NOW APPROVED

IN **FIRST-LINE** ADVANCED RCC

CABOMETYX®
(cabozantinib) tablets
60 mg | 40 mg | 20 mg

Dear Healthcare Professional,

Exelixis® is pleased to announce an important update regarding the treatment of advanced renal cell carcinoma (RCC). CABOMETYX® (cabozantinib) is now FDA approved for the treatment of patients with advanced RCC—an expanded approval from the previous indication for patients who received prior anti-angiogenic therapy that was received in 2016.[1]

This new approval in the first line is supported by clinical data from the CABOSUN trial, which included a statistically superior PFS with a median difference of 3.3 months, making CABOMETYX the **first and only TKI to surpass the efficacy of sunitinib** in advanced RCC.[1]*

There were no new safety signals demonstrated with CABOMETYX in the CABOSUN trial. The most commonly reported (≥25%) adverse reactions are: diarrhea, fatigue, nausea, decreased appetite, hypertension, PPE, weight decreased, vomiting, dysgeusia, and stomatitis.[1]

See more details from the CABOSUN trial throughout.

Sincerely,

Gisela M. Schwab, MD
President, Product Development and Medical Affairs and Chief Medical Officer

EXELIXIS®

*Patients had ≥1 IMDC risk factors.[1]

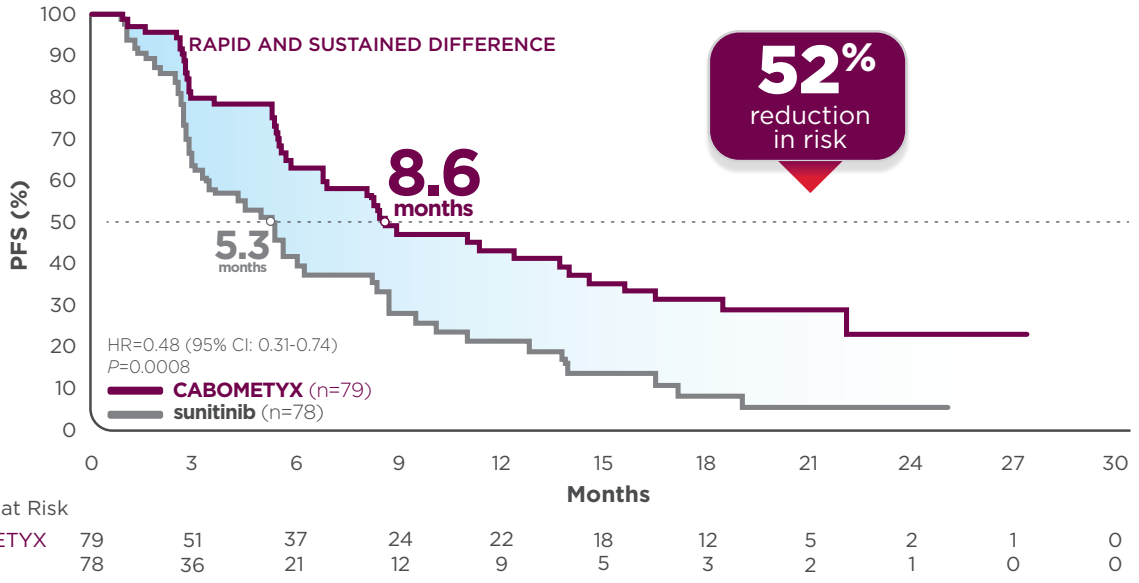
FDA=US Food and Drug Administration; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; PFS=progression-free survival; PPE=palmar-plantar erythrodysesthesia; TKI=tyrosine kinase inhibitor.

Please see Important Safety Information throughout and accompanying full Prescribing Information.

