HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OMCAZIO safely and effectively. See full prescribing information for OMCAZIO.

OMCAZIO™ (cabozantinib) capsules, for oral use
Initial U.S. Approval: 2012

WARNING: RISK OF SERIOUS ADVERSE REACTIONS OR REDUCED EFFECTIVENESS DUE TO MEDICATION ERRORS
See full prescribing information for complete boxed warning.

OMCAZIO is not substitutable on a mg-to-mg basis with other cabozantinib products. Inappropriate substitution or incorrect conversion of OMCAZIO capsules for another cabozantinib product can increase the risk of serious adverse reactions. Confirm that the intended cabozantinib product at the intended dosage and strength is being prescribed and dispensed. (2.1, 2.3, 5.1)

----------INDICATIONS AND USAGE----------
OMCAZIO is a kinase inhibitor indicated for the treatment of
- patients with advanced renal cell carcinoma (RCC). (1.1)
- patients with advanced renal cell carcinoma, as a first-line treatment in combination with nivolumab. (1.1)
- patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. (1.2)
- adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated extra-pancreatic neuroendocrine tumors (epNET). (1.3)

----------DOSAGE AND ADMINISTRATION----------
- OMCAZIO is NOT substitutable on a mg-to-mg basis with other cabozantinib products. (2.1)
- Stop treatment with OMCAZIO at least 3 weeks prior to scheduled surgery, including dental surgery. (2.2)
- OMCAZIO may be administered with or without food. (2.2)
- Recommended Dose:
  - RCC: 34.5 mg orally once daily as a single agent. (2.2)
  - RCC: 23 mg orally once daily in combination with nivolumab or nivolumab and hyaluronidase-nvhy. (2.2)
  - HCC: 34.5 mg orally, once daily. (2.2)
  - epNET:
    - Adult patients and pediatric patients 12 years of age and older with bodyweight greater than or equal to 40 kg: 34.5 mg orally once daily. (2.2)
    - Pediatric patients 12 years of age and older with bodyweight less than 40 kg: 23 mg orally once daily. (2.2)
- See Full Prescribing Information for dosage modifications of OMCAZIO due to adverse reactions. (2.4)
- Hepatic Impairment: Reduce the OMCAZIO dosage for patients with moderate hepatic impairment. Avoid in patients with severe hepatic impairment. (2.6, 8.6)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 34.5 mg, 23 mg, 11.5 mg. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Risk of Serious Adverse Reactions or Reduced Effectiveness Due to Medication Errors: Cabozantinib is available in multiple dosage forms and strengths. OMCAZIO is not substitutable on a mg-to-mg basis with other cabozantinib products. Confirm that the intended cabozantinib product is being prescribed and dispensed. (5.1)
- Hemorrhage: Do not administer OMCAZIO if recent history of hemorrhage. (5.2)
- Perforations and Fistulas: Monitor for symptoms. Discontinue OMCAZIO for Grade 4 fistula or perforation. (5.3)
- Thromboembolic Events: Discontinue OMCAZIO for myocardial infarction or serious venous or arterial thromboembolic events. (5.4)
- Hypertension and Hypertensive Crisis: Monitor blood pressure regularly. Interrupt for hypertension that is not adequately controlled with anti-hypertensive therapy. Discontinue OMCAZIO for hypertensive crisis or severe hypertension that cannot be controlled with anti-hypertensive therapy. (5.5)
- Cardiac Failure: Monitor patients for signs and symptoms of cardiac failure throughout treatment. (5.6)
- Diarrhea: May be severe. Interrupt OMCAZIO until diarrhea resolves or decreases to ≤Grade 1, resume at reduced dose. Recommend standard antidiarrheal treatments. (5.7)
- Palmar-Plantar Erythrodysesthesia (PPE): Interrupt OMCAZIO treatment until PPE resolves or decreases to Grade 1. (5.8)
- Hepatotoxicity: When used in combination with nivolumab, higher frequencies of Grade 3 and 4 ALT and AST elevation may occur than with OMCAZIO alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider withholding OMCAZIO and/or nivolumab, initiating corticosteroid therapy, and/or permanently discontinuing the combination for severe or life- threatening hepatotoxicity. (5.9)
- Adrenal Insufficiency: When used in combination with nivolumab, primary or secondary adrenal insufficiency may occur. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold OMCAZIO and/or nivolumab depending on severity. (5.10)
- Proteinuria: Monitor urine protein. Interrupt OMCAZIO until proteinuria resolves to ≤Grade 1, resume OMCAZIO at a reduced dose. Discontinue for nephrotic syndrome. (5.11)
- Osteonecrosis of the jaw (ONJ): Withhold OMCAZIO for at least 3 weeks prior to invasive dental procedures and for development of ONJ. (5.12)
- Impaired Wound Healing: Withhold OMCAZIO for at least 3 weeks before elective surgery. Do not administer for at least 2 weeks following major surgery and adequate wound healing. The safety of resumption of OMCAZIO after resolution of wound healing complications has not been established. (5.13)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Discontinue OMCAZIO. (5.14)
- Thyroid Dysfunction: Monitor thyroid function before and during treatment with OMCAZIO. (5.15)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.16, 8.1, 8.3)

----------ADVERSE REACTIONS----------
The most common (≥20%) adverse reactions are:
- as a single agent: diarrhea, fatigue, PPE, decreased appetite, hypertension, nausea, vomiting, decreased weight, constipation. (6.1)
- in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Handa Oncology, LLC. at 1-844-204-8384 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong CYP3A inhibitors: Reduce the OMCAZIO dosage if coadministration cannot be avoided. (2.5, 7.1)
- Strong or moderate CYP3A inducers: Increase the OMCAZIO dosage if coadministration cannot be avoided. (2.5, 7.1)

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Advise not to breastfeed. (8.2)
- Pediatric Use: Monitor open growth plates in adolescent patients. Consider interrupting or discontinuing OMCAZIO if abnormalities occur. (8.4)

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

Revised: 09/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Renal Cell Carcinoma
1.2 Hepatocellular Carcinoma
1.3 Extra-pancreatic Neuroendocrine Tumors
2 DOSAGE AND ADMINISTRATION
2.1 Important Dosage Information
2.2 Recommended Dosage
2.3 Conversion Instructions
2.4 Dosage Modifications for Adverse Reactions
2.5 Dosage Modifications for Drug Interactions
2.6 Dosage Modifications for Patients with Moderate Hepatic Impairment
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Risk of Serious Adverse Reactions or Reduced Effectiveness Due to Medication Errors
5.2 Hemorrhage
5.3 Perforations and Fistulas
5.4 Thromboembolic Events
5.5 Hypertension and Hypertensive Crisis
5.6 Cardiac Failure
5.7 Diarrhea
5.8 Palmar-Plantar Erythrodysesthesia
5.9 Hepatotoxicity
5.10 Adrenal Insufficiency
5.11 Proteinuria
5.12 Osteonecrosis of the Jaw
5.13 Impaired Wound Healing
5.14 Reversible Posterior Leukoencephalopathy Syndrome
5.15 Thyroid Dysfunction
5.16 Embryo-Fetal Toxicity
6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Effects of Other Drugs on OMCAZIO
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Hepatic Impairment
8.7 Renal Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Renal Cell Carcinoma
14.2 Hepatocellular Carcinoma
14.3 Extra-pancreatic Neuroendocrine Tumors
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS ADVERSE REACTIONS OR REDUCED EFFECTIVENESS DUE TO MEDICATION ERRORS

OMCAZIO is not substitutable on a mg-to-mg basis with other cabozantinib products. Inappropriate substitution or incorrect conversion of OMCAZIO capsules for another cabozantinib product can increase the risk of serious adverse reactions. Confirm that the intended cabozantinib product at the intended dosage and strength is being prescribed and dispensed. (2.1, 2.3, 5.1)

1. INDICATIONS AND USAGE

1.1 Renal Cell Carcinoma

OMCAZIO is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC).

OMCAZIO, in combination with nivolumab, is indicated for the first-line treatment of adult patients with advanced RCC.

1.2 Hepatocellular Carcinoma

OMCAZIO is indicated for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

1.3 Extra-pancreatic Neuroendocrine Tumors

OMCAZIO is indicated for the treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated extra-pancreatic neuroendocrine tumors (epNET).

2. DOSAGE AND ADMINISTRATION

2.1 Important Dosage Information

- Cabozantinib is available in multiple dosage forms and strengths. Recommended dosages depend on the specific cabozantinib product prescribed.
- OMCAZIO is **NOT** substitutable on a mg-to-mg basis with other cabozantinib products *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.
- To avoid medication errors, including overdosage or underdosage, prescribe the recommended dosage specific for OMCAZIO *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.

2.2 Recommended Dosage

- OMCAZIO may be taken with or without food *[see Clinical Pharmacology (12.3)]*.
- Swallow OMCAZIO capsules whole. Do not crush, chew, or open OMCAZIO capsules.
- If a dose of OMCAZIO is missed, take the missed dose as soon as possible. If a dose is missed by more than 12 hours, skip the missed dose and take the next dose at the scheduled time. Do not take 2 doses

at the same time to make up for the missed dose.

- Stop OMCAZIO at least 3 weeks prior to scheduled surgery, including dental surgery to reduce the risk of hemorrhage. Do not administer OMCAZIO for at least 2 weeks after major surgery and until adequate wound healing *[see Warnings and Precautions (5.2, 5.12, 5.13)]*.

The recommended dosages of OMCAZIO are presented in Table 1.

Table 1. Recommended Dosage for OMCAZIO

Indication	Recommended Dosage	Duration
Renal Cell Carcinoma	Single Agent 34.5 mg orally once daily	Until disease progression or unacceptable toxicity
	Combination Therapy 23 mg orally once daily in combination with nivolumab or nivolumab and hyaluronidase-nvhy[1]	Until disease progression or unacceptable toxicity
Hepatocellular Carcinoma	34.5 mg orally once daily	Until disease progression or unacceptable toxicity
Extra-pancreatic Neuroendocrine Tumors	Adult Patients and Pediatric Patients 12 years of age and older with bodyweight greater than or equal to 40 kg 34.5 mg orally once daily Pediatric patients 12 years of age and older with bodyweight less than 40 kg 23 mg orally once daily	Until disease progression or unacceptable toxicity

[1] Refer to the Prescribing Information for nivolumab or nivolumab and hyaluronidase-nvhy for the recommended dosage information.

2.3 Conversion Instructions

If converting from CABOMETYX, discontinue CABOMETYX, and use Table 2 to determine OMCAZIO dosage based on dosage equivalence.

Table 2. Recommendations for Conversion Between OMCAZIO and CABOMETYX

CABOMETYX tablets dosage	OMCAZIO capsules dosage
60 mg once daily	34.5 mg once daily
40 mg once daily	23 mg once daily
20 mg once daily	11.5 mg once daily

2.4 Dosage Modifications for Adverse Reactions

Withhold OMCAZIO for:

- Intolerable Grade 2 adverse reactions
- Grade 3 or 4 adverse reactions
- Osteonecrosis of the jaw

Upon resolution/improvement (i.e., return to baseline or resolution to Grade 1) of an adverse reaction, reduce the dose as follows:

The recommended dosage reduction levels for OMCAZIO for adverse reactions are listed in Table 3.

Table 3. Recommended Dosage Reductions for OMCAZIO for Adverse Reactions

Recommended Dosage	First Dosage Reduction To	Second Dosage Reduction To
OMCAZIO 34.5 mg daily in adult and pediatric patients 12 years of age and older with bodyweight greater than or equal to 40 kg	23 mg daily	11.5 mg daily*
OMCAZIO 23 mg daily in pediatric patients 12 years of age and older with bodyweight less than 40 kg	11.5 mg daily	11.5 mg every other day*
OMCAZIO 23 mg daily in combination with nivolumab or nivolumab and hyaluronidase-nvhy	11.5 mg daily	11.5 mg every other day*

* If previously receiving lowest dose, resume at same dose. If lowest dose not tolerated, permanently discontinue OMCAZIO.

The recommended dosage modifications for adverse reactions for OMCAZIO and for OMCAZIO administered in combination with nivolumab are described in Tables 4 and 5, respectively.

Table 4. Recommended Dosage Modifications for OMCAZIO Adverse Reactions

Adverse Reaction	Severity*	OMCAZIO Dosage Modification
Hemorrhage *[see Warnings and Precautions (5.2)]*	Grade 3 or 4	• Permanently discontinue OMCAZIO
Perforations and Fistulas *[see Warnings and Precautions (5.3)]*	Any grade gastrointestinal perforation or Grade 4 fistula	• Permanently discontinue OMCAZIO

Thromboembolic Events *[see Warnings and Precautions (5.4)]*	Any grade acute myocardial infarction or Grade 2 or higher cerebral infarction or Grade 3 or 4 arterial thromboembolic events or Grade 4 venous thromboembolic events	• Permanently discontinue OMCAZIO
Hypertension and Hypertensive Crisis *[see Warnings and Precautions (5.5)]*	Grade 3	• Withhold OMCAZIO until hypertension is adequately controlled to ≤Grade 2 • Resume at reduced dose • Permanently discontinue OMCAZIO for hypertension that cannot be controlled
	Grade 4	• Permanently discontinue OMCAZIO
Diarrhea *[see Warnings and Precautions (5.7)]*	Grade 2, Grade 3, or Grade 4	• Withhold OMCAZIO until ≤Grade 1 • Resume at reduced dose
Palmar-Plantar Erythrodysesthesia *[see Warnings and Precautions (5.8)]*	Intolerable Grade 2 or Grade 3	• Withhold OMCAZIO until ≤Grade 1 • Resume at reduced dose
Proteinuria *[see Warnings and Precautions (5.11)]*	Grade 2 or 3	• Withhold OMCAZIO until improvement to ≤Grade 1 proteinuria • Resume at a reduced dose • Permanently discontinue OMCAZIO for nephrotic syndrome
Osteonecrosis of the jaw (ONJ) *[see Warnings and Precautions (5.12)]*	Any grade	• Withhold OMCAZIO for development of ONJ until complete resolution • Resume at reduced dose
Reversible Posterior Leukoencephalopathy Syndrome *[see Warnings and Precautions (5.14)]*	Any grade	• Permanently discontinue OMCAZIO

Other Adverse Reactions *[see Adverse Reactions (6.1)]*	Intolerable Grade 2, or Grade 3, or Grade 4	• Withhold OMCAZIO until improvement to baseline or ≤Grade 1 • Resume at reduced dose

* Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0)

Table 5. Recommended Specific Dosage Modifications for Hepatic Adverse Reactions for OMCAZIO in Combination with Nivolumab or Nivolumab and Hyaluronidase-nvhy [a]

Adverse Reaction	Severity	Dosage Modification
Hepatotoxicity *[see Warnings and Precautions (5.9)]*	ALT or AST >3 times ULN but ≤10 times ULN with concurrent total bilirubin <2 times ULN	Withhold[b] both OMCAZIO and nivolumab or nivolumab and hyaluronidase-nvhy until adverse reactions recover[c] to Grades 0 or 1
	ALT or AST >10 times ULN or >3 times ULN with concurrent total bilirubin ≥2 times ULN	Permanently discontinue[b] both OMCAZIO and nivolumab or nivolumab and hyaluronidase-nvhy

[a] When administering OMCAZIO in combination with nivolumab or nivolumab and hyaluronidase-nvhy for the treatment of advanced RCC, refer to their respective Prescribing Information for dosage modifications for adverse reactions.

[b] Consider corticosteroid therapy for hepatic adverse reactions if OMCAZIO is withheld or discontinued when administered in combination with nivolumab or nivolumab and hyaluronidase-nvhy

[c] After recovery, rechallenge with one or both of OMCAZIO and nivolumab or nivolumab and hyaluronidase-nvhy may be considered. If rechallenging with nivolumab or nivolumab and hyaluronidase-nvhy with or without OMCAZIO, refer to their respective Prescribing Information.

2.5 Dosage Modifications for Drug Interactions

Strong CYP3A Inhibitors

Avoid coadministration of strong CYP3A inhibitors with OMCAZIO. If coadministration of a strong CYP3A inhibitor cannot be avoided, reduce the OMCAZIO dose as recommended in Table 6. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume OMCAZIO at the dosage taken prior to initiating the CYP3A inhibitor *[see Drug Interactions (7.1)]*.

Table 6. Recommended OMCAZIO Dose Modification for Coadministration of Strong CYP3A Inhibitors

Current OMCAZIO Dosage	OMCAZIO Dosage Modification
34.5 mg daily	23 mg daily
23 mg daily	11.5 mg daily
11.5 mg daily	11.5 mg every other day

Strong and Moderate CYP3A Inducers

Avoid coadministration of strong and moderate CYP3A inducers with OMCAZIO. If coadministration of a strong or moderate CYP3A inducer cannot be avoided, increase the OMCAZIO dose as recommended in Table 7. After the inducer has been discontinued for 2 to 3 days, resume OMCAZIO at the dosage taken

prior to initiating the CYP3A inducer *[see Drug Interactions (7.1)]*. Do not exceed a dosage of 46 mg daily.

Table 7. Recommended OMCAZIO Dosage Modification for Coadministration of Strong and Moderate CYP3A Inducers

Current OMCAZIO Dosage	OMCAZIO Dosage Modification
34.5 mg daily	46 mg daily
23 mg daily	34.5 mg daily
11.5 mg daily	23 mg daily

2.6 Dosage Modifications for Patients with Moderate Hepatic Impairment

The recommended dosage of OMCAZIO for patients with moderate hepatic impairment (Child-Pugh B) is 23 mg daily as a single agent in adults and pediatric patients 12 years of age and older with bodyweight greater than or equal to 40 kg or 11.5 mg daily in combination with nivolumab or as a single agent in pediatric patients 12 years of age and older with bodyweight less than 40 kg *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Capsules:

- 34.5 mg: Opaque white hard gelatin capsules with black imprint “CZB 34.5” on capsule body.
- 23 mg: Opaque blue cap and opaque white body, hard gelatin capsules with a black imprint “CZB 23” on capsule body.
- 11.5 mg: Opaque blue hard gelatin capsules with a black imprint “CZB 11.5” on capsule body.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Adverse Reactions or Reduced Effectiveness Due to Medication Errors

Cabozantinib is available in multiple dosage forms and strengths. The recommended dosage depends on the specific cabozantinib product prescribed. OMCAZIO is not substitutable on a mg-to-mg basis with other cabozantinib products *[see Dosage and Administration (2.1, 2.2, 2.3)]*. Inappropriate substitution or incorrect conversion of OMCAZIO capsules for another cabozantinib product can:

- Increase the risk of serious adverse reactions OR
- Reduce its effectiveness.

Confirm that the intended cabozantinib product at the intended dosage and strength is being prescribed and dispensed.

5.2 Hemorrhage

OMCAZIO can cause severe and fatal hemorrhages.

Do not administer OMCAZIO to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

The incidence of Grade 3 to 5 hemorrhagic events was 5% in cabozantinib-treated patients in RCC and HCC studies *[see Adverse Reactions (6.1)]*.

Withhold OMCAZIO for 3 weeks prior to scheduled surgery, including dental surgery to reduce the risk of hemorrhage. Permanently discontinue OMCAZIO for Grade 3 or 4 hemorrhage and prior to surgery as recommended *[see Dosage and Administration (2.4), Warnings and Precautions (5.12, 5.13)]*.

5.3 Perforations and Fistulas

OMCAZIO can cause gastrointestinal (GI) perforations and fistulas.

Fistulas, including fatal cases, occurred in 1% of cabozantinib-treated patients *[see Adverse Reactions (6.1)]*. GI perforations, including fatal cases, occurred in 1% of cabozantinib-treated patients.

Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Permanently discontinue OMCAZIO in patients who experience a Grade 4 fistula or a GI perforation *[see Dosage and Administration (2.4)]*.

5.4 Thromboembolic Events

OMCAZIO can cause arterial or venous thromboembolic events.

Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism occurred in 2% of cabozantinib-treated patients. Fatal thromboembolic events occurred in cabozantinib-treated patients *[see Adverse Reactions (6.1)]*.

Permanently discontinue OMCAZIO in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention *[see Dosage and Administration (2.4)]*.

5.5 Hypertension and Hypertensive Crisis

OMCAZIO can cause hypertension, including hypertensive crisis *[see Adverse Reactions (6.1)]*.

Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of cabozantinib-treated patients. In patients with epNET in CABINET (n=132) *[see Clinical Studies (14.3)]*, hypertension was reported in 64% (27% Grade 3-4) of cabozantinib-treated patients.

Do not initiate OMCAZIO in patients with uncontrolled hypertension. Monitor blood pressure regularly during OMCAZIO treatment. Withhold OMCAZIO for hypertension that is not adequately controlled with medical management; when controlled, resume OMCAZIO at a reduced dose. Permanently discontinue OMCAZIO for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis *[see Dosage and Administration (2.4)]*.

5.6 Cardiac Failure

OMCAZIO can cause severe and fatal cardiac failure [see *Adverse Reactions (6.1)*].

Cardiac failure occurred in 0.5% of patients treated with cabozantinib as a single agent, including fatal cardiac failure in 0.1% of patients. Median time to onset of cardiac failure was 73 days (range: 44 days to 159 days).

Consider baseline and periodic evaluations of left ventricular ejection fraction. Monitor for signs and symptoms of cardiovascular events. Withhold and resume at a reduced dose upon recovery or permanently discontinue OMCAZIO depending on the severity [see *Dosage and Administration (2.4)*].

5.7 Diarrhea

OMCAZIO can cause diarrhea.

Diarrhea occurred in 62% of patients treated with cabozantinib. Grade 3 diarrhea occurred in 10% of patients treated with cabozantinib *[see Adverse Reactions (6.1)]*.

Monitor and manage patients using antidiarrheals as indicated. Withhold OMCAZIO until improvement to ≤Grade 1, resume OMCAZIO at a reduced dose *[see Dosage and Administration (2.4)]*.

5.8 Palmar-Plantar Erythrodysesthesia

OMCAZIO can cause palmar-plantar erythrodysesthesia (PPE).

PPE occurred in 45% of patients treated with cabozantinib *[see Adverse Reactions (6.1)]*. Grade 3 PPE occurred in 13% of patients treated with cabozantinib.

Withhold OMCAZIO until improvement to Grade 1 and resume OMCAZIO at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE *[see Dosage and Administration (2.4)]*.

5.9 Hepatotoxicity

OMCAZIO in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to cabozantinib alone.

Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt OMCAZIO and nivolumab and consider administering corticosteroids *[see Dosage and Administration (2.4)]*.

With the combination of cabozantinib and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients *[see Adverse Reactions (6.1)]*. ALT or AST >3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either cabozantinib (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving cabozantinib, 2 patients receiving nivolumab, and 7 patients receiving both cabozantinib and nivolumab.

Withhold and then resume OMCAZIO at a reduced dose based on severity *[see Dosage and Administration (2.4)]*.

5.10 Adrenal Insufficiency

OMCAZIO in combination with nivolumab can cause primary or secondary adrenal insufficiency.

Adrenal insufficiency occurred in 4.7% (15/320) of patients treated with the combination of cabozantinib and nivolumab including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions *[see Adverse Reactions (6.1)]*. Adrenal insufficiency led to permanent discontinuation of cabozantinib and nivolumab in 0.9% and withholding of cabozantinib and nivolumab in 2.8% of patients with renal cell carcinoma.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom cabozantinib with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold OMCAZIO and/or nivolumab and resume OMCAZIO at a reduced dose depending on severity *[see Dosage and Administration (2.4)]*.

5.11 Proteinuria

OMCAZIO can cause proteinuria.

Proteinuria was observed in 8% of patients receiving cabozantinib *[see Adverse Reactions (6.1)]*.

Monitor urine protein regularly during OMCAZIO treatment. For Grade 2 or 3 proteinuria, withhold OMCAZIO until improvement to ≤Grade 1 proteinuria, resume OMCAZIO at a reduced dose. Permanently discontinue OMCAZIO in patients who develop nephrotic syndrome *[see Dosage and Administration (2.4)]*.

5.12 Osteonecrosis of the Jaw

OMCAZIO can cause osteonecrosis of the jaw (ONJ).

ONJ occurred in <1% of patients treated with cabozantinib *[see Adverse Reactions (6.1)]*.

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 OMCAZIO and periodically during treatment with OMCAZIO. Advise patients regarding good oral hygiene practices. Withhold OMCAZIO for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold OMCAZIO for development of ONJ until complete resolution, resume at a reduced dose *[see Dosage and Administration (2.4)]*.

5.13 Impaired Wound Healing

OMCAZIO can cause impaired wound healing *[see Adverse Reactions (6.1)]*.

Withhold OMCAZIO for at least 3 weeks prior to elective surgery *[see Dosage and Administration (2.2)]*. Do not administer OMCAZIO for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of OMCAZIO after resolution of wound healing complications has not been established *[see Dosage and Administration (2.2, 2.4)]*.

5.14 Reversible Posterior Leukoencephalopathy Syndrome

OMCAZIO can cause reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI.

Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Permanently discontinue OMCAZIO in patients who develop RPLS *[see Dosage and Administration (2.4)]*.

5.15 Thyroid Dysfunction

OMCAZIO can cause thyroid dysfunction, primarily hypothyroidism.

Thyroid dysfunction occurred in 19% of patients treated with cabozantinib, including Grade 3 in 0.4% of patients *[see Adverse Reactions (6.1)]*.

Assess patients for signs of thyroid dysfunction prior to the initiation of OMCAZIO and monitor for signs and symptoms of thyroid dysfunction during OMCAZIO treatment.

Perform thyroid function testing and management of dysfunction as clinically indicated *[see Dosage and Administration (2.4)]*.

5.16 Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, cabozantinib 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 OMCAZIO and for 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

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

- Hemorrhage *[see Warnings and Precautions (5.2)]*
- Perforations and Fistulas *[see Warnings and Precautions (5.3)]*
- Thromboembolic Events *[see Warnings and Precautions (5.4)]*
- Hypertension and Hypertensive Crisis *[see Warnings and Precautions (5.5)]*
- Cardiac Failure [see *Warnings and Precautions (5.6)*]
- Diarrhea *[see Warnings and Precautions (5.7)]*
- Palmar-Plantar Erythrodysesthesia *[see Warnings and Precautions (5.8)]*
- Hepatotoxicity *[see Warnings and Precautions (5.9)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.10)]*
- Proteinuria *[see Warnings and Precautions (5.11)]*
- Osteonecrosis of the Jaw *[see Warnings and Precautions (5.12)]*
- Impaired Wound Healing *[see Warnings and Precautions (5.13)]*
- Reversible Posterior Leukoencephalopathy Syndrome *[see Warnings and Precautions (5.14)]*
- Thyroid Dysfunction *[see Warnings and Precautions (5.15)]*

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 OMCAZIO (cabozantinib) capsules has been established from adequate and well-controlled studies of CABOMETYX® (cabozantinib) tablets, which has different recommended dosages than OMCAZIO.

The data described in the WARNINGS AND PRECAUTIONS section and below reflect the adverse reactions of CABOMETYX® (cabozantinib) tablets in these adequate and well-controlled studies. These data reflect exposure to CABOMETYX® (cabozantinib) tablets as a single agent at 60 mg orally once daily until disease progression or unacceptable toxicity in 409 patients with renal cell carcinoma (RCC) enrolled in a randomized, active-controlled trial (CABOSUN, METEOR), 467 patients with hepatocellular carcinoma (HCC) enrolled in a randomized, placebo- controlled trial (CELESTIAL), 132 patients with extra-pancreatic neuroendocrine tumors (epNET) enrolled in a randomized, placebo-controlled trial (CABINET), and at 40 mg CABOMETYX® (cabozantinib) tablets in combination with nivolumab 240 mg/m^2 every 2 weeks, in 320 patients with RCC enrolled in a randomized, active-controlled trial (CHECKMATE-9ER).

Renal Cell Carcinoma

METEOR

The safety of cabozantinib was evaluated in METEOR, a randomized, open-label trial in which 331 patients with advanced renal cell carcinoma received cabozantinib tablets 60 mg once daily (equivalent to

OMCAZIO 34.5 mg) and 322 patients received everolimus 10 mg once daily until disease progression or unacceptable toxicity. Patients on both arms who had disease progression could continue treatment at the discretion of the investigator *[see Clinical Studies (14.1)]*. The median duration of treatment was 7.6 months (range 0.3 – 20.5) for patients receiving cabozantinib and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

Adverse reactions which occurred in ≥25% of cabozantinib-treated patients, in order of decreasing frequency, were: diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia (PPE), hypertension, vomiting, weight decreased, and constipation. Grade 3-4 adverse reactions and laboratory abnormalities which occurred in ≥5% of patients were hypertension, diarrhea, fatigue, PPE, hyponatremia, hypophosphatemia, hypomagnesemia, lymphopenia, anemia, hypokalemia, and increased GGT.

The dose was reduced in 60% of patients receiving cabozantinib and in 24% of patients receiving everolimus. Twenty percent (20%) of patients received cabozantinib tablets 20 mg once daily (equivalent to OMCAZIO 11.5 mg) as their lowest dose. The most frequent adverse reactions leading to dose reduction in patients treated with cabozantinib were: diarrhea, PPE, fatigue, and hypertension. Adverse reactions leading to dose interruption occurred in 70% patients receiving cabozantinib and in 59% patients receiving everolimus. Adverse reactions led to study treatment discontinuation in 10% of patients receiving cabozantinib and in 10% of patients receiving everolimus. The most frequent adverse reactions leading to permanent discontinuation in patients treated with cabozantinib were decreased appetite (2%) and fatigue (1%).

Table 8. Adverse Reactions Occurring in ≥10% Patients Who Received Cabozantinib in METEOR

Adverse Reaction	Cabozantinib (n=331) [1]		Everolimus (n=322)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	74	11	28	2
Nausea	50	4	28	<1
Vomiting	32	2	14	<1
Stomatitis	22	2	24	2
Constipation	25	<1	19	<1
Abdominal pain [3]	23	4	13	2
Dyspepsia	12	<1	5	0
General				
Fatigue	56	9	47	7
Mucosal inflammation	19	<1	23	3
Asthenia	19	4	16	2
Metabolism and Nutrition				
Decreased appetite	46	3	34	<1
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	42	8	6	<1
Rash [4]	23	<1	43	<1
Dry skin	11	0	10	0
Vascular				
Hypertension [5]	39	16	8	3
Investigations				
Weight decreased	31	2	12	0

Nervous System				
Dysgeusia	24	0	9	0
Headache	11	<1	12	<1
Dizziness	11	0	7	0
Endocrine				
Hypothyroidism	21	0	<1	<1
Respiratory, Thoracic, and Mediastinal				
Dysphonia	20	<1	4	0
Dyspnea	19	3	29	4
Cough	18	<1	33	<1
Blood and Lymphatic				
Anemia	17	5	38	16
Musculoskeletal and Connective Tissue				
Pain in extremity	14	1	8	<1
Muscle spasms	13	0	5	0
Arthralgia	11	<1	14	1
Renal and Urinary				
Proteinuria	12	2	9	<1

[1] One subject randomized to everolimus received cabozantinib.

[2] National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

[3] Includes the following terms: abdominal pain, abdominal pain upper, and abdominal pain lower

[4] Includes the following terms: rash, rash erythematous, rash follicular, rash macular, rash papular, rash pustular, rash vesicular, genital rash, intermittent leg rash, rash on scrotum and penis, rash maculo-papular, rash pruritic, contact dermatitis, dermatitis acneiform

[5] Includes the following terms: hypertension, blood pressure increased, hypertensive crisis, blood pressure fluctuation

Other clinically relevant adverse reactions (all grades) that were reported in <10% of patients treated with cabozantinib included: wound complications (2%), cardiac failure (<1%), convulsion (<1%), pancreatitis (<1%), osteonecrosis of the jaw (<1%), and hepatitis cholestatic (<1%).

Table 9. Laboratory Abnormalities Occurring in ≥25% Patients Who Received Cabozantinib in METEOR

	Cabozantinib (n=331)		**Everolimus (n=322)**	
Laboratory Abnormality	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
	Percentage (%) of Patients			
Chemistry				
Increased AST	74	3	40	<1
Increased ALT	68	3	32	<1
Increased creatinine	58	<1	71	0
Increased triglycerides	53	4	73	13
Hypophosphatemia	48	8	36	5
Hyperglycemia	37	2	59	8
Hypoalbuminemia	36	2	28	<1
Increased ALP	35	2	29	1
Hypomagnesemia	31	7	4	<1

Hyponatremia	30	8	26	6
Increased GGT	27	5	43	9
Hematology				
Leukopenia	35	<1	31	<1
Neutropenia	31	2	17	<1
Anemia[1]	31	4	71	17
Lymphopenia	25	7	39	12
Thrombocytopenia	25	<1	27	<1

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.
NCI CTCAE, Version 4.0
[1] Based on laboratory abnormalities

CABOSUN

The safety of cabozantinib was evaluated in CABOSUN, a randomized, open-label trial in patients with advanced renal cell carcinoma, in which 78 patients received cabozantinib tablets 60 mg once daily (equivalent to OMCAZIO 34.5 mg) and 72 patients received sunitinib 50 mg once daily (4 weeks on treatment followed by 2 weeks off), until disease progression or unacceptable toxicity *[see Clinical Studies (14.1)]*. The median duration of treatment was 6.5 months (range 0.2 – 28.7) for patients receiving cabozantinib and 3.1 months (range 0.2 – 25.5) for patients receiving sunitinib.

Within 30 days of treatment, there were 4 deaths in patients treated with cabozantinib and 6 deaths in patients treated with sunitinib. Of the 4 patients treated with cabozantinib, 2 patients died due to gastrointestinal perforation, 1 patient had acute renal failure, and 1 patient died due to clinical deterioration. All Grade 3-4 adverse reactions were collected in the entire safety population. The most frequent Grade 3-4 adverse reactions (≥5%) in patients treated with cabozantinib were hypertension, diarrhea, hyponatremia, hypophosphatemia, PPE, fatigue, increased ALT, decreased appetite, stomatitis, pain, hypotension, and syncope.

The median average daily dose was 50.3 mg for cabozantinib and 44.7 mg for sunitinib (excluding scheduled sunitinib non-dosing days). The dose was reduced in 46% of patients receiving cabozantinib and in 35% of patients receiving sunitinib. The dose was held in 73% of patients receiving cabozantinib and in 71% of patients receiving sunitinib. Based on patient disposition, 21% of patients receiving cabozantinib and 22% of patients receiving sunitinib discontinued due to an adverse reaction.

Table 10. Grade 3-4 Adverse Reactions Occurring in ≥1% Patients Who Received Cabozantinib in CABOSUN

	Cabozantinib (n = 78)	**Sunitinib (n = 72)**
	Grade 3-4[1]	**Grade 3-4[1]**
Adverse Reaction	**Percentage (%) of Patients**	
Patients with any Grade 3-4 Adverse Reaction	68	65
Gastrointestinal		
Diarrhea	10	11
Stomatitis	5	6
Nausea	3	4
Vomiting	1	3
Constipation	1	0
General		

Fatigue	6	17
Pain	5	0
Metabolism and Nutrition		
Hyponatremia[2]	9	8
Hypophosphatemia[2]	9	7
Decreased appetite	5	1
Dehydration	4	1
Hypocalcemia[2]	3	0
Hypomagnesemia[2]	3	0
Hyperkalemia[2]	1	3
Skin and Subcutaneous Tissue		
Palmar-plantar erythrodysesthesia	8	4
Skin ulcer	3	0
Vascular		
Hypertension[3]	28	21
Hypotension	5	1
Angiopathy	1	1
Investigations		
Increased ALT[2]	5	0
Weight decreased	4	0
Increased AST [2]	3	3
Increased blood creatinine [2]	3	3
Lymphopenia [2]	1	6
Thrombocytopenia [2]	1	11
Nervous System		
Syncope	5	0
Respiratory, Thoracic, and Mediastinal		
Dyspnea	1	6
Dysphonia	1	0
Blood and Lymphatic		
Anemia	1	3
Psychiatric		
Depression	4	0
Confusional state	1	1
Infections		
Lung infection	4	0
Musculoskeletal and Connective Tissue		
Back pain	4	0
Bone pain	3	1
Pain in extremity	3	0
Arthralgia	1	0
Renal and Urinary		
Renal failure acute	4	1
Proteinuria	3	1

ALT, alanine aminotransferase; AST, aspartate aminotransferase

[1] NCI CTCAE Version 4.0

[2] Laboratory abnormalities are reported as adverse reactions and not based on shifts in laboratory values

[3] Includes the following term: hypertension

CHECKMATE-9ER

The safety of cabozantinib with nivolumab was evaluated in CHECKMATE-9ER, a randomized, open-label study in patients with previously untreated advanced RCC *[see Clinical Studies (14.1)]*. Patients received cabozantinib tablets 40 mg orally once daily (equivalent to OMCAZIO 23 mg) with nivolumab 240 mg over 30 minutes every 2 weeks (n=320) or sunitinib 50 mg daily, administered orally for 4 weeks on treatment followed by 2 weeks off (n=320) *[see Clinical Studies (14.1)]*.

Cabozantinib tablets could be interrupted or reduced to 20 mg daily or 20 mg every other day (equivalent to OMCAZIO 11.5 mg). The median duration of treatment was 14 months (range: 0.2 to 27 months) in cabozantinib and nivolumab-treated patients. In this trial, 82% of patients in the cabozantinib and nivolumab arm were exposed to treatment for >6 months and 60% of patients were exposed to treatment for >1 year.

Serious adverse reactions occurred in 48% of patients receiving cabozantinib and nivolumab. The most frequent (≥2%) serious adverse reactions were diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia. Fatal intestinal perforations occurred in 3 (0.9%) patients.

Adverse reactions leading to discontinuation of either cabozantinib or nivolumab occurred in 20% of patients: 8% cabozantinib only, 7% nivolumab only, and 6% both drugs due to the same adverse reaction at the same time. Adverse reactions leading to dose interruption or reduction of either cabozantinib or nivolumab occurred in 83% of patients: 46% cabozantinib only, 3% nivolumab only, and 21% both drugs due to the same adverse reaction at the same time, and 6% both drugs sequentially.

The most common adverse reactions reported in ≥20% of patients treated with cabozantinib and nivolumab were diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

Table 11. Adverse Reactions in >15% of Patients Receiving Cabozantinib and Nivolumab - CHECKMATE-9ER

Adverse Reaction	Cabozantinib and Nivolumab (n=320)		Sunitinib (n=320)	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	64	7	47	4.4
Nausea	27	0.6	31	0.3
Abdominal pain[a]	22	1.9	15	0.3
Vomiting	17	1.9	21	0.3
Dyspepsia[b]	15	0	22	0.3
General				
Fatigue[c]	51	8	50	8
Hepatobiliary				
Hepatotoxicity[d]	44	11	26	5
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	40	8	41	8
Stomatitis[e]	37	3.4	46	4.4
Rash[f]	36	3.1	14	0
Pruritus	19	0.3	4.4	0
Vascular				

Hypertension[g]	36	13	39	14
Endocrine				
Hypothyroidism[h]	34	0.3	30	0.3
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[i]	33	3.8	29	3.1
Arthralgia	18	0.3	9	0.3
Metabolism and Nutrition				
Decreased appetite	28	1.9	20	1.3
Nervous System Disorders				
Dysgeusia	24	0	22	0
Headache	16	0	12	0.6
Respiratory, Thoracic and Mediastinal				
Cough[j]	20	0.3	17	0
Dysphonia	17	0.3	3.4	0
Infections and Infestations				
Upper respiratory tract infection[k]	20	0.3	8	0.3

Toxicity was graded per NCI CTCAE v4.

[a] Includes abdominal discomfort, abdominal pain lower, abdominal pain upper.

[b] Includes gastroesophageal reflux disease.

[c] Includes asthenia.

[d] Includes hepatotoxicity, ALT increased, AST increased, blood alkaline phosphatase increased, gamma-glutamyl transferase increased, autoimmune hepatitis, blood bilirubin increased, drug induced liver injury, hepatic enzyme increased, hepatitis, hyperbilirubinemia, liver function test increased, liver function test abnormal, transaminases increased, hepatic failure.

[e] Includes mucosal inflammation, aphthous ulcer, mouth ulceration.

[f] Includes dermatitis, dermatitis acneiform, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic.

[g] Includes blood pressure increased, blood pressure systolic increased.

[h] Includes primary hypothyroidism.

[i] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.

[j] Includes productive cough.

[k] Includes nasopharyngitis, pharyngitis, rhinitis.

Table 12. Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients Receiving Cabozantinib and Nivolumab - CHECKMATE-9ER

Laboratory Abnormality	Cabozantinib and Nivolumab		Sunitinib	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
	Percentage (%) of Patients			
Chemistry				
Increased ALT	79	9.8	39	3.5
Increased AST	77	7.9	57	2.6
Hypophosphatemia	69	28	48	10
Hypocalcemia	54	1.9	24	0.6
Hypomagnesemia	47	1.3	25	0.3
Hyperglycemia	44	3.5	44	1.7
Hyponatremia	43	11	36	12
Increased lipase	41	14	38	13
Increased amylase	41	10	28	6

Increased alkaline phosphatase	41	2.8	37	1.6
Increased creatinine	39	1.3	42	0.6
Hyperkalemia	35	4.7	27	1
Hypoglycemia	26	0.8	14	0.4
Hematology				
Lymphopenia	42	6.6	45	10
Thrombocytopenia	41	0.3	70	9.7
Anemia	37	2.5	61	4.8
Leukopenia	37	0.3	66	5.1
Neutropenia	35	3.2	67	12

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: cabozantinib and nivolumab group (range: 170 to 317 patients) and sunitinib group (range: 173 to 311 patients).

Hepatocellular Carcinoma

The safety of cabozantinib was evaluated in CELESTIAL, a randomized, double-blind, placebo-controlled trial in which 704 patients with advanced hepatocellular carcinoma were randomized to receive cabozantinib tablets 60 mg orally once daily (equivalent to OMCAZIO 34.5 mg) (n=467) or placebo (n=237) until disease progression or unacceptable toxicity *[see Clinical Studies (14.2)]*. The median duration of treatment was 3.8 months (range 0.1 – 37.3) for patients receiving cabozantinib and 2.0 months (range 0.0 – 27.2) for patients receiving placebo. The population exposed to cabozantinib was 81% male, 56% White, and had a median age of 64 years.

Adverse reactions occurring in ≥25% of cabozantinib-treated patients, in order of decreasing frequency were: diarrhea, decreased appetite, PPE, fatigue, nausea, hypertension, and vomiting. Grade 3-4 adverse reactions which occurred in ≥5% of patients were PPE, hypertension, fatigue, diarrhea, asthenia, and decreased appetite. There were 6 adverse reactions leading to death in patients receiving cabozantinib (hepatic failure, hepatorenal syndrome, esophagobronchial fistula, portal vein thrombosis, pulmonary embolism, upper gastrointestinal hemorrhage).

The median average daily dose was 35.8 mg for cabozantinib. The dose was reduced in 62% of patients receiving cabozantinib; 33% of patients required a reduction to 20 mg daily (equivalent to OMCAZIO 11.5 mg). The most frequent adverse reactions or laboratory abnormalities leading to dose reduction of cabozantinib were: PPE, diarrhea, fatigue, hypertension, and increased AST. Adverse reactions leading to dose interruption occurred in 84% patients receiving cabozantinib. Adverse reactions leading to permanent discontinuation of cabozantinib occurred in 16% of patients. The most frequent adverse reactions leading to permanent discontinuation of cabozantinib were PPE (2%), fatigue (2%), decreased appetite (1%), diarrhea (1%), and nausea (1%).

Table 13. Adverse Reactions Occurring in ≥5% of Cabozantinib-Treated Patients in CELESTIAL[1]

	Cabozantinib (n = 467)		**Placebo (n = 237)**	
Adverse Reaction	**All Grades[2]**	**Grade 3-4**	**All Grades[2]**	**Grade 3-4**
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	54	10	19	2
Nausea	31	2	18	2
Vomiting	26	<1	12	3

Stomatitis	13	2	2	0
Dyspepsia	10	0	3	0
General				
Fatigue	45	10	30	4
Asthenia	22	7	8	2
Mucosal inflammation	14	2	2	<1
Metabolism and Nutrition				
Decreased appetite	48	6	18	<1
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	46	17	5	0
Rash[3]	21	2	9	<1
Vascular				
Hypertension[4]	30	16	6	2
Investigations				
Weight decreased	17	1	6	0
Nervous System				
Dysgeusia	12	0	2	0
Endocrine				
Hypothyroidism	8	<1	<1	0
Respiratory, Thoracic, and Mediastinal				
Dysphonia	19	1	2	0
Dyspnea	12	3	10	<1
Musculoskeletal and Connective Tissue				
Pain in extremity	9	<1	4	1
Muscle spasms	8	<1	2	0

[1] Includes terms with a between-arm difference of ≥5% (all grades) or ≥2% (Grade 3-4)
[2] NCI CTCAE Version 4.0
[3] Includes the following terms: rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, dermatitis, dermatitis acneiform, dermatitis contact, dermatitis diaper, dermatitis exfoliative, dermatitis infected
[4] Includes the following terms: hypertension, blood pressure diastolic increased, blood pressure increased

Table 14. Laboratory Abnormalities Occurring in ≥5% of Cabozantinib-Treated Patients in CELESTIAL[1]

	Cabozantinib (n=467)		**Placebo (n=237)**	
Laboratory Abnormality	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
	Percentage of Patients			
Chemistry				
Increased LDH	84	9	29	2
Increased ALT	73	12	37	6
Increased AST	73	24	46	19
Hypoalbuminemia	51	1	32	1
Increased ALP	43	8	38	6
Hypophosphatemia	25	9	8	4
Hypokalemia	23	6	6	1
Hypomagnesemia	22	3	3	0
Increased amylase	16	2	9	2
Hypocalcemia	8	2	0	0

Hematology				
Decreased platelets	54	10	16	1
Neutropenia	43	7	8	1
Increased hemoglobin	8	0	1	0

[1] Includes laboratory abnormalities with a between-arm difference of ≥5% (all grades) or ≥2% (Grade 3-4)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, blood lactate dehydrogenase

Extra-pancreatic Neuroendocrine Tumors

The safety of cabozantinib was evaluated in adult patients with unresectable, locally advanced or metastatic, well-differentiated neuroendocrine tumors in the CABINET trial *[see Clinical Studies (14.3)]*. Patients received cabozantinib tablets 60 mg (equivalent to OMCAZIO 34.5 mg) (n=132) or placebo (n=67) orally once daily until disease progression or unacceptable toxicity. Patients with epNET were required to have disease progression after prior treatment with at least one FDA approved therapy (everolimus or lutetium Lu 177 dotatate), other than somatostatin analogs. The median duration of treatment was 5.4 months (range 0.1 to 32.4) for patients receiving cabozantinib and 2.8 months (range 0.5 to 22.8) for patients receiving placebo.

The median age was 66 years (range 28 to 86), 55% were female, 86% were White, 7% were Black, 2.3% were Asian, 5% had unknown race or race not reported, and 6% were Hispanic or Latino.

Serious adverse reactions occurred in 44% of patients who received cabozantinib. Serious adverse reactions in ≥2% included hypertension (6%), abdominal pain (5%), musculoskeletal pain (5%), diarrhea (3.0%), vomiting (3.0%), blood bilirubin increased (3.0%), thromboembolic events (3.0%), nausea (2.3%), hemoglobin decreased (2.3%), muscular weakness (2.3%), fatigue (2.3%), sepsis (2.3%), and syncope (2.3%). Fatal adverse reactions occurred in 4.5% of patients who received cabozantinib, including hepatic failure, multi-organ dysfunction, gastrointestinal hemorrhage, cardiac arrest, ruptured ascending aortic aneurysm, and sudden death not otherwise specified, occurring in one patient each.

Permanent discontinuation of cabozantinib due to an adverse reaction occurred in 28% of patients receiving cabozantinib. Adverse reactions which resulted in permanent discontinuation of cabozantinib included diarrhea, fatigue, increased AST, increased ALT, blood bilirubin increased, rash, thromboembolic events, hypertension, increased ALP, nausea, and stomatitis.

The median average daily dose was 42.9 mg for cabozantinib tablets. Dosage interruptions of cabozantinib due to an adverse reaction occurred in 81% of patients. Adverse reactions which required dosage interruption in ≥5% of patients included diarrhea, fatigue, rash, hypertension, nausea, stomatitis, abdominal pain, increased AST, vomiting, and musculoskeletal pain.

Dose reductions of cabozantinib due to an adverse reaction occurred in 38% of patients. Adverse reactions which required dose reductions in ≥5% of patients included rash, fatigue, diarrhea, and hypertension.

The most common adverse reactions occurring in ≥20% of cabozantinib-treated patients were fatigue, increased AST, diarrhea, hypertension, increased ALT, platelet count decreased, rash, stomatitis, nausea, white blood cell count decreased, neutrophil count decreased, musculoskeletal pain, dysgeusia, hypothyroidism, decreased appetite, hemoglobin decreased, hyperglycemia, abdominal pain, increased ALP, lymphocyte count decreased, weight decreased, blood creatinine increased, hypoalbuminemia, blood bilirubin increased, hypocalcemia, hypokalemia, and hypomagnesemia.

Table 15 summarizes the adverse reactions in patients with epNET in CABINET.

Table 15. Adverse Reactions (≥15%) in Patients with epNET Who Received Cabozantinib in CABINET

Adverse Reaction	Cabozantinib (n=132)		Placebo (n=67)	
	All Grades[1]	Grade 3-4	All Grades[1]	Grade 3-4
	Percentage (%) of Patients			
General				
Fatigue[2]	73	14	58	9
Edema[3]	16	1.5	10	0
Gastrointestinal				
Diarrhea[4]	65	11	42	4.5
Stomatitis[5]	40	3.8	10	0
Nausea	39	2.3	21	0
Abdominal pain[6]	29	9	43	8
Vomiting	17	2.3	10	1.5
Vascular				
Hypertension[7]	64	27	37	6
Skin and Subcutaneous Tissue				
Rash[8]	50	3.0	10	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[9]	36	8	33	1.5
Endocrine System				
Hypothyroidism[10]	34	0	4.5	0
Metabolism and Nutrition				
Decreased appetite	33	1.5	15	1.5
Nervous System				
Dysgeusia[11]	35	0	1.5	0
Dizziness[12]	17	0	6	0
Investigations				
Weight decreased	27	4.5	8	0
Respiratory, Thoracic, and Mediastinal				
Cough[13]	17	0	10	0

[1] NCI CTCAE Version 5.0
[2] Includes fatigue, asthenia
[3] Includes edema, edema peripheral, generalized edema, localized edema, periorbital edema, face edema, eye edema
[4] Includes diarrhea, colitis
[5] Includes stomatitis, aphthous ulcer, mucosal inflammation, cheilitis, glossitis
[6] Includes abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain, abdominal discomfort, hepatic pain
[7] Includes hypertension, blood pressure increased, blood pressure systolic increased, systolic hypertension
[8] Includes rash, palmar-plantar erythrodysesthesia syndrome, dermatitis acneiform, skin exfoliation, rash macular, rash pustular, dermatitis bullous, dermatitis, erythema multiforme, rash maculo-papular, dermatitis contact, erythema, dermatitis psoriasiform
[9] Includes musculoskeletal pain, non-cardiac chest pain, back pain, arthralgia, pain in extremity, myalgia, bone pain, arthritis, neck pain, musculoskeletal chest pain, musculoskeletal stiffness, chest discomfort
[10] Includes hypothyroidism, blood thyroid stimulating hormone increased
[11] Includes dysgeusia, taste disorder, ageusia, anosmia
[12] Includes dizziness, vertigo
[13] Includes cough, upper-airway cough syndrome, productive cough

Clinically relevant adverse reactions in <15% of patients who received cabozantinib included cardiac arrhythmia, hemorrhage, thromboembolic events, kidney injury, proteinuria, hypotension, peripheral neuropathy, reversible posterior leukoencephalopathy syndrome, alopecia, hair color changes, and cardiac failure.

Table 16 summarizes the laboratory abnormalities in patients with epNET in CABINET.

Table 16. Select Laboratory Abnormalities (≥10%) Reported as Adverse Reactions in Patients with epNET Who Received Cabozantinib in CABINET

	Cabozantinib (n=132)		Placebo (n=67)	
Laboratory Abnormality	**All Grades[1] (%)**	**Grade 3 or 4 (%)**	**All Grades[1] (%)**	**Grade 3 or 4 (%)**
Chemistry				
Increased AST	70	3.8	21	1.5
Increased ALT	63	0.8	18	1.5
Hyperglycemia[2]	30	0.8	39	1.5
Increased ALP[3]	29	4.5	30	6
Blood creatinine increased	23	0	12	1.5
Blood bilirubin increased[4]	20	3	10	6
Hypoalbuminemia[5]	20	0.8	9	0
Hypocalcemia[6]	20	0	4.5	0
Hypokalemia[7]	20	2.3	10	1.5
Hypomagnesemia[8]	20	0.8	4.5	0
Hypophosphatemia[9]	19	0.8	4.5	0
Hyponatremia[10]	16	2.3	7	1.5
Hematology				
Platelet count decreased[11]	55	1.5	13	1.5
White blood cell count decreased[12]	37	3	4.5	0
Neutrophil count decreased[13]	36	3	6	0
Hemoglobin decreased[14]	30	2.3	19	0
Lymphocyte count decreased[15]	28	9	18	1.5

[1] NCI CTCAE Version 5.0
[2] Includes hyperglycemia, blood glucose increased
[3] Includes blood alkaline phosphatase, blood alkaline phosphatase increased
[4] Includes blood bilirubin increased, hyperbilirubinemia
[5] Includes hypoalbuminemia, blood albumin decreased
[6] Includes hypocalcemia, blood calcium decreased, adjusted calcium decreased
[7] Includes hypokalemia, blood potassium decreased
[8] Includes hypomagnesemia, blood magnesium decreased
[9] Includes hypophosphatemia, blood phosphorus decreased
[10] Includes hyponatremia, blood sodium decreased
[11] Includes platelet count decreased, thrombocytopenia
[12] Includes white blood cell count decreased, leukopenia
[13] Includes neutrophil count decreased, neutropenia
[14] Includes hemoglobin decreased, anemia
[15] Includes lymphocyte count decreased, lymphopenia

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of cabozantinib. 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.

Vascular Disorders: Arterial (including aortic) aneurysms, dissections, and rupture

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on OMCAZIO

Strong CYP3A Inhibitors

Avoid coadministration of OMCAZIO with strong CYP3A inhibitors. If coadministration cannot be avoided, reduce the dosage of OMCAZIO *[see Dosage and Administration (2.5)]*.

Cabozantinib is a CYP3A substrate. Coadministration with a strong CYP3A inhibitor increases cabozantinib exposure *[see Clinical Pharmacology (12.3)]*, which may increase the risk of OMCAZIO-associated adverse reactions.

Strong or Moderate CYP3A Inducers

Avoid coadministration of OMCAZIO with strong or moderate CYP3A inducers. If coadministration cannot be avoided, increase the dosage of OMCAZIO *[see Dosage and Administration (2.5)]*.

Cabozantinib is a CYP3A substrate. Coadministration with a strong CYP3A inducer decreases cabozantinib exposure, which may reduce effectiveness of OMCAZIO *[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 *[see Clinical Pharmacology (12.1)]*, OMCAZIO can cause fetal harm when administered to a pregnant woman. 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 of the potential risk to a fetus.

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 (approximately 0.12-fold of human area under the curve [AUC] at the recommended dose). Findings included delayed ossification and skeletal variations at a dose of 0.01 mg/kg/day (approximately 0.04-fold of human AUC at the recommended 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 1.1-fold of the human AUC at the recommended 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 (0.05-fold of the maximum recommended clinical dose).

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 child or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with OMCAZIO and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

Females

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

Infertility

Females and Males

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

8.4 Pediatric Use

The safety and effectiveness of OMCAZIO for the treatment of previously treated, unresectable, locally advanced or metastatic, well-differentiated extra-pancreatic neuroendocrine tumors (epNET) have been established in pediatric patients aged 12 years and older.

Use of OMCAZIO in pediatric patients aged 12 years and older for epNET is supported by evidence from adequate and well-controlled studies of cabozantinib tablets in adults with additional population pharmacokinetic data demonstrating that cabozantinib exposure is within the same range between adults and pediatric patients aged 12 years and older at the recommended dosages *[see Dosage and Administration (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.3)]*.

Physeal widening has been observed in pediatric patients with open growth plates who received cabozantinib. Based on the limited available data of the effects of cabozantinib on longitudinal growth, physeal and longitudinal growth monitoring is recommended in children with open growth plates.

The safety and effectiveness of OMCAZIO for the treatment of epNET in pediatric patients less than 12 years of age have not been established.

The safety and effectiveness of OMCAZIO have not been established in pediatric patients with RCC and HCC *[see Indications and Usage (1)]*.

Juvenile Animal Toxicity Data

Juvenile rats were administered cabozantinib 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 ≥1 mg/kg/day (approximately 0.16 times the clinical dose of 60 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 a dose of 2 mg/kg (approximately 0.32 times the clinical dose of 60 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

In CABOSUN and METEOR, 41% of 409 patients treated with cabozantinib were age 65 years and older, and 8% were 75 years and older. In CELESTIAL, 49% of 467 patients treated with cabozantinib were age 65 years and older, and 15% were 75 years and older. In CABINET, 55% of 132 patients treated with cabozantinib were age 65 years and older, and 13% were 75 years and older in the epNET cohort *[see Clinical Studies (14)]*.

No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 320 patients with RCC treated with cabozantinib in combination with nivolumab in CHECKMATE-9ER, 41% were 65 years or older and 9% were 75 years or older *[see Clinical Studies (14.1)]*.

No overall difference in safety was reported between older and younger patients receiving both cabozantinib and nivolumab.

8.6 Hepatic Impairment

Increased exposure to cabozantinib has been observed in patients with moderate (Child-Pugh B) hepatic impairment. Reduce the OMCAZIO dose in patients with moderate hepatic impairment.

Avoid OMCAZIO in patients with severe hepatic impairment (Child-Pugh C), since it has not been studied in this population *[see Dosage and Administration (2.2, 2.6), Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

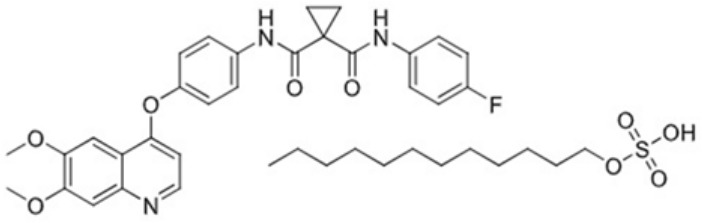
One case of overdosage was reported following administration of another formulation of cabozantinib; a patient inadvertently took twice the intended dose for 9 days. The patient suffered Grade 3 memory impairment, Grade 3 mental status changes, Grade 3 cognitive disturbance, Grade 2 weight loss, and Grade 1 increase in BUN. The extent of recovery was not documented.

Closely monitor patients suspected of receiving an overdose, including signs and symptoms of adverse reactions, and administer appropriate supportive treatment.

Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

OMCAZIO is the laurylsulfate salt of cabozantinib, a kinase inhibitor. Cabozantinib laurylsulfate is described chemically as *N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, Laurylsulfate*. The molecular formula is $C_{40}H_{50}FN_3O_9S$ and the molecular weight is 767.9 Daltons as laurylsulfate salt. The chemical structure of cabozantinib laurylsulfate salt is:



Cabozantinib laurylsulfate salt is a white to off-white solid that is practically insoluble in aqueous media.

OMCAZIO (cabozantinib) capsules for oral use are supplied as hard gelatin capsules containing 11.5 mg, 23 mg, or 34.5 mg of cabozantinib, which is equivalent to 17.6 mg, 35.2 mg, or 52.8 mg of cabozantinib laurylsulfate, respectively.

OMCAZIO also contains the following inactive ingredient: ammonia solution, ascorbic palmitate, black iron oxide, FD&C Blue #1, gelatin, polyoxyl 32 stearate, potassium hydroxide, propylene glycol, shellac, titanium dioxide, and tocopherol.

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 MET, VEGFR-1, -2 and -3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, 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

Cabozantinib exposure-response relationships and time course of pharmacodynamic response are not fully characterized.

Cardiac Electrophysiology

The mean increase in QTcF interval is 10 to 15 ms after administration of a different cabozantinib capsule formulation for 4 weeks.

Changes in cardiac wave form morphology or new rhythms were not observed. No patients in this study had a confirmed QTcF >500 ms nor did any patients in METEOR, CABOSUN, CELESTIAL, CHECKMATE-9ER, or CABINET.

12.3 Pharmacokinetics

Cabozantinib pharmacokinetics were observed after a single dose in healthy subjects and are presented as mean (CV%) unless otherwise specified. Cabozantinib maximum concentration (C_{max}) is 394 (22%) ng/mL and systemic exposure (AUC) is 10290 (25%) ng*hr/mL.

Cabozantinib accumulation is 4- to 5-fold (based on AUC) following administration of a different cabozantinib capsule formulation. Cabozantinib steady state is reached by Day 15.

Absorption

Cabozantinib median (min, max) time to maximum plasma concentration (Tmax) is 3.3 (1.5, 5) hours.

Food Effect

No clinically significant differences in cabozantinib exposure were observed following administration of OMCAZIO with a high-fat meal (approximately 926 calories, 57% fat).

Distribution

Cabozantinib apparent (oral) volume of distribution is approximately 319 L in patients. Cabozantinib plasma protein binding is ≥ 99.7%.

Elimination

Cabozantinib predicted terminal half-life is approximately 3.7 days and the apparent (oral) clearance at steady state is estimated to be 2.2 L/hr in patients.

Metabolism

Cabozantinib is primarily metabolized by CYP3A.

Excretion

After a single dose of radiolabeled ^{14}C-cabozantinib to healthy participants, approximately 81% of the total administered radioactivity was recovered within 1.6 months. Approximately 54% (43% unchanged) was recovered in feces and 27% in urine. Unchanged cabozantinib was not detectable in urine following a 72-hour collection.

Specific Populations

No clinically significant differences in the pharmacokinetics of cabozantinib were observed based on age (32 to 86 years), sex, race (White and non-White), or eGFR ≥ 30 mL/min/1.73m^2 (as estimated by MDRD). The pharmacokinetics of cabozantinib is unknown in patients with eGFR < 30 mL/min/1.73m^2 or in those requiring dialysis.

Pediatric Patients

The systemic exposures to cabozantinib in pediatric patients 12 years and older at the recommended dosages are expected to be comparable to the exposure in adults at the dose of OMCAZIO 34.5 mg once daily.

Patients with Hepatic Impairment

No clinically significant differences in the mean cabozantinib exposure were observed in subjects with mild hepatic impairment (Child-Pugh A). Cabozantinib exposure (AUC) increased 1.6-fold in patients with moderate hepatic impairment (Child-Pugh B). The effect of severe hepatic impairment (Child-Pugh C) on cabozantinib pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies

Strong CYP3A4 Inhibitors: Single-dose cabozantinib exposure (AUC) increased 1.4-fold following concomitant administration of ketoconazole 400 mg daily for 27 days (strong CYP3A inhibitor) with a different cabozantinib capsule formulation.

Strong CYP3A4 Inducers: Single-dose cabozantinib exposure (AUC) decreased by 77% following concomitant administration of rifampin 600 mg daily for 31 days (strong CYP3A inducer) with a different cabozantinib capsule formulation.

Other Drugs: No clinically significant differences in the pharmacokinetics of the following drugs were observed when used concomitantly with a different cabozantinib capsule formulation: rosiglitazone (a CYP2C8 substrate).

In Vitro Studies

CYP Enzymes: Cabozantinib inhibits CYP2C9, CYP2C19, and CYP3A. Cabozantinib does not inhibit CYP1A2 and CYP2D6.

Cabozantinib induces CYP1A1. Cabozantinib does not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP3A.

Transporters: Cabozantinib is an inhibitor, but not a substrate, of P-gp. Cabozantinib is a substrate of MRP2.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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 5 times the human exposure by AUC at the recommended 60 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.

Mutagenesis

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.

Impairment of Fertility

Based on nonclinical findings, male and female fertility may be impaired by treatment with OMCAZIO. 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 13-fold of human 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 (5-fold of human 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 plasma exposures (AUC) approximately 0.5-fold (males) and <0.1-fold (females) of those expected in humans at the recommended dose. In addition, female rats administered 5 mg/kg/day for 14 days (approximately 9-fold of human AUC at the recommended dose) exhibited ovarian necrosis.

14 CLINICAL STUDIES

14.1 Renal Cell Carcinoma

The effectiveness of 34.5 mg once daily of OMCAZIO (cabozantinib) capsules for the treatment of renal cell carcinoma has been established from an adequate and well-controlled study of CABOMETYX® (cabozantinib) tablets, which has a different recommended dosage than OMCAZIO. Below is a display of the results of CABOMETYX® (cabozantinib) tablets in this adequate and well-controlled study.

Previously Treated with Anti-angiogenic Therapy

The efficacy of cabozantinib was evaluated in METEOR (NCT01865747), a randomized (1:1), open-label, multicenter trial of cabozantinib versus everolimus conducted in patients with advanced RCC who had received at least 1 prior anti-angiogenic therapy. Patients had to have a Karnofsky Performance Score (KPS) ≥70%. Patients were stratified by the number of prior VEGFR tyrosine kinase inhibitors (TKIs) and Memorial Sloan Kettering Cancer Center (MSKCC) Risk Group.

Patients were randomized to receive cabozantinib tablets (N=330) 60 mg orally once daily (equivalent to OMCAZIO 34.5 mg) or everolimus (N=328) 10 mg orally once daily. The majority of the patients were male (75%), with a median age of 62 years. Sixty-nine percent (69%) received only one prior anti-angiogenic therapy. Patient distribution by MSKCC risk groups was 46% favorable (0 risk factors), 42% intermediate (1 risk factor), and 13% poor (2 or 3 risk factors). Fifty-four percent (54%) of patients had 3 or more organs with metastatic disease, including lung (63%), lymph nodes (62%), liver (29%), and bone (22%).

The main efficacy outcome measure was progression-free survival (PFS) assessed by a blinded independent radiology review committee among the first 375 subjects randomized. Other efficacy endpoints were objective response rate (ORR) and overall survival (OS) in the Intent-to- Treat (ITT) population. Tumor assessments were conducted every 8 weeks for the first 12 months, then every 12 weeks thereafter. Patients received treatment until disease progression or experiencing unacceptable toxicity. Patients on both arms who had disease progression could continue treatment at the discretion of the investigator.

Statistically significant improvements in PFS, OS, and ORR were demonstrated for cabozantinib compared to everolimus. Efficacy results are presented in Tables 17 and 18 and Figures 1 and 2.

Table 17. Efficacy Results in METEOR (First 375 Randomized)

Endpoint	**Cabozantinib** (n = 187)	**Everolimus** (n = 188)
Median PFS (95% CI), months	7.4 (5.6, 9.1)	3.8 (3.7, 5.4)
HR (95% CI), p-value[1]	0.58 (0.45, 0.74), p<0.0001	

[1] stratified log-rank test with prior VEGFR-targeting TKI therapy (1 vs 2 or more) and MSKCC prognostic criteria for previously treated patients with RCC (0 vs 1 vs 2 or 3) as stratification factors (per IVRS data)

Figure 1. Kaplan-Meier Curves of Progression-Free Survival in METEOR (First 375 Randomized)

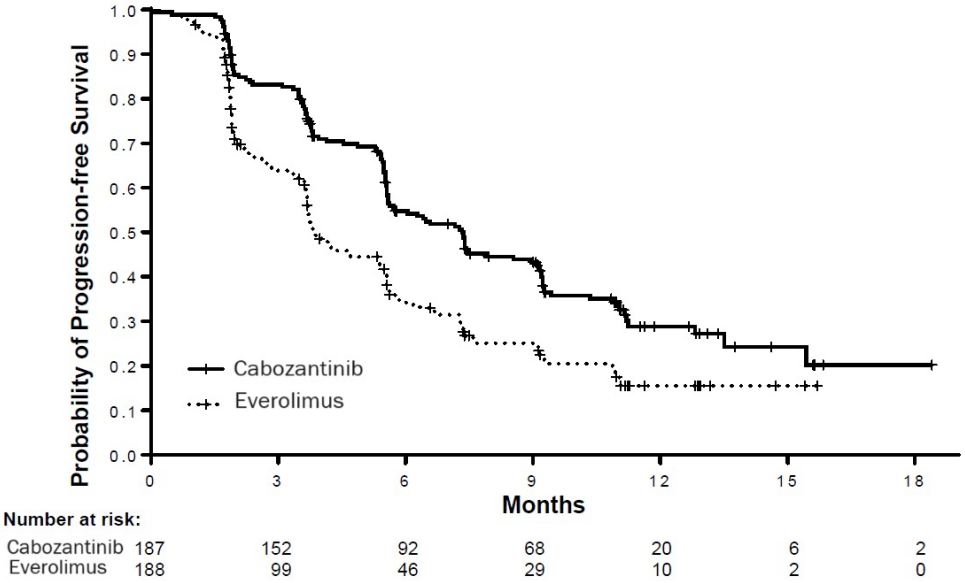


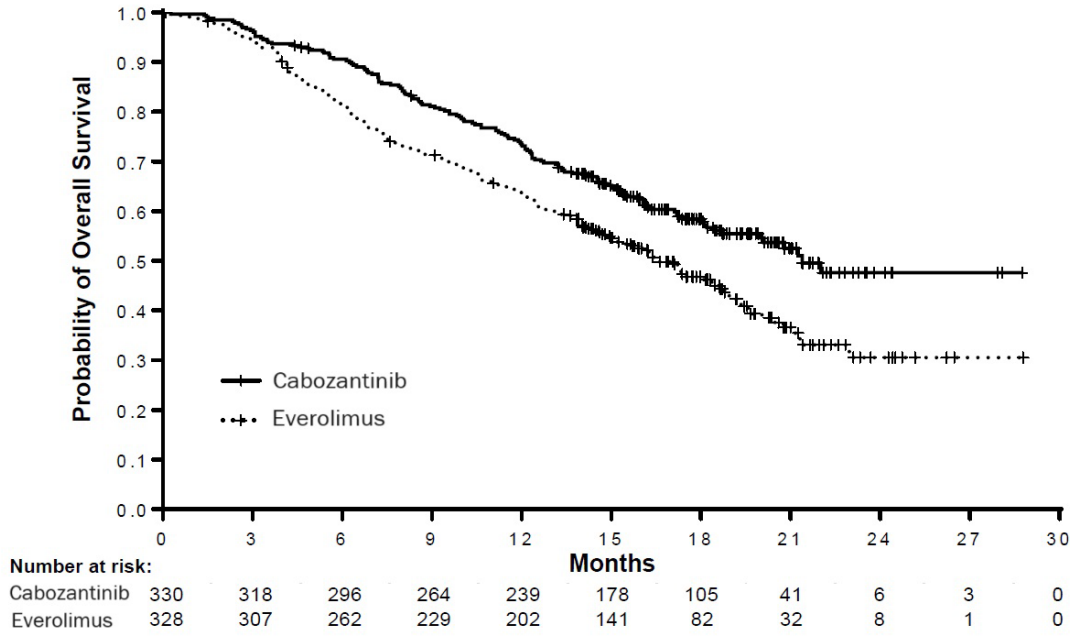
Table 18. Efficacy Results in METEOR (ITT)

Endpoint	**Cabozantinib** (n = 330)	**Everolimus** (n = 328)
Median OS (95% CI), months	21.4 (18.7, NE)	16.5 (14.7, 18.8)
HR (95% CI), p-value[1]	0.66 (0.53, 0.83), p=0.0003	
Confirmed ORR (partial responses only) (95% CI)	17% (13%, 22%)	3% (2%, 6%)
p-value[2]	p<0.0001	

[1] stratified log-rank test with prior VEGFR-targeting TKI therapy (1 vs 2 or more) and MSKCC prognostic criteria for previously treated patients with RCC (0 vs 1 vs 2 or 3) as stratification factors (per IVRS data)

[2] chi-squared test

Figure 2. Kaplan-Meier Curve of Overall Survival in METEOR (ITT)



First-line Treatment

CABOSUN

The efficacy of cabozantinib was evaluated in CABOSUN (NCT01835158), a randomized (1:1), open-label, multicenter trial of cabozantinib versus sunitinib conducted in patients with advanced RCC who had not received prior therapy. Patients were randomized to receive cabozantinib tablets (N=79) 60 mg orally once daily (equivalent to OMCAZIO 34.5 mg) or sunitinib (N=78) 50 mg orally once daily (4 weeks on treatment followed by 2 weeks off) until disease progression or unacceptable toxicity. All patients were required to have intermediate or poor risk disease as defined by the International Metastatic RCC Database Consortium (IMDC) risk group categories. Patients were stratified by IMDC risk group and presence of bone metastases (yes/no).

The majority of patients were male (78%), with a median age of 63 years. Patient distribution by IMDC risk groups was 81% intermediate (1-2 risk factors) and 19% poor (≥3 risk factors).

Thirty-six percent (36%) patients had bone metastases. Forty-six percent (46%) of patients were ECOG 0, 41% ECOG 1, and 13% ECOG 2.

The major efficacy outcome measure was progression-free survival (PFS) by a retrospective blinded independent radiology review committee (BIRC).

A statistically significant improvement in PFS, as assessed by a blinded independent radiology review committee, was demonstrated for cabozantinib compared to sunitinib. Efficacy results are presented in Table 19, Figure 3, and Figure 4.

Table 19. Efficacy Results in CABOSUN

Endpoint	**Cabozantinib** (n = 79)	**Sunitinib** (n = 78)
Progression-Free Survival[1]		
Events, n(%)	43 (54)	49 (63)
Median PFS (95% CI), months[1]	8.6 (6.8, 14.0)	5.3 (3.0, 8.2)
Hazard Ratio[2] (95% CI), p-value[3]	0.48 (0.31, 0.74), p=0.0008	

Overall Survival		
Events, n(%)	43 (54)	47 (60)
Hazard Ratio[2,4] (95% CI)	0.80 (0.53, 1.21)	
Confirmed ORR, partial responses only (95% CI)[1,4]	20% (12.0, 30.8)	9% (3.7, 17.6)

[1] as assessed by a retrospective blinded independent radiology review committee (BIRC)

[2] estimated from stratified Cox proportional hazards model with stratification factors IMDC risk group and presence of bone metastases and treatment as covariate

[3] two-sided stratified log-rank test with stratification factors IMDC risk group and presence of bone metastases

[4] no multiplicity adjustments were made for overall survival or ORR

Figure 3. Kaplan-Meier Curve of Progression-Free Survival in CABOSUN

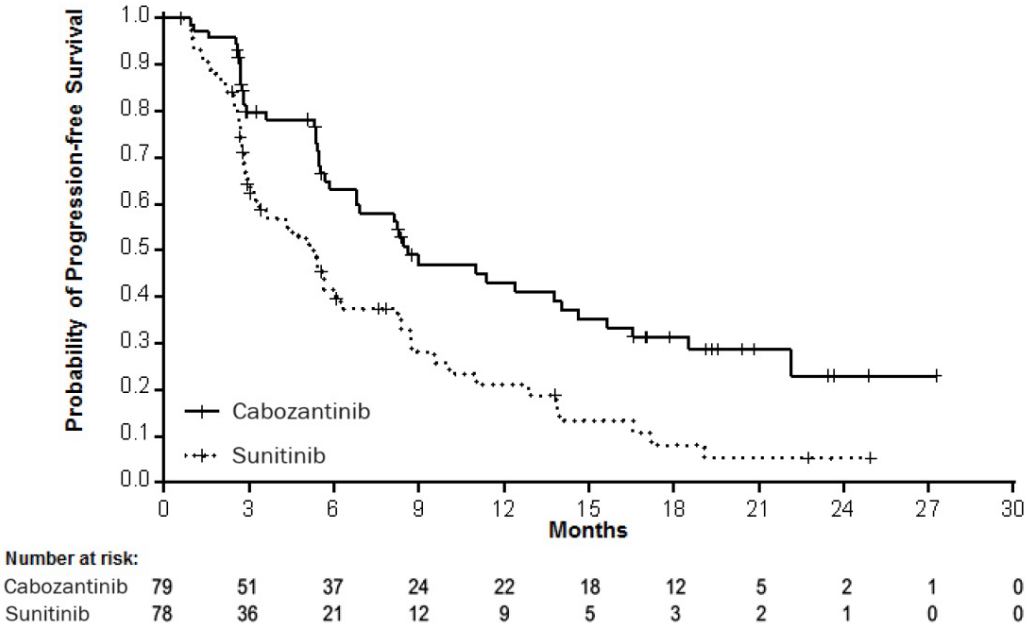
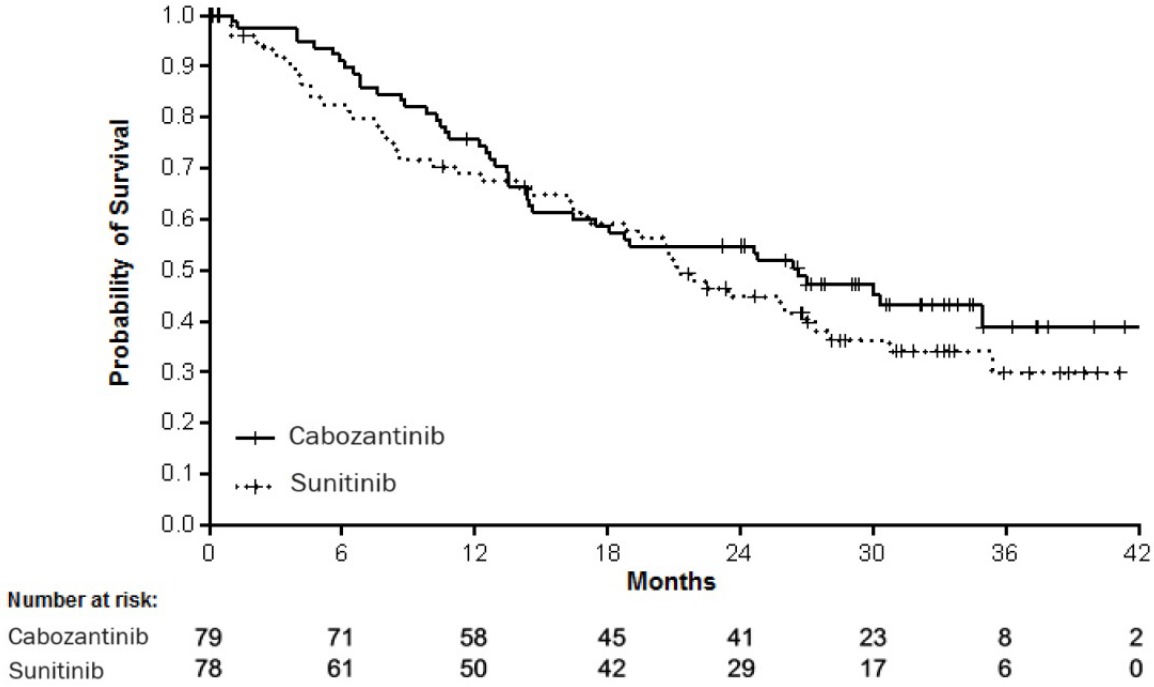


Figure 4. Kaplan-Meier Curve of Overall Survival in CABOSUN



CHECKMATE-9ER

CHECKMATE-9ER (NCT03141177) was a randomized, open-label study of cabozantinib combined with nivolumab versus sunitinib in patients with previously untreated advanced RCC. CHECKMATE-9ER excluded patients with autoimmune disease or other medical conditions requiring systemic immunosuppression. Patients were stratified by IMDC prognostic score (favorable vs. intermediate vs. poor), PD-L1 tumor expression (≥1% vs. <1% or indeterminate), and region (US/Canada/Western Europe/Northern Europe vs. Rest of World).

Patients were randomized to cabozantinib tablets 40 mg orally daily (equivalent to OMCAZIO 23 mg) and nivolumab 240 mg intravenously every 2 weeks (n=323), or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (4 weeks on treatment followed by 2 weeks off) (n=328). Treatment continued until disease progression per RECIST v1.1 or unacceptable toxicity. Treatment beyond RECIST- defined disease progression was permitted if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Tumor assessments were performed at baseline, after randomization at Week 12, then every 6 weeks until Week 60, and then every 12 weeks thereafter.

The trial population characteristics were: median age 61 years (range: 28 to 90) with 38% ≥65 years of age and 10% ≥75 years of age. The majority of patients were male (74%) and White (82%) and 23% and 77% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively. Patient distribution by IMDC risk categories was 22% favorable, 58% intermediate, and 20% poor.

The major efficacy outcome measure was PFS (BICR assessed). Additional efficacy outcome measures were OS and ORR (BICR assessed). The trial demonstrated a statistically significant improvement in PFS, OS, and ORR for patients randomized to cabozantinib and nivolumab compared with sunitinib. Consistent results for PFS were observed across pre-specified subgroups of IMDC risk categories and PD-L1 tumor expression status. An updated efficacy analysis was conducted when 271 deaths were observed based on the pre-specified number of deaths for the pre-planned final analysis of OS. Efficacy results are shown in Table 20 and Figures 5 and 6.

Table 20. Efficacy Results in CHECKMATE-9ER

	Cabozantinib and Nivolumab (n=323)	Sunitinib (n=328)
Progression-free Survival		
Disease progression or deaths (%)	144 (45)	191 (58)
Median PFS (months)[a] (95% CI)	16.6 (12.5, 24.9)	8.3 (7.0, 9.7)
Hazard ratio (95% CI)[b]	0.51 (0.41, 0.64)	
p-value[c,d]	<0.0001	
Overall Survival		
Deaths (%)	67 (21)	99 (30)
Median OS (months)[a] (95% CI)	NR[e]	NR (22.6, NR[e])
Hazard ratio (98.89% CI)[b]	0.60 (0.40, 0.89)	
p-value[c,d,f]	0.0010	
Updated Overall Survival		
Deaths (%)	121 (37)	150 (46)
Median OS (months)[a] (95% CI)	37.7 (35.5, NR[e])	34.3 (29.0, NR[e])
Hazard ratio (95% CI)[b]	0.70 (0.55, 0.90)	
Confirmed Objective Response Rate (95% CI)[g]	55.7% (50.1, 61.2)	27.1% (22.4, 32.3)
p-value[h]	<0.0001	
Complete Response (CR)	26 (8%)	15 (4.6%)
Partial Response (PR)	154 (48%)	74 (23%)
Median duration of response in months (95% CI)[a]	20.2 (17.3, NR[e])	11.5 (8.3, 18.4)

[a] Based on Kaplan-Meier estimates.

[b] Stratified Cox proportional hazards model.

[c] Based on stratified log-rank test.

[d] 2-sided p-values from stratified log-rank test.

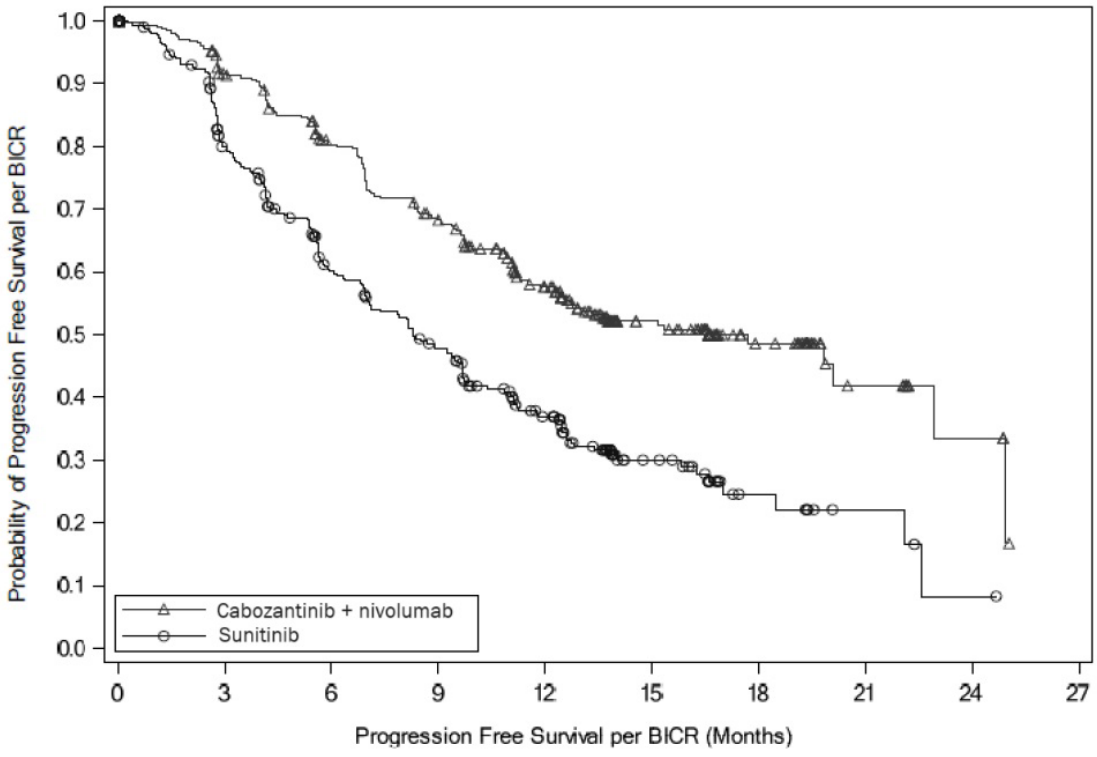
[e] Not Reached.

[f] p-value is compared with the allocated alpha of 0.0111 for this interim analysis.

[g] CI based on the Clopper and Pearson method.

[h] 2-sided p-value from Cochran-Mantel-Haenszel test.

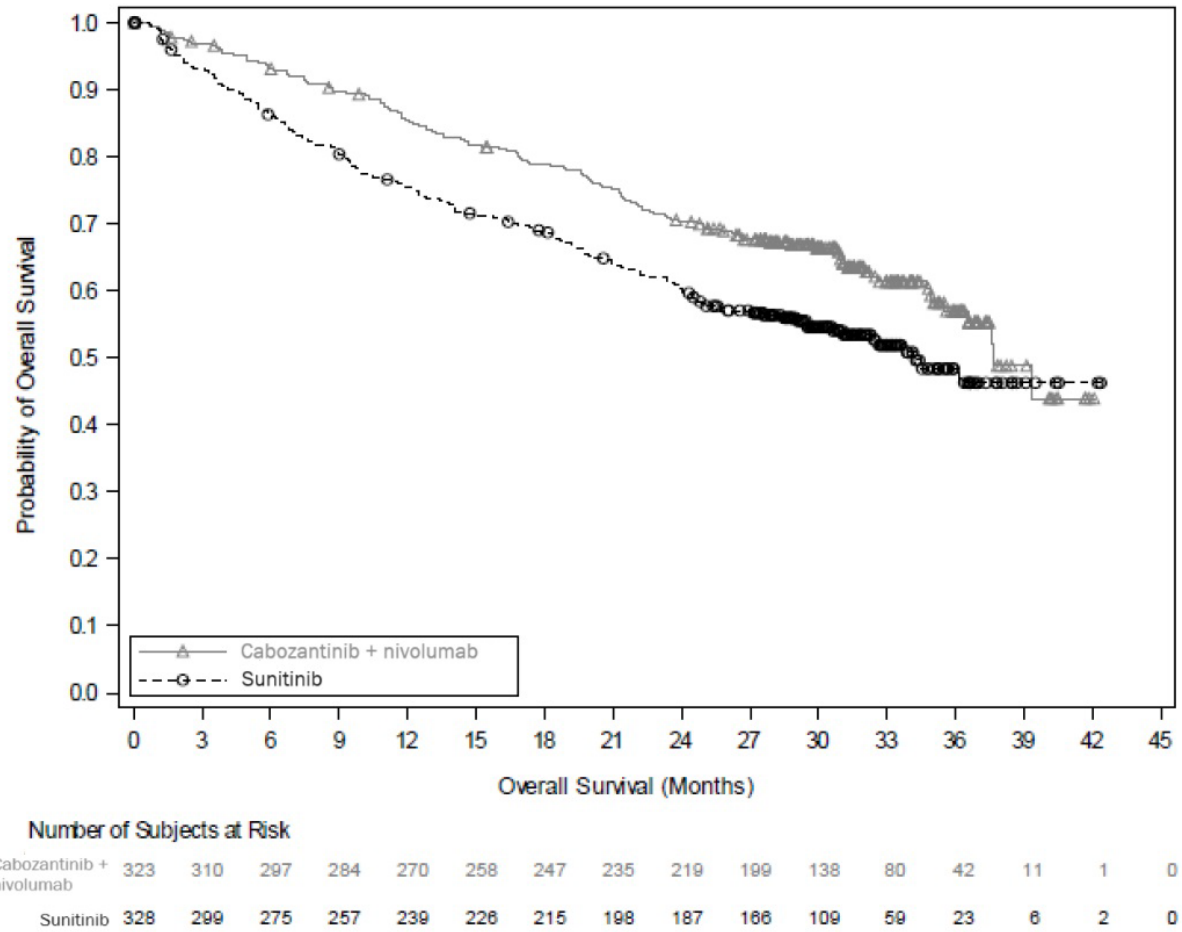
Figure 5. Kaplan-Meier Curve of Progression-Free Survival in CHECKMATE-9ER



Number of Subjects at Risk

Cabozantinib + nivolumab	323	279	234	196	144	77	35	11	4	0
Sunitinib	328	228	159	122	79	31	10	4	1	0

Figure 6. Kaplan-Meier Curve of Updated Overall Survival in CHECKMATE-9ER



In an exploratory analysis, the updated analysis of OS in patients with IMDC favorable, intermediate, intermediate/poor, and poor risk demonstrated a HR (95% CI) of 1.03 (0.55, 1.92), 0.74 (0.54, 1.01), 0.65 (0.50, 0.85), and 0.49 (0.31, 0.79), respectively.

14.2 Hepatocellular Carcinoma

The effectiveness of 34.5 mg once daily of OMCAZIO (cabozantinib) capsules for the treatment of hepatocellular carcinoma has been established from an adequate and well-controlled study of CABOMETYX® (cabozantinib) tablets, which has a different recommended dosage than OMCAZIO. Below is a display of the results of CABOMETYX® (cabozantinib) tablets in this adequate and well-controlled study.

The efficacy of cabozantinib was evaluated in CELESTIAL (NCT01908426), a randomized (2:1), double-blind, placebo-controlled, multicenter trial in patients with hepatocellular carcinoma (HCC) who had previously received sorafenib and had Child Pugh Class A liver impairment. Patients were randomized to receive cabozantinib tablets 60 mg orally once daily (equivalent to OMCAZIO 34.5 mg) or placebo until disease progression or unacceptable toxicity. Randomization was stratified by etiology of disease (hepatitis B virus [HBV] with or without hepatitis C virus [HCV] vs. HCV [without HBV] vs. other [without HBV and HCV]), geographic region (Asia vs. other regions), and presence of extrahepatic spread of disease and/or macrovascular invasion (yes vs. no). The primary efficacy outcome measure was overall survival (OS). Additional outcome measures were progression-free survival (PFS) and objective response rate

(ORR), as assessed by investigators per RECIST 1.1. Tumor assessments were conducted every 8 weeks.

In CELESTIAL, a total of 707 patients were randomized, 470 to cabozantinib and 237 to placebo. The median age was 64 years (range 22 to 86 years), 82% were male, 56% were White and 34% were Asian. Baseline ECOG performance status was 0 (53%) or 1 (47%). The etiology of HCC was attributed to HBV in 38% of patients and HCV in 21%; etiology was attributed to causes other than HBV or HCV in 40%. Macroscopic vascular invasion or extra-hepatic tumor spread was present in 78% of patients and 41% had alpha-fetoprotein (AFP) levels ≥400 mcg/L. All patients received prior sorafenib and 27% received two prior systemic therapy regimens.

Efficacy results are summarized in Table 21, Figure 7, and Figure 8.

Table 21. Efficacy Results from CELESTIAL

Endpoint	**Cabozantinib (n = 470)**	**Placebo (n = 237)**
Overall Survival		
Number of Deaths, (%)	317 (67)	167 (70)
Median OS in Months (95% CI)	10.2 (9.1, 12.0)	8.0 (6.8, 9.4)
Hazard Ratio (95% CI)[1]	0.76 (0.63, 0.92)	
p-value[2]	p=0.0049[3]	
Progression-Free Survival		
Number of Events, (%)	349 (74)	205 (86)
Progressive Disease	284 (60)	186 (78)
Death	65 (14)	19 (8)
Median PFS in Months (95% CI)	5.2 (4.0, 5.5)	1.9 (1.9, 1.9)
Hazard Ratio (95% CI)[1]	0.44 (0.36, 0.52)	
p-value[2]	p<0.0001	
Overall Response Rate (ORR)		
Confirmed ORR (partial responses only) (95% CI)[3]	4% (2.3, 6.0)	0.4% (0.0, 2.3)
p-value[4]	p=0.0086	

CI, confidence interval

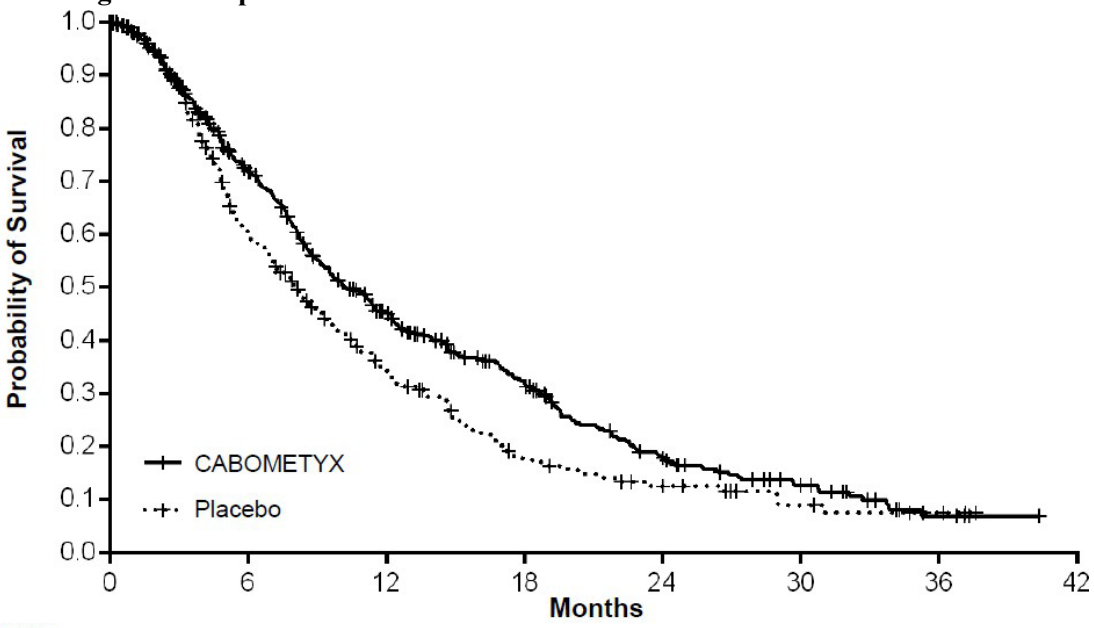
[1] estimated using the Cox proportional-hazard model

[2] log-rank test stratified by etiology of disease (HBV [with or without HCV], HCV [without HBV], or Other), geographic region (Asia, Other Regions), and presence of extrahepatic spread of disease and/or macrovascular invasion (Yes, No) as stratification factors (per IVRS data)

[3] significance level = 0.021 for 78% information (484 deaths) based on O'Brien-Fleming method

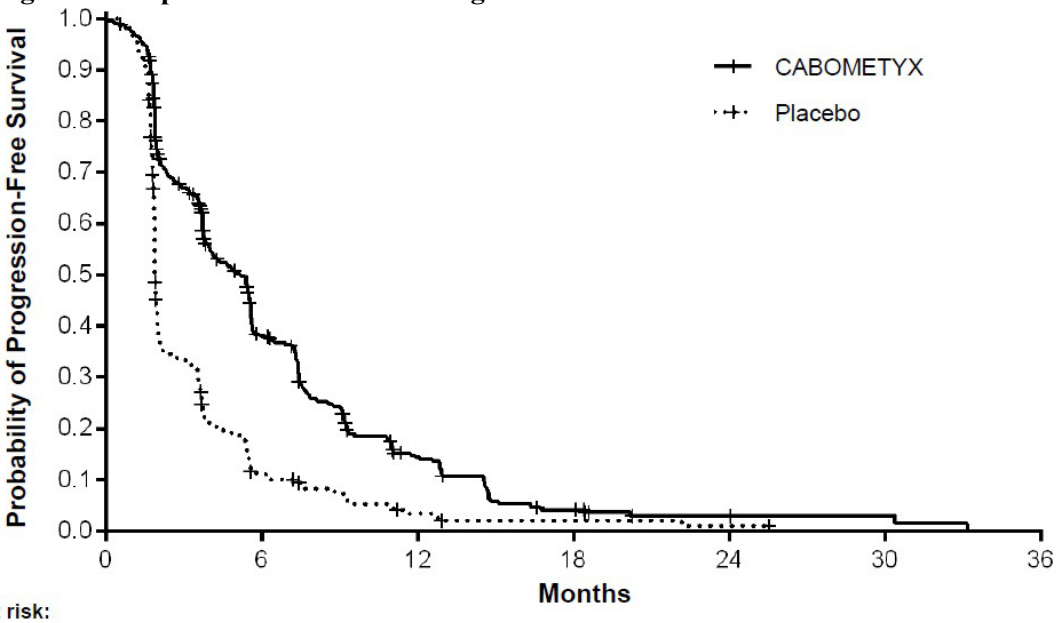
[4] Fisher's exact test

Figure 7. Kaplan-Meier Curve of Overall Survival in CELESTIAL



Number at risk:								
CABOMETYX	470	281	159	93	44	22	4	0
Placebo	237	117	57	25	15	7	3	0

Figure 8. Kaplan-Meier Curve of Progression-Free Survival in CELESTIAL



Number at risk:							
CABOMETYX	470	131	39	10	3	2	0
Placebo	237	21	5	2	1	0	0

14.3 Extra-pancreatic Neuroendocrine Tumors

The effectiveness of 34.5 mg once daily of OMCAZIO (cabozantinib) capsules for the treatment of extra-pancreatic neuroendocrine tumors has been established from an adequate and well-controlled study of CABOMETYX® (cabozantinib) tablets, which has a different recommended dosage than OMCAZIO. Below

is a display of the results of CABOMETYX® (cabozantinib) tablets in this adequate and well-controlled study.

The efficacy of cabozantinib for the treatment of extra-pancreatic neuroendocrine tumors (epNET) was evaluated in CABINET (NCT03375320), a randomized, double-blind, placebo- controlled, multicenter study in patients with unresectable, locally advanced or metastatic epNET that had progressed on prior therapy. Eligible patients were required to have been previously treated with at least one FDA approved therapy (everolimus or lutetium Lu 177 dotatate), other than somatostatin analogs. Patients with active brain metastases or cranial epidural disease, and those who had prior treatment with cabozantinib were excluded. The study also excluded patients with clinically significant gastrointestinal (GI) bleeding, GI abnormalities, and tumor with invasion into the GI tract that may increase the risk for GI bleeding or perforation, and patients with tumor invading or encasing major blood vessels. Patients were randomized (2:1) to receive treatment with cabozantinib tablets 60 mg orally once daily (equivalent to OMCAZIO 34.5 mg) or placebo until disease progression or unacceptable toxicity. Randomization was stratified by concurrent somatostatin analog (SSA) use (yes/no) and primary site (midgut GI/unknown vs non-midgut GI/lung/other). Tumor assessments were performed every 12 weeks. The study included patients with functional and non-functional tumors, and use of somatostatin analogs at a stable dose was permitted for symptom control. Eligible patients randomized to the placebo arm were allowed to crossover to cabozantinib upon confirmation of progressive disease by blinded real time central review.

The major efficacy outcome measure was progression-free survival (PFS) assessed by blinded independent radiology review committee (BIRC) per RECIST 1.1. Additional efficacy outcome measures included overall response rate (ORR), duration of response (DOR) and overall survival (OS).

A total of 199 epNET patients were randomized (2:1) to receive cabozantinib tablets 60 mg orally once daily (n=132) or placebo (n=67). The median age was 66 years (range: 28 to 86), 51% were female; 84% were White; 8% were Black or African American; 2.0% were Asian; 6% had race unknown or race not reported; and 8% were Hispanic or Latino. The primary sites of tumor were small bowel (34%) including duodenum, jejunum & ileum; lung (20%); thymus (5%); rectum (6%); cecum (2.0%); stomach (3.0%); non-cecum colon (1.0%); appendix (0.5%); others (18%); and unknown (12%). In the 199 patients with epNET, 46% had received one prior systemic therapy, 29% had received two prior systemic therapies and 25% had received three or more prior systemic therapies.

The trial demonstrated a statistically significant improvement in PFS as assessed by BIRC, for cabozantinib compared to placebo. An updated OS analysis was conducted when 123 deaths were observed. OS data were not mature with 83 (63%) deaths in cabozantinib arm and 40 (60%) deaths in placebo arm (OS HR=1.05 [95% CI: 0.71, 1.54]). Thirty-seven percent of placebo arm patients crossed over to open label cabozantinib, which may impact the OS endpoint.

Efficacy results are summarized in Table 22 and Figure 9.

Table 22. Efficacy Results in Patients with epNET in CABINET

	Cabozantinib (n=132)	Placebo (n=67)
Progression-Free Survival (PFS)		
Number of Events (%)	68 (52)	39 (58)
Median (95% CI)[1], in months	8.5 (6.8, 12.5)	4.2 (3.0, 5.7)
Hazard Ratio (95% CI)[2]	0.40 (0.26, 0.61)	
p-value[3]	<0.0001	
Overall Response Rate (ORR)		
ORR (95% CI)[4], %	5 (2.2, 11)	0 (0, 5)
Duration of Response (DOR)		
Median (95% CI)[1], in months	8.3 (4.5, NE)	NE

CI, confidence interval; NE, not evaluable

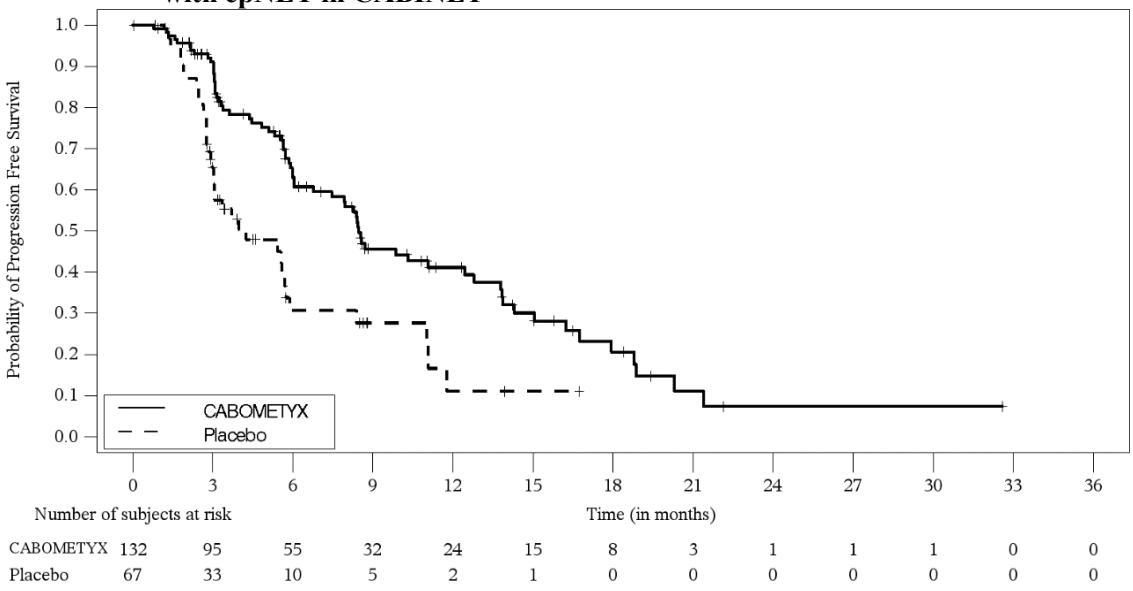
[1] Kaplan-Meier method

[2] Stratified Cox proportional hazards model stratified by concurrent somatostatin analog (SSA) use (yes/no) and primary site (midgut GI/unknown vs non-midgut GI/lung/other)

[3] Stratified log-rank test stratified by concurrent somatostatin analog (SSA) use (yes/no) and primary site (midgut GI/unknown vs non-midgut GI/lung/other) (compared to one-sided alpha=0.001)

[4] Clopper-Pearson method

Figure 9. Kaplan-Meier Curve of Progression-Free Survival in Patients with epNET in CABINET



16 HOW SUPPLIED/STORAGE AND HANDLING

OMCAZIO capsules are supplied in 30-count bottles in a carton as follows:

Strength (mg)	Description	NDC
34.5 mg	opaque white hard gelatin capsules with black imprint “CZB 34.5” on capsule body	NDC 17201-013-30
23 mg	opaque blue cap and opaque white body, hard gelatin capsules with a black imprint “CZB 23” on capsule body	NDC 17201-012-30
11.5 mg	opaque blue hard gelatin capsules with a black imprint “CZB 11.5” on capsule body	NDC 17201-011-30

Store OMCAZIO 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 the patient to read the FDA-approved patient labeling (Patient Information).

- Risk of Medication Errors and Important Administration Information: Advise patients that OMCAZIO is not substitutable with other cabozantinib products on a mg-to-mg basis. Advise patients to take OMCAZIO exactly as prescribed *[see Warnings and Precautions (5.1)]*. Advise patients to swallow the capsules whole with water and not to crush, chew, or open the capsules. Advise patients to take OMCAZIO with or without food *[see Dosage and Administration (2.2)]*.
- 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)]*.
- Perforations and fistulas: Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during OMCAZIO treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain *[see Warnings and Precautions (5.3)]*.
- Thromboembolic events: Inform patients of the risk of arterial and venous thromboembolic events. Advise patients to immediately contact their health care provider for signs and symptoms suggestive of a blood clot such as dyspnea, chest pain, or localized limb edema *[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)]*.
- Cardiac Failure: Advise patients that OMCAZIO can cause cardiac failure. Advise patients to immediately contact their healthcare provider for signs or symptoms of cardiac failure [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)]*.

- Hepatotoxicity: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (5.9)]*.
- Adrenal insufficiency: Advise patients receiving OMCAZIO in combination with nivolumab to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency *[see Warnings and Precautions (5.10)]*.
- Proteinuria: Advise patients to contact their healthcare provider for signs or symptoms of proteinuria *[see Warnings and Precautions (5.11)]*.
- 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 (5.12)]*.
- Impaired wound healing: Advise patients that OMCAZIO can impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure *[see Dosage and Administration (2.2), Warnings and Precautions (5.13)]*.
- Reversible posterior leukoencephalopathy syndrome: Advise patients to immediately contact their health care provider for new onset or worsening neurological function *[see Warnings and Precautions (5.14)]*.
- Thyroid dysfunction: Advise patients that OMCAZIO can cause thyroid dysfunction and that their thyroid function should be monitored regularly during treatment. Advise patients to immediately contact their healthcare provider for signs or symptoms of thyroid dysfunction *[see Warnings and Precautions (5.15)]*.
- Embryo-fetal toxicity:

  Advise females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.16), Use in Specific Populations (8.1)]*.

  Advise females of reproductive potential to use effective contraception during treatment with OMCAZIO and for 4 months after the final dose *[see Use in Specific Populations (8.3)]*.
- Lactation: Advise women not to breastfeed during treatment with OMCAZIO 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)]*.

Manufactured for:
Handa Oncology, LLC. San Jose, CA 95110

PATIENT INFORMATION
OMCAZIO™ (om-KAW-zee-oh)
cabozantinib
capsules, for oral use

If your healthcare provider prescribes OMCAZIO in combination with nivolumab, also read the Medication Guide that comes with nivolumab.

What is OMCAZIO?

OMCAZIO is a prescription medicine used to treat:

- adults with kidney cancer (renal cell carcinoma). OMCAZIO may be used:
  - alone to treat people with renal cell carcinoma (RCC) that has spread (advanced RCC).
  - in combination with nivolumab when your cancer has spread (advanced RCC), and you have not had treatment for your advanced RCC.
- adults with liver cancer (hepatocellular carcinoma) who have been previously treated with the medicine sorafenib.
- adults and children 12 years of age and older who have a type of cancer called extra-pancreatic neuroendocrine tumors (epNET) that has been previously treated, cannot be treated by surgery, and has spread (locally advanced or metastatic).

It is not known if OMCAZIO for the treatment of epNET is safe and effective in children younger than 12 years of age.

It is not known if OMCAZIO is safe and effective in children with renal cell carcinoma or hepatocellular carcinoma.

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

- have had a liver problem other than liver cancer
- have a recent history of bleeding, including coughing up or vomiting blood, or black tarry stools.
- have an open or healing wound
- have high blood pressure
- have heart problems
- plan to have any surgery, dental procedure, or have had a recent surgery. You should stop taking OMCAZIO at least 3 weeks before any planned surgery. See **"What are the possible side effects of OMCAZIO?"**
- are pregnant, or plan to become pregnant. OMCAZIO can harm your unborn baby.

  For females who are able to become pregnant:
  - Your healthcare provider will check your pregnancy status before you start treatment with OMCAZIO
  - Use effective birth control (contraception) during treatment and for 4 months after your last dose of OMCAZIO.
  - Talk to your healthcare provider about birth control methods that may be right for you.
  - Tell your healthcare provider right away if you become pregnant or think that you are pregnant during treatment with OMCAZIO.
- are breastfeeding or plan to breastfeed. It is not known if OMCAZIO passes into your breast milk. Do not breastfeed during treatment and for 4 months after your last dose of OMCAZIO.

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

How should I take OMCAZIO?

- Do not switch from OMCAZIO to other medicines that contain cabozantinib without talking to your healthcare provider. The amount of cabozantinib in a dose of OMCAZIO may not be the same as the amount in other medicines that contain cabozantinib.
- Make sure you receive the correct dosage form each time you or your child's prescription is filled to avoid using the wrong medicine.
- Take OMCAZIO exactly as your healthcare provider tells you to take it.
- Take OMCAZIO with or without food.
- Swallow OMCAZIO capsules whole with water.
- **Do not** crush, chew or open OMCAZIO capsules.
- If you miss a dose of OMCAZIO, take the missed dose as soon as possible. If a dose is missed by more than 12 hours, skip the missed dose and take your next dose at the normal time. **Do not** take 2 doses at the same time to make up for the missed dose.
- If you take too much OMCAZIO, call your healthcare provider or the Poison Help line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What should I avoid while taking OMCAZIO?

Avoid drinking grapefruit juice, eating grapefruit or taking supplements that contain grapefruit and taking St. John's wort during treatment with OMCAZIO.

What are the possible side effects of OMCAZIO?

OMCAZIO can cause serious side effects, including:

- **bleeding (hemorrhage).** OMCAZIO 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 OMCAZIO, including:
  - coughing up blood or blood clots
  - vomiting blood or if your vomit looks like coffee-grounds
  - red or black (looks like tar) stools
  - menstrual bleeding that is heavier than normal
  - any unusual or heavy bleeding
- **a tear in your stomach or intestinal wall (perforation) or an abnormal connection between 2 parts of your body (fistula).** Tell your healthcare provider right away if you get tenderness or pain in your stomach-area (abdomen) that is severe or that does not go away.
- **blood clots, stroke, heart attack, and chest pain.** Get emergency help right away if you get:
  - swelling or pain in your arms or legs
  - shortness of breath
  - feel lightheaded or faint
  - sweating more than usual
  - numbness or weakness of your face, arm or leg, especially on one side of your body
  - sudden confusion, trouble speaking or understanding
  - sudden trouble seeing in one or both eyes
  - sudden trouble walking
  - dizziness, loss of balance or coordination
  - a sudden severe headache
- **high blood pressure (hypertension).** Hypertension is common with OMCAZIO and sometimes can be severe. Your healthcare provider will check your blood pressure before starting OMCAZIO and regularly during treatment with OMCAZIO. If needed, your healthcare provider may prescribe medicine to treat your high blood pressure. Tell your healthcare provider if you develop severe headaches, nose bleeds, tiredness or confusion, vision changes, chest pain, trouble breathing, irregular heartbeat, or blood in your urine.
- **heart problems.** OMCAZIO can cause heart failure that may lead to death. Your healthcare provider may check your heart function before and during treatment with OMCAZIO. Tell your healthcare provider right away if you get any of the following signs and symptoms:
  - feeling like your heart is pounding, racing, or beating irregularly
  - shortness of breath
  - swelling of your ankles or feet

- feeling lightheaded
- tiredness

- **diarrhea.** Diarrhea is common with OMCAZIO 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 OMCAZIO 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.
- **liver problems.** Liver problems may happen during treatment with OMCAZIO. When OMCAZIO is taken in combination with nivolumab, severe changes in liver function tests may happen more often than if you take OMCAZIO alone. Your healthcare provider will do blood tests to check your liver function before and during treatment with OMCAZIO. Tell your healthcare provider right away if you develop symptoms of liver problems including: yellowing of your skin or the whites of your eyes, severe nausea or vomiting, pain on the right side of your stomach-area (abdomen), dark urine, bleeding or bruising more easily than normal.
- **adrenal gland problems.** Your healthcare provider will monitor you for this problem. Your healthcare provider may prescribe hormone replacement therapy or corticosteroid medicines if needed. Tell your healthcare provider right away if you develop any of the following signs or symptoms: extreme tiredness, dizziness or fainting, weakness, nausea, or vomiting.
- **protein in your urine and possible kidney problems.** Symptoms may include swelling in your hands, arms, legs, or feet. Your healthcare provider will check you for this problem during treatment with OMCAZIO.
- **severe jaw bone problems (osteonecrosis).** Your healthcare provider should examine your mouth before you start and during treatment with OMCAZIO. Tell your dentist that you are taking OMCAZIO. It is important for you to practice good mouth care during treatment with OMCAZIO. Tell your healthcare provider right away if you develop any symptoms of jaw problems, including: jaw pain, toothache, or sores on your gums.
- **wound healing problems.** Wound healing problems have happened in people who take OMCAZIO. Tell your healthcare provider if you plan to have any surgery before or during treatment with OMCAZIO.
  - You should stop taking OMCAZIO at least 3 weeks before any planned surgery.
  - Your healthcare provider should tell you when you may start taking OMCAZIO again after surgery.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** A condition called reversible posterior leukoencephalopathy syndrome can happen during treatment with OMCAZIO. Tell your healthcare provider right away if you have new or worsening headaches, seizures, confusion, changes in vision, or problems thinking.
- **change in thyroid function.** OMCAZIO can cause changes in your thyroid function, including changes to thyroid hormone levels in your blood. Your healthcare provider will do blood tests to check your thyroid function before and during treatment with OMCAZIO.

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

The most common side effects of OMCAZIO include:

- tiredness
- nausea and vomiting
- decreased appetite
- weight decreased
- constipation

The most common side effects of OMCAZIO when used in combination with nivolumab include:

- tiredness
- mouth sores
- rash
- low thyroid hormone levels (hypothyroidism)

- pain in muscles, bones, and joints
- decreased appetite
- nausea
- changes in the way things taste
- stomach-area (abdominal) pain
- cough
- upper respiratory tract infection

OMCAZIO may cause fertility problems in females and males, which may affect your ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all of the possible side effects of OMCAZIO. 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 OMCAZIO?

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

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

General information about the safe and effective use of OMCAZIO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use OMCAZIO for a condition for which it was not prescribed. Do not give OMCAZIO to other people, even if they have the same symptoms you have. It may harm them.
You can ask your pharmacist or healthcare provider for information about OMCAZIO that is written for health professionals.

What are the ingredients in OMCAZIO?

Active ingredient: cabozantinib

Inactive ingredients: ammonia solution, ascorbic palmitate, black iron oxide, FD&C Blue #1, gelatin, polyoxyl 32 stearate, potassium hydroxide, propylene glycol, shellac, titanium dioxide, and tocopherol.

Manufactured for Handa Oncology LLC, Inc. San Jose, CA 95110
For more information, go to www.OMCAZIO.com or call 1-844-204-8384.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 09/2026