancer. On May 20, 2019, FDA issued a "Prior Approval Supplement Request" letter. Specifically, FDA requested Exelixis to make the following changes to the Cometriq prescribing information (PI):

- Remove the Boxed Warning
- Modify the Warnings and Precautions subsection 5.4 ("Wound Complications") to revise the minimum time to withhold Cometriq before elective surgery and include a minimum time for withholding Cometriq following any major surgical procedure to reduce the risk of impaired wound healing
- Include a new Warnings and Precautions subsection for "Diarrhea" that contains the same information as described in the FDA-approved labeling for Cabometyx

FDA notes that labels of other drug products with a similar incidence and spectrum of VEGFR related toxicities to Cometriq do not carry a Boxed Warning for "Perforations and Fistulas, and Hemorrhage." There is no evidence that these products expose patients to greater risk; therefore, FDA concluded that a Boxed Warning is not necessary to mitigate these risks.

FDA also recommended that Cometriq be withheld prior to elective surgery for at least five half-lives of cabozantinib. The sponsor was advised to take into consideration an analysis of wound healing complications based on its global safety database, as well as a thoughtful assessment and review of biomedical literature regarding wound healing complications associated with cabozantinib and with VEGF-inhibiting drugs in general when determining the appropriate timeframe for withholding the drug. Further, FDA stated that the proposed minimum duration of time (e.g., at least 28 days and until the wound is fully healed) after any major surgical procedure prior to resuming Cometriq should also be based on an analysis of Exelixis' global safety database and scientific literature regarding VEGF involvement in wound healing physiology.

On July 31, 2019, Exelixis submitted a response to FDA's Prior Approval Supplement (PAS) Request. The submission (SDN 185 in DARRTS) consists of a summary of the proposed changes, a "Cabozantinib Wound Complications Analysis" and draft labeling. Exelixis provided a revised PI in which:

- The Boxed Warning was removed (edits made as indicated throughout the PI and in the patient leaflet).
- "Perforations and Fistulas" and "Hemorrhage" were added to the Warnings and Precautions section.
- No changes proposed to "Wound Complications" in section 5.4 (see below for sponsor's rationale)
- "Diarrhea" was added to section 5 (edits made as indicated throughout the PI and in the patient leaflet). The text is consistent with that included in the Cabometyx label.

The current approved label of Cometriq states patients should “stop treatment with Cometriq at least 28 days prior to scheduled surgery” and advises patients to “resume Cometriq therapy after surgery based on clinical judgement of adequate wound healing” and to “withhold Cometriq in patients with dehiscence or wound healing complications requiring medical intervention.” Exelixis stated that data evaluated from cabozantinib clinical studies, post-marketing experience and the literature to identify an optimal duration of time to interrupt treatment following surgery are insufficient to determine a scientific data-driven minimum timeframe to minimize or prevent the risk of wound healing complications.

On December 3, 2019, FDA had a teleconference (TCON) with Exelixis to discuss Exelixis’s July 31, 2019 response to FDA’s PAS request. FDA informed Exelixis that based upon review of preclinical and clinical data for multiple drug products with VEGF pathway antagonism, FDA has determined that the labeling for drug products with VEGF inhibition will include consistent instructions to withhold a drug product with VEGF pathway antagonism before surgery (i.e., 5 times the elimination half-lives of the drug substance or metabolites or a maximum of 28 days) and for at least 2 weeks following surgery and until adequate wound healing. Exelixis was amenable to revising the “Wound Complications” subsection in the Warnings and Precautions section of the label.

3. Background and Review of Clinical Data

Exelixis’s Rationale for Initial Proposal

In the July 31, 2019, response to FDA’s PAS request, Exelixis proposes no changes to the “Wound Complications” subsection. Exelixis states that a review of available data from clinical studies of cabozantinib and post-marketing showed no clear trend of dose interruptions, nor was there a correlation between timing of dose interruptions (including no interruption) and the occurrence of a wound complication. Exelixis also states that their literature review which included retrospective and prospective studies that investigated interruption of VEGF tyrosine kinase inhibitors (TKIs) pre- and post-surgery and wound complication rates did not provide additional insight for cabozantinib or other VEGF TKIs.

Additionally, Exelixis notes that the individual benefit-risk of a patient should be taken into consideration given that patients with advanced cancer are treated with Cometriq and prolonged interruption of drug administration due to a procedure in the absence of a wound healing issue may not be necessary. It is Exelixis’s viewpoint that the treating physician is in the optimal position to assess when adequate wound healing has occurred for each patient, and to assess the individual patient’s therapeutic needs. Exelixis contends that the current wording in the approved labeling of section 5.4 of the PI of Cometriq is appropriate due to variability in surgical procedures and an individual’s wound healing process following surgery.

Safety Database Query

Exelixis reports conducting a search the global safety database (cut-off date April 28, 2019) to identify “surgical and medical procedures” in non-Exelixis sponsored studies or post-marketing data. The sponsor states 1214 individual cases were detected, and this subset was further mined for terms relevant to wound healing which yielded 186 individual cases that were the focus of further review. Exelixis classified these procedures into 5 categories (“major”, “minor”, “dental”, “pre-existing wound issues” and “other”) and also determined timing of the surgery in relation to cabozantinib treatment (“pre-treatment”, “during treatment”, “post-treatment”, “undetermined/outside of review interval”). This narrowed the search to 41 major procedures, 43

minor procedures, 20 dental procedures, 13 pre-existing wound issues and 5 cases of other that occurred during the pre-, during or post-treatment phases.

In Exelixis-sponsored studies, surgical procedures were captured on the case report form (CRF) for all patients enrolled in pivotal studies, and these procedures were retrieved by the sponsor in the clinical database. A total of 634 cabozantinib-exposed patients had a surgical procedure, and the data from these patients was similarly reviewed to characterize the type of surgical procedure and determine temporal relationship to cabozantinib treatment yielding the following: 67 major procedures (in 60 patients), 282 minor procedures (in 132 patients), 17 dental procedures (in 15 patients), 13 pre-existing wound issues (in 10 patients) and 264 cases of other (in 140 patients).

Exelixis states that all selected cases were further evaluated through case narrative review for patients from non-Exelixis sponsored studies and post-marketing experience, and review of patient profiles for individual patients from the clinical database for Exelixis-sponsored studies and case narratives for relevant serious adverse events (SAEs). Exelixis notes that no specific CRF data collection for wound complications was included in Exelixis-sponsored studies. Exelixis defined wound complications as surgical site infections, disruption of sutured tissue, slow/impaired healing at the surgical site, and surgical site bleeding.

Exelixis identified 208 surgical procedures in total that occurred during the pre-defined review period, mostly occurring during cabozantinib treatment and largely consisting of major and minor procedures. Exelixis notes for patients who interrupted cabozantinib prior to surgery, the mean duration of treatment interruption prior to the procedure was 9.1 days for major surgery (range: 0-80), 11.8 days for minor surgery (range: 0-30), 5.5 days for dental procedures (range: 0-14), 11.5 days for pre-existing wound issues (range: 0-36), and 4 days for other procedures range: 0-8). Of the patients who had surgery during the cabozantinib treatment period and interrupted cabozantinib prior to surgery, the mean duration of treatment interruption of patients who restarted cabozantinib after their surgery was: 26.4 days for major surgery (range: 1-44), 47.7 days for minor surgery (range: 15-100), 17.2 days for dental procedures (range: 3-28), unknown for pre-existing wound issue and for other procedures.

Exelixis reports that cabozantinib was interrupted or permanently discontinued prior to the surgeries for approximately 74% of the minor and major surgeries, while there was no interruption for 13% of the surgeries and action taken was unknown in another 13% of cases. The mean duration of cabozantinib interruption following surgery across minor and major procedures was 23 days (range: 1-90 days). Exelixis reports that wound complications were observed in 58 (27.9%) of the 208 cases while no wound complication was observed in 42 (20.2%) cases, and the occurrence of wound complications was unknown in 108 (51.9%) cases. Wound complications primarily consisted of impaired/delayed wound healing and infection.

Exelixis notes that in many major and minor procedures with and without wound complications, no information was provided regarding the length of cabozantinib treatment interruption (~55% and ~45%, respectively). Exelixis contends that the available data on length of cabozantinib treatment interruption in major and minor surgeries is very limited and precludes a comprehensive evaluation of this parameter on wound complications.

The following tables are copied from the “Cabozantinib Wound Complication Analysis” document.

Table 6 Cabozantinib interruption length by outcome and surgery category for procedures conducted during cabozantinib treatment period

Cabozantinib treatment interruption length	Wound complication		No wound complication	
	Major surgery (n=16)	Minor surgery (n=15)	Major surgery (n=20)	Minor surgery (n=11)
No interrupted	2 (12.5%)	5 (33.3%)	3 (15%)	2 (18.2%)
0-7 days	0	0	1 (5%)	0
8-14 days	0	0	1 (5%)	0
15-21 days	1 (6.3%)	1 (6.7%)	1 (5%)	0
22-28 days	0	0	0	0
>28 days	0	1 (6.7%)	4 (20%)	1 (9.1%)
Not restarted	3 (18.8%)	0	3 (15%)	0
Unknown	10 (62.5%)	8 (53.3%)	7 (35%)	8 (72.7%)

Table 7 Wound complication characteristics by surgery category

Surgery category	Impaired/delayed healing	Dehiscence/disruption	Infection	Bleeding	Other
Major (n=16)	6	1	5	1	3
Minor (n=15)	5	3	4	1	2
Surgery for pre-existing wound issues (n=2)	0	0	0	0	2
Other (n=1)	0	0	0	1	0
	Impaired/delayed healing	Osteonecrosis of jaw	Infection	Other	
Dental (n=9)	6	2	0	1	

Reviewer Assessment: This reviewer agrees that the clinical data, including contextual details regarding dose interruption and wound healing impairment, compiled by Exelixis from a search of the cabozantinib global safety database are limited to allow for adequate interpretation and formulation of a standard recommendation for the optimal time to resume cabozantinib post-operatively. From the reports described, there is no appreciable pattern or well-supported conclusion that can be made regarding how long to withhold cabozantinib post-operatively in order to mitigate the risk of impaired wound healing.

Further, a number of factors including the invasiveness and type of surgery performed, co-morbid conditions, age, nutritional status, and the use of other drugs that may impair the healing process impact an individual patient’s wound-healing ability and must be considered by the physician. This reviewer also finds that the status of post-surgical wound healing, which is largely determined by clinical judgment, is key in the determination of when to restart VEGF-inhibitors and must be weighed against the health detriments posed by the patient’s cancer diagnosis, particularly in advanced disease where there are limited anticancer treatments available and a greater risk of morbidity and mortality.

Exelixis Literature Review

Exelixis reports conducting a search of the scientific literature, including abstracts from scientific/clinical meetings, reviews and research articles on wound healing complications reported for cabozantinib, Cometriq, Cabometyx and other VEGFR-targeted TKIs in the biomedical databases Embase, Medline and Pubmed. The sponsor identified 1128 publications

as of June 2, 2019 and reviewed this literature for relevant information on wound healing complications. Exelixis states 16 publications, including 7 small prospective or retrospective studies, had information relating to post-surgery dose interruptions and wound healing complications in patients receiving cabozantinib or other VEGF TKIs. Exelixis states these studies were small and the post-surgery treatment holds were variable and did not yield meaningful data sufficient to formulation a recommendation for cabozantinib.

Reviewer Assessment: This reviewer notes that there is a lack of consistency across available literature regarding the ideal time to restart TKI treatment after a surgical procedure. Due to limited information on post-surgical re-initiation, the decision to resume TKIs is typically based on clinician assessment of wound healing status. Although general recommendations in the literature are largely based on clinical studies of bevacizumab, which has a notably longer half-life, and there is no clear consensus regarding development of wound healing complications in patients specifically receiving cabozantinib, a general recommendation can be proposed based on wound healing physiology.

Successful wound healing depends upon angiogenesis, a prominent feature of the repair process. Studies examining VEGFR have shown that it plays a key role in several facets of the wound healing. According to literature (see references cited at the end of this document), angiogenesis starts and peaks during the proliferative phase of healing (approximately 3-10 days), when new capillaries are being formed, and their appearance is synonymous with granulation, the creation of a provisional matrix comprised of blood vessels, migrating fibroblasts and new collagen. It is during this period that VEGF inhibition may have the most deleterious effect. Based on review of preclinical and clinical data for multiple drug products with VEGF pathway antagonism, FDA has determined that the labeling for drug products with VEGF inhibition will include consistent instructions to withhold such a drug product for at least 2 weeks following surgery and until adequate wound healing.

Exelixis agreed with these proposed changes in a TCON with FDA on December 3, 2019.

4. Labeling changes

Agreed-Upon Labeling Changes:
The major changes to the “Highlights of PI” on the first page of the label are:

- Removal of boxed warning for “Perforations and Fistulas, and Hemorrhage”
- Addition of “Perforations and Fistulas” and “Hemorrhage” to the Warnings and Precautions section.
- Addition of “Diarrhea.”

The major changes to section 5 Warnings and Precautions are:

- Recommendation to withhold Cometriq for at least 3 weeks prior to elective surgery
- Recommendation to withhold Cometriq for at least 2 weeks after major surgery and until adequate wound healing.
- Addition of “Diarrhea”

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Additional changes were proposed by Exelixis and agreed upon by FDA in the following Warnings & Precautions sections:

- 5.1: Perforations and Fistulas
- 5.2: Hemorrhage
- 5.4: Hypertension and Hypertensive Crisis
- 5.6: Osteonecrosis of the Jaw

5. Recommended Regulatory Action

The clinical review team recommends approval of this labeling supplement as summarized in this review and included in the revised product label.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203756Orig1s008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

Application Number	NDA 208692; NDA 203756
Submission Date	7/15/2019; 7/31/2019
Submission Type	Labeling Supplement
Submission link (path)	\\cdsesub1\evsprod\nda203756\0097\ \\cdsesub1\evsprod\NDA208692\0102
Product Name	Cabozantinib
Route of Administration	P.O.
Proposed Indication(s)	Advanced Renal Cell Carcinoma; Hepatocellular Carcinoma
Sponsor	EXELIXIS INC
Related INDs/NDAs	N.A.
Primary Reviewer	Huiming Xia, PhD
Team Leader	Pengfei Song, PhD; Hong Zhao, PhD

I. Introduction

The purpose of this review is to evaluate the accuracy of the cabozantinib half-lives determined in prior submissions [tablet (NDA 208692) and capsule (NDA 203756)], to support the Labeling Supplements to update labeling regarding wound healing issue for VEGF inhibitors.

II. Background

Inconsistency in labeling on how wound healing is handled for VEGF inhibitors was discovered. For example, some VEGF Inhibitors such as, Avastin (BLA 125085, https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125085s331lbl.pdf) and Cometriq (NDA 203756, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203756s005lbl.pdf) contain boxed warnings related to wounds (perforations, fistulas, etc.) and others do not contain this boxed warning. Internal discussion was held on April 10, 2019 and September 11, 2019, with a decision that all drugs claiming anti-VEGF inhibition activity should state a duration of time for wound healing to hold the drug prior to surgery and the time to resume the drug postoperatively in the Warnings & Precautions section. Labeling update requests were sent to sponsors of VEGF Inhibitors proposing changes to the approved labeling to update the Warning and Precautions subsection (5.12): “Wound Healing” to provide a minimum duration of time (e.g., at least 28 days and until the wound is fully healed) after any major surgical procedure.

Cabozantinib is a tyrosine kinase inhibitor that inhibits activity of a variety of kinases including VEGFR-1, -2, -3. Cabozantinib has been developed both as capsule (COMETRIQ) and tablet (CABOMETYX) formulations.

1. Summary of regulatory history

   - Cabozantinib capsule (COMETRIQ) received FDA approval for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC) on 11/29/2012 (NDA 203756).
   - Cabozantinib tablet (CABOMETYX) received FDA approval for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy on 4/25/2016 (NDA 208692). A postmarketing commitment (No. 3063-1) was issued to '*combine all available pharmacokinetics (PK) data from different patient populations and healthy subjects in an integrated population PK model to evaluate the potential impact of tumor types on the PK of cabozantinib.*'(Source: NDA 208692 Approval letter: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/208692Orig1s000ltr.pdf)
   - Population PK analysis (Report No. XL184-308.PopPK.002) report was submitted to fulfil the aforementioned PMC (NDA 208962, SDN 64, 6/27/2016)

2. Difference in the statement of cabozantinib half-lives in COMETRIQ and CABOMETYX label

   - COMETRIQ (Capsules) (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203756s005lbl.pdf):

     The predicted effective half-life is approximately 55 hours and the clearance (CL/F) at steady-state is estimated to be 4.4 L/hr.

   - CABOMETYX (Tablets)

     (https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208692s003lbl.pdf)

     The predicted terminal half-life is approximately 99 hours and the clearance (CL/F) at steady-state is estimated to be 2.2 L/hr.

III. Clinical Pharmacology Evaluation

- Evaluation with intensive PK sampling and noncompartmental analysis (NCA)

  Study XL184-010 assessed bioequivalence (BE) between a tablet formulation (Test) and the capsule formulation (Reference) of cabozantinib.

  Study Design:

  - General Design: Phase 1, open-label, randomized, single-dose, comparative, 2-treatment, 2-way crossover, BE study
  - Population: a total of 77 healthy adult subjects with 72 subjects having evaluable PK data from both treatments.
  - Washout Period: minimum of 30 days.
  - PK Sampling: Serial blood samples for measurement of cabozantinib plasma concentrations were collected at following timepoints: prior to cabozantinib dosing and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 14, 24, 48, 72, 120,

168, 240, 288, 336, 408, and 504 hours post cabozantinib dosing in each study period.

- Bioanalysis: Plasma concentrations of cabozantinib were measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The lower limit of quantitation (LLOQ) for cabozantinib in plasma was 0.500 ng/mL.
- PK parameters Calculation: by employing a NCA approach using WinNonlin with plasma cabozantinib concentration-time data.

Key PK Results

The mean (CV%) half-life is estimated to be 112 (26%) hours with apparent clearance (CL/F) estimated to be 2.6 L/hr. The geometric LS means for AUC were similar (<10% difference) between tablet and capsule formulations and the 90% CIs around the ratio of LS means were within the BE limits of 80% -125%. The geometric LS mean Cmax value was 19% higher for the tablet formulation as compared to the capsule formulation.

- Evaluation with population PK Approach

  Population PK analysis (Report No. XL184-308.PopPK.002) was carried out to investigate the potential impact of tumor types on the PK of cabozantinib.

  Study Design:

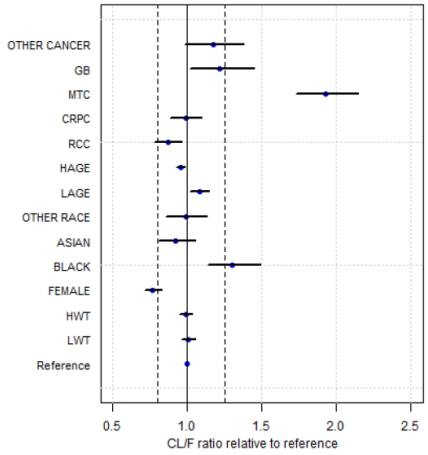
  - Clinical Studies Included in the Analysis

    A total of 9 studies with both capsule and tablet formulations in health subjects, patients with GB, patients with CRPC, patients with MTC and patients with RCC (Appendix 3) were included in the analysis.

  Key results:

  - Cabozantinib exposure was similar across healthy subject and patient populations except for patients with metastatic medullary thyroid cancer (MTC) who were predicted to have > 40% lower $C_{max,ss}$, > 50% lower $C_{min,ss}$, and > 90% increase in CL/F relative to healthy subjects (Figure 1).

Figure 1. Impact of Covariates on Steady State CL/F



- Other healthy subject and patient factors (demographic covariates) did not account for the exposure differences, and patient dropout was also not likely to be a key factor in MTC patients.

- Potential factors explaining the different half-lives and clearance estimated between patients with MTC and patients with RCC.

  In a publication by the applicant, several factors that may underlie the higher cabozantinib clearance observed in MTC patients were discussed. However, these factors appear not capable of fully explaining the shorter half-life and higher clearance in patients with MTC than other populations. The exact cause has yet to be identified.

  - Treatment-emergent hypocalcemia

    Advanced MTC patients who undergo thyroidectomy when the parathyroid glands are also partially or completely removed resulting in decreased plasma parathyroid hormone levels. Hypocalcemia may affect drug clearance indirectly via stimulation of active vitamin D metabolite 1,25 dihydroxyvitamin D3 (1,25(OH)2D3) synthesis, and subsequent induction of CYP3A4 by 1α,25(OH)2D3 [27, 28]. Since cabozantinib is metabolized by CYP3A4, hypocalcemia was considered as a potential contributing factor in reducing cabozantinib clearance in MTC patients. However, overall no evidence of altered calcium levels was noted in patients with MTC compared to other cancers to suggest that hypocalcemia was responsible for increased cabozantinib clearance in this population.

  - Differences in concomitant medication use, particularly administration of strong CYP3A4 inducers in MTC patients

    The cabozantinib is a substrate of CYP3A4 and also a substrate of efflux transporter MRP2. However, only 1.4% of patients (3 of 207 total) were reported to have used a concomitant strong CYP3A4 inducer in the MTC phase III study of cabozantinib and only 5.5% of MTC patients (12 of

219) administered cabozantinib were reported to have received MRP2 inducer (and moderate CYP3A4 inducer) dexamethasone.

- Estimates of CL/F values from MTC patients who tolerated a 140-mg daily cabozantinib dose may be higher than the overall study population if they reflect a sub-population that tolerates this higher dose at steady state based on a faster relative intrinsic clearance. This scenario is unlikely considering 79% of the patients in the MTC popPK analysis contributed PK samples on both days 1 and 29.
- Cabozantinib plasma clearance may be higher if oral bioavailability decreased with increasing dose.

  This factor is unlikely as no decrease in cabozantinib oral bioavailability was evident in a cross-study analysis indicating generally dose-linear PK for tablet and capsule formulations over a broad dose range (20-140 mg).
- Less detailed PK sampling of terminal phase in MTC patients

  A more detailed PK sampling of the terminal elimination phase was included in the RCC popPK analysis than in the MTC popPK analysis. However, magnitude of most demographic and population-specific covariate effects on cabozantinib PK was small, except for MTC patient population who had a substantially larger estimated cabozantinib CL/F.

IV. Conclusion:

Based on the evaluation above, the available data and analyses confirm that the apparent clearance of cabozantinib in the MTC cancer population is >90% higher than the rest studied patient population and healthy subjects. The exact cause for this difference remains unknown. The half-lives for both capsule and tablet were estimated to be 112 hours in healthy subjects. Given the increased apparent clearance in MTC cancer patients and similar apparent clearance in the rest of cancer patients based on integrated population PK analysis, and determined half-live of 112 hours in healthy subjects in BA/BE study, the estimated half-life is 59 hours in MTC patients and 112 hours for the rest of patients with other cancer types.

This conclusion is consistent with the original labeling statement. MTC was the first approved indication for COMETRIQ (capsules) and the label stated half-life was 55 hours. RCC was the first approved indication for CABOMETYX (tablets) and the label stated half-life was 99 hours. The exact cause of higher clearance in MTC population has yet to be identified.

OCP review team has the following labeling recommendations for the wound healing issue for cabozantinib:

Do not administer COMETRIQ or CABOMETYX for 12 days (or two weeks) following major surgery and until surgical wound is fully healed in patients with metastatic medullary thyroid cancer (MTC).

Do not administer COMETRIQ or CABOMETYX for 21 days (or three weeks) following major surgery and until surgical wound is fully healed in patients with cancer types other than MTC.

V. Action:

The above recommendation is to be conveyed to the review team of two labeling supplements. No further action is indication.

Appendix 1: Individual PK parameters for Half-life and Clearance

Subject Number	Sequence	Period	Group	Parameters: kel (1/hr)	t1/2 (hr)	CL/F (L/hr)	Vz/F (L)
(b) (6)	BA	1	1	0.00580	120	2.70	466
	AB	2	1	0.00560	124	2.32	414
	AB	2	1	0.00680	101	2.80	409
	BA	1	1	0.00450	155	3.38	756
	BA	1	1	0.00870	80.0	2.26	261
	AB	2	1	0.00660	105	4.86	735
	BA	1	1	0.00630	109	2.61	412
	AB	2	1	0.00630	111	3.73	595
	BA	1	1	0.00970	71.5	3.02	311
	AB	2	1	0.00510	136	2.48	486
	AB	2	1	0.00760	91.3	2.89	380
	BA	1	1	0.00700	98.7	2.48	353
	AB	2	1	0.00860	80.3	4.81	558
	BA	1	1	0.00610	113	3.08	502
	BA	1	1	0.00780	88.9	2.65	340
	AB	2	1	0.00570	121	1.61	281
	AB	2	1	0.00460	150	0.796	172
	BA	1	1	0.00630	109	2.27	358
	AB	2	1	0.00930	74.2	3.71	397
	BA	1	1	0.0102	67.9	2.68	263
	BA	1	1	0.00820	84.4	3.15	384
	AB	2	1	0.00460	151	1.89	411
	BA	1	1	0.00540	128	1.47	271
	AB	2	1	0.00830	83.7	2.82	341
	BA	1	1	0.00680	101	1.83	268
	AB	2	1	0.00590	117	1.77	297
	AB	2	1	0.00730	94.6	2.61	357
	BA	1	1	0.00640	109	2.40	376

Subject Number	Sequence	Period	Group	Parameters: kel (1/hr)	t1/2 (hr)	CL/F (L/hr)	Vz/F (L)
(b) (6)	AB	2	1	0.00680	102	2.58	380
	BA	1	1	0.00780	88.6	2.94	376
	AB	2	1	0.00550	125	3.80	687
	B	1	1	0.00750	91.9	2.32	308
	BA	1	1	0.00490	142	2.30	470
	AB	2	1	0.00500	138	2.94	584
	AB	2	1	0.00490	140	2.04	412
	BA	1	1	0.00790	87.5	1.81	228
	AB	2	1	0.00820	84.3	4.42	537
	BA	1	1	0.00610	114	2.40	393
	AB	2	2	0.00660	105	2.42	366
	BA	1	2	0.00980	70.7	2.31	235
	AB	2	2	0.00440	158	2.79	637
	BA	1	2	0.00640	108	2.51	391
	BA	1	2	0.00370	186	1.81	487
	BA	1	2	0.00530	130	1.86	349
	AB	2	2	0.0120	57.7	3.02	251
	BA	1	2	0.00620	111	2.33	374
	AB	2	2	0.00530	132	1.30	247
	BA	1	2	0.00630	109	3.59	567
	AB	2	2	0.00560	123	3.37	598
	AB	2	2	0.00460	150	2.90	627
	BA	1	2	0.00680	101	2.74	402
	AB	2	2	0.00790	87.2	1.57	197
	BA	1	2	0.00520	135	2.21	429
	AB	2	2	0.00680	101	5.24	767
	BA	1	2	0.00420	166	1.51	361

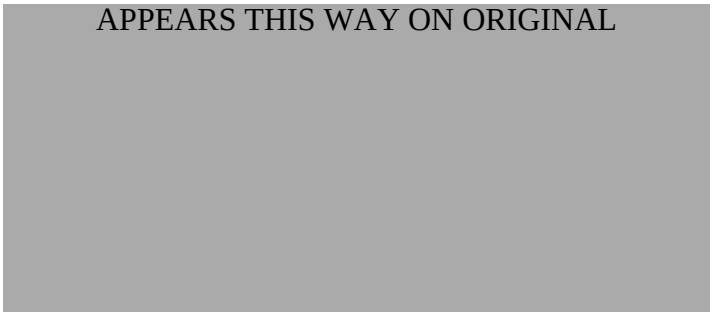
Subject Number	Sequence	Period	Group	Parameters: kel (1/hr)	t1/2 (hr)	CL/F (L/hr)	Vz/F (L)
(b) (6)	AB	2	2	0.00430	161	4.18	971
	BA	1	2	0.00690	101	3.30	479
	BA	1	2	0.00470	147	3.56	757
	AB	2	2	0.00450	155	2.13	475
	BA	1	2	0.00720	95.8	3.40	470
	AB	2	2	0.00570	122	3.38	593
	BA	1	2	0.00870	79.9	2.07	238
	BA	1	2	0.00410	171	1.46	360
	AB	2	2	0.00790	87.7	3.08	389
	BA	1	2	0.00790	87.5	2.39	301
	AB	2	2	0.00400	172	1.72	427
	AB	2	2	0.00810	85.5	3.26	402
	BA	1	2	0.00890	77.7	2.42	271
	B	1	2	0.00720	96.8	2.70	377
	AB	2	2	0.00580	119	2.66	457
	AB	2	2	0.00600	115	3.63	600
	BA	1	2	0.00640	108	1.44	224
	AB	2	2	0.00550	126	4.24	770
	BA	1	2	0.00820	84.3	2.62	319
	AB	2	1	0.00820	84.3	2.41	293
N				72	72	72	72
Mean				0.00657	112	2.69	426
SD				0.00169	28.7	0.872	159
CV (%)				26	26	32	37
Geo. Mean				.	.	.	.
Minimum				0.00370	57.7	0.796	172
Median				0.00635	109	2.61	392
Maximum				0.0120	186	5.24	971

Appendix 2: Individual PK parameters for Overall Bioavailability

Parameter	Geometric LS Means: Treatment A (N=72)	Geometric LS Means: Treatment B (N=72)	Geometric Mean Ratio (%) (Test/Reference)	Confidence Intervals (90% Confidence)	P-Values	Intra-subject %CV
AUC0-inf (ng*hr/mL)	59437.04	54913.22	108.24	100.38 - 116.71	0.0842	27.57
AUC0-t (ng*hr/mL)	56271.18	51980.35	108.25	100.40 - 116.73	0.0837	27.58
Cmax (ng/mL)	601.580	506.817	118.70	107.02 - 131.65	0.0074	38.54

Appendix 3: Studies included in the population PK Analysis

Study No.	Design	Subject Type	Nominal Doses	Planned PK Sampling
XL184-001	Phase 1, non-randomized, open-label, dose-finding, FIH study of cabozantinib (XL184) in subjects with advanced malignancies	Cancer patients with mixed malignancies	175 or 250 mg (salt form) capsules (140 or 200 mg free base equivalent [FBE])	Day1 and 19: pre-dose, 30 minutes and 1, 2, 4, 8, and 24 hours post-dose; Day5: predose and 4 hours post dose; Day15 and 29: predose
XL184-010	Phase 1 two-way cross-over pharmacokinetic studies to compare BE of tablet and capsule formulations in healthy subjects	Healthy volunteers	140 mg FBE, single dose	Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 24 48, 72, 120, 168, 240, 288, 336, 408, and 504 hour each period
XL184-020	Phase 1 pharmacokinetic study of cabozantinib (XL184) tablet formulation in healthy adult subjects	Healthy volunteers	20, 40, 60 mg FBE, single dose	Pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 14, 24, 48, 72, 120, 168, 240, 288, 336, 408, and 504 hours post-dose
XL184-201	Phase 2 multi-center, open-label, single-agent cabozantinib (XL184), non-comparator study in subjects with recurrent or progressive glioblastoma multiforme (GB)	Cancer patients with GB	Cohort A: 175 mg salt form (140 mg FBE) qd	Every 28 days as a cycle Cycle 1: pre-dose and 4 hrs post-dose on C1D1 (day 1) and C1D15 (day 15) Cycle 2: pre-dose and 4 hrs post-dose on C2D1 (day 29) and C2D15 (day 43) Cycle 3 and beyond: pre-dose on Day 1 (± 4 Days)
XL184-203	Phase 2, randomized discontinuation study of cabozantinib (XL184) in subjects with advanced solid tumors (only subjects with castration resistant prostate cancer [CRPC] included in analysis)	Cancer patients with CRPC	RDT cohort: 100 mg FBE qd; NRE cohort: 40 mg or 100 mg FBE qd	RDT: predose at the end of "even" weeks after week 12 lead-in period (e.g., 18, 24 et al.), or early termination or adverse event; NRE: pre-dose on W1D1, pre-dose on End of Week 3, End of Week 6, End of Week 12, End of Week 18, and End of Week 24, unscheduled, early termination or adverse event.
XL184-301	Phase 3, randomized, double-blinded, parallel-group, placebo-controlled study of cabozantinib (XL184) in subjects with unresectable, locally advanced, or metastatic medullary thyroid cancer (MTC)	Cancer patients with MTC	175 mg salt form (140 mg FBE) qd	C1D1 (Day 1): pre-dose and 2, 4, and 6 hours post-dose C2D1 (Day 29): pre-dose and 2, 4, and 6 hours post-dose
XL184-306	Phase 3, randomized, double-blind, controlled trial of cabozantinib (XL184) vs. mitoxantrone plus prednisone in men with previously treated symptomatic CRPC	Cancer patients with CRPC	100 mg FBE qd	Week 1 Day 1, Week 4 Day 1, Week 7 Day 1, and Week 13 Day 1
XL184-307	Phase 3, randomized, double-blind, controlled study of cabozantinib (XL184) vs. prednisone in metastatic castration-resistant prostate cancer patients who have received prior docetaxel and prior abiraterone or MDV3100	Cancer patients with CRPC	60 mg FBE qd	End of Week 3 and end of Week 12
XL184-308	Phase 3, randomized, controlled study of cabozantinib (XL184) vs everolimus in subjects with metastatic renal cell carcinoma (RCC) that has progressed after prior VEGFR tyrosine kinase inhibitor therapy	Cancer patients with RCC	60 mg FBE cabozantinib tablets po qd	~8 or more hours after the prior evening dose on the W5D1 (Day 29) and W9D1 (Day 57) visits



This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HUIMING XIA
11/15/2019 10:28:01 AM

PENGFEI SONG
11/15/2019 11:15:50 AM

HONG ZHAO
11/15/2019 11:20:29 AM
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203756Orig1s008

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

NDA 203756//S-008

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Exelixis, Inc.
Attention: Lisa Sauer
Vice President, Regulatory Affairs and Quality Assurance
1851 Harbor Bay Parkway
Alameda, CA 94502

Dear Ms. Sauer:

We have received your supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 203756

SUPPLEMENT NUMBER: 008

PRODUCT NAME: Cometriq (cabozantinib) capsules, 20 mg and 80 mg

DATE OF SUBMISSION: July 31, 2019

DATE OF RECEIPT: July 31, 2019

This supplemental application, submitted in response to our May 20, 2019, Supplement Request communication, proposes to update the package insert to:

- Remove the Boxed Warning
- Include a new Warnings and Precautions subsection for “Diarrhea” that contains the same information as described in the FDA-approved labeling for Cabometyx.

Additional proposed revisions include updating container closure labels to include minor editorial changes.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 29, 2019, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be January 31, 2020.

If you have questions, call Gina Davis, Senior Regulatory Health Project Manager at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Melanie Pierce
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MELANIE B PIERCE
09/23/2019 02:38:44 PM