CABOSUN Clinical Trial Results

CABOMETYX demonstrated a statistically significant improvement in median PFS vs sunitinib[1]*

PRIMARY ENDPOINT: PFS



Patients at Risk

CABOMETYX	79	51	37	24	22	18	12	5	2	1	0
sunitinib	78	36	21	12	9	5	3	2	1	0	0

- Sustained separation of the PFS curve at 12 and 18 months (median follow-up of 25 months)[1,2]

CABOSUN: A head-to-head, randomized (1:1), open-label, multicenter trial of CABOMETYX (n=79) 60 mg administered orally once daily or sunitinib (n=78) 50 mg administered orally once daily on a schedule of 4 weeks on treatment followed by 2 weeks off in first-line patients with advanced RCC, conducted by a cooperative group in the US. Patients had to have intermediate- or poor-risk disease, as defined by IMDC risk categories, clear-cell component, measurable disease, and ECOG PS 0-2. The primary endpoint was PFS. Secondary endpoints included ORR, OS, and safety. Stratification was based on IMDC risk and presence or absence of bone metastases.[1-3]

*PFS was assessed by a retrospective blinded IRRC.[1]

CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; IRRC=independent radiology review committee; ORR=objective response rate; OS=overall survival; PS=performance status.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Severe and fatal hemorrhages have occurred with CABOMETYX. In RCC trials, the incidence of Grade ≥3 hemorrhagic events was 3% in CABOMETYX patients. Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

CABOMETYX® (cabozantinib) tablets
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SECONDARY ENDPOINT: OS[3]

Reduction in the risk of death was reported as 20%[1]

- The hazard ratio for CABOMETYX vs sunitinib was 0.80 (95% CI: 0.53-1.21)[1]
- The trial did not have a prespecified hypothesis for OS, and statistical testing of this endpoint was not performed[1-3]

SECONDARY ENDPOINT: ORR[3]

CABOMETYX more than doubled ORR vs sunitinib[1]

- ORR was 20% for CABOMETYX (95% CI: 12.0%-30.8%) vs 9% for sunitinib (95% CI: 3.7%-17.6%)[1]
  - As assessed by a retrospective blinded IRRC, all responses were partial responses
- The trial did not have a prespecified hypothesis for ORR, and statistical testing of this endpoint was not performed[1,2]

INDICATION

CABOMETYX® (cabozantinib) is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Gastrointestinal (GI) Perforations and Fistulas: In RCC trials, GI perforations were reported in 1% of CABOMETYX patients. Fatal perforations occurred in patients treated with CABOMETYX. In RCC studies, fistulas were reported in 1% of CABOMETYX patients. Monitor patients for symptoms of perforations and fistulas, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a GI perforation or a fistula that cannot be appropriately managed.

Thrombotic Events: Thrombotic events increased with CABOMETYX. In RCC trials, venous thromboembolism occurred in 9% (including 5% pulmonary embolism) and arterial thromboembolism occurred in 1% of CABOMETYX patients. Fatal thrombotic events occurred in the cabozantinib clinical program. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or any other arterial thromboembolic complication.

Hypertension and Hypertensive Crisis: Treatment-emergent hypertension, including hypertensive crisis, increased with CABOMETYX. In RCC trials, hypertension was reported in 44% (18% Grade ≥3) of CABOMETYX patients. Monitor blood pressure prior to initiation and regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX if there is evidence of hypertensive crisis or for severe hypertension that cannot be controlled with antihypertensive therapy or medical management.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

CABOMETYX®
(cabozantinib) tablets
60 mg | 40 mg | 20 mg

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Diarrhea: In RCC trials, diarrhea occurred in 74% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 diarrhea or Grade 3-4 diarrhea that cannot be managed with standard antidiarrheal treatments until improvement to Grade 1; resume CABOMETYX at a reduced dose.

Palmar-Plantar Erythrodysesthesia (PPE): In RCC trials, PPE occurred in 42% of CABOMETYX patients. Grade 3 PPE occurred in 8% of CABOMETYX patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPE or Grade 3 PPE until improvement to Grade 1; resume CABOMETYX at a reduced dose.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in the cabozantinib clinical program. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Embryo-fetal Toxicity: CABOMETYX can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during CABOMETYX treatment and for 4 months after the last dose.

ADVERSE REACTIONS

The most commonly reported (≥25%) adverse reactions were: diarrhea, fatigue, nausea, decreased appetite, hypertension, PPE, weight decreased, vomiting, dysgeusia, and stomatitis.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If concomitant use with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage.

Strong CYP3A4 Inducers: If concomitant use with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed while taking CABOMETYX and for 4 months after the final dose.

Hepatic Impairment: In patients with mild to moderate hepatic impairment, reduce the CABOMETYX dosage. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

References: 1. CABOMETYX® (cabozantinib) Prescribing Information. Exelixis, Inc, 2017. **2.** Data on file. Exelixis, Inc. **3.** Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the Alliance A031203 CABOSUN trial. *J Clin Oncol.* 2017;35(6):591-597.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

Learn more at CABOMETYX.com

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(cabozantinib) tablets
60 mg | 40 mg | 20 mg

EXELIXIS®

CA-0605 12/17

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

RECENT MAJOR CHANGES

Indications and Usage (1)	12/2017
Warnings and Precautions (5)	12/2017

INDICATIONS AND USAGE

CABOMETYX is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

DOSAGE AND ADMINISTRATION

- Recommended Dose: 60 mg orally, once daily. (2.1)
- Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking CABOMETYX. (2.1)
- Do NOT substitute CABOMETYX tablets with cabozantinib capsules. (2.1)

DOSAGE FORMS AND STRENGTHS

20 mg, 40 mg, and 60 mg tablets. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Hemorrhage: Do not administer CABOMETYX if recent history of severe hemorrhage. (5.1)
- GI Perforations and Fistulas: Monitor for symptoms. Discontinue CABOMETYX for fistulas that cannot be adequately managed or perforations. (5.2)
- Thrombotic Events: Discontinue CABOMETYX for myocardial infarction, cerebral infarction, or other serious arterial thromboembolic events. (5.3)
- Hypertension and Hypertensive Crisis: Monitor blood pressure regularly. Discontinue CABOMETYX for hypertensive crisis or severe hypertension that cannot be controlled with anti-hypertensive therapy. (5.4)
- Diarrhea: May be severe. Interrupt CABOMETYX treatment immediately until diarrhea resolves or decreases to Grade 1. Recommend standard antidiarrheal treatments. (5.5)
- Palmar-plantar erythrodysesthesia (PPE): Interrupt CABOMETYX treatment until PPE resolves or decreases to Grade 1. (5.6)
- Reversible posterior leukoencephalopathy syndrome (RPLS): Discontinue CABOMETYX. (5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.8, 8.1, 8.3)

ADVERSE REACTIONS

The most commonly reported (≥ 25%) adverse reactions are: diarrhea, fatigue, nausea, decreased appetite, hypertension, palmar-plantar erythrodysesthesia (PPE), weight decreased, vomiting, dysgeusia, and stomatitis. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Exelixis, Inc. at 1-855-500-3935 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Strong CYP3A4 inhibitors: Reduce the CABOMETYX dosage. (2.2, 7)
- Strong CYP3A4 inducers: Increase the CABOMETYX dosage. (2.2, 7)

USE IN SPECIFIC POPULATIONS

- Mild to Moderate Hepatic Impairment: Reduce the CABOMETYX dosage. (2.2, 8.6)
- Lactation: Advise not to breastfeed while taking CABOMETYX. (8.2)

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

Revised: 12/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

Do not substitute CABOMETYX tablets with cabozantinib capsules.

The recommended oral daily dose of CABOMETYX is 60 mg. Do not administer CABOMETYX with food. Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking CABOMETYX. Continue treatment until patient no longer experiences clinical benefit or experiences unacceptable toxicity.

Swallow CABOMETYX tablets whole. Do not crush CABOMETYX tablets.

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

Do not ingest foods (e.g., grapefruit, grapefruit juice) or nutritional supplements that are known to inhibit cytochrome P450 during CABOMETYX treatment *[see Drug Interactions (7)]*.

2.2 Dosage Adjustments

For Patients Undergoing Surgery

Stop treatment with CABOMETYX at least 28 days prior to scheduled surgery, including dental surgery *[see Warnings and Precautions (5.1)]*.

For Adverse Reactions

Management of Grade ≤3 adverse reactions may require dose modifications and/or supportive care. If dose reduction is required, a 20 mg decrease from the previously administered dose is recommended. If Grade ≤3 adverse reaction is intolerable, withhold CABOMETYX. Withhold CABOMETYX for NCI CTCAE Grade 4 adverse reactions.

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

- If previously receiving 60 mg daily dose, resume treatment at 40 mg daily
- If previously receiving 40 mg daily dose, resume treatment at 20 mg daily
- If previously receiving 20 mg daily dose, resume at 20 mg if tolerated, otherwise, discontinue CABOMETYX

Permanently discontinue CABOMETYX for any of the following:

- development of unmanageable fistula or GI perforation
- severe hemorrhage

- arterial thromboembolic event (e.g., myocardial infarction, cerebral infarction)
- hypertensive crisis or severe hypertension despite optimal medical management
- nephrotic syndrome
- reversible posterior leukoencephalopathy syndrome

In Patients Concurrently Taking a Strong CYP3A4 Inhibitor

Reduce the daily CABOMETYX dose by 20 mg (for example, from 60 mg to 40 mg daily or from 40 mg to 20 mg daily). Resume the dose that was used prior to initiating the CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.

In Patients Concurrently Taking a Strong CYP3A4 Inducer

Increase the daily CABOMETYX dose by 20 mg (for example, from 60 mg to 80 mg daily or from 40 mg to 60 mg daily) as tolerated. Resume the dose that was used prior to initiating the CYP3A4 inducer 2 to 3 days after discontinuation of the strong inducer. The daily dose of CABOMETYX should not exceed 80 mg *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.

In Patients with Hepatic Impairment

Reduce the starting dose of CABOMETYX to 40 mg once daily in patients with mild or moderate hepatic impairment. CABOMETYX is not recommended for use in patients with severe hepatic impairment *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

60 mg CABOMETYX tablets are yellow film-coated, oval shaped with no score, and debossed with “XL” on one side and “60” on the other side.

40 mg CABOMETYX tablets are yellow film-coated, triangle shaped with no score, and debossed with “XL” on one side and “40” on the other side.

20 mg CABOMETYX tablets are yellow film-coated, round with no score, and debossed with “XL” on one side and “20” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Severe and fatal hemorrhages have occurred with CABOMETYX. In two RCC studies, the incidence of Grade ≥ 3 hemorrhagic events was 3% in CABOMETYX-treated patients.

Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage *[see Dosage and Administration (2.2)]*.

5.2 GI Perforations and Fistulas

In RCC studies, fistulas were reported in 1% of CABOMETYX-treated patients. Fatal perforations occurred in patients treated with CABOMETYX. In RCC studies, gastrointestinal (GI) perforations were reported in 1% of CABOMETYX-treated patients.

Monitor patients for symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a fistula which cannot be appropriately managed or a GI perforation.

5.3 Thrombotic Events

CABOMETYX treatment results in an increased incidence of thrombotic events. In RCC studies, venous thromboembolism occurred in 9% (including 5% pulmonary embolism) and arterial thromboembolism occurred in 1% of CABOMETYX-treated patients. Fatal thrombotic events occurred in the cabozantinib clinical program.

Discontinue CABOMETYX in patients who develop an acute myocardial infarction or any other arterial thromboembolic complication.

5.4 Hypertension and Hypertensive Crisis

CABOMETYX treatment results in an increased incidence of treatment-emergent hypertension, including hypertensive crisis. In RCC studies, hypertension was reported in 44% (18% Grade ≥ 3) of CABOMETYX-treated patients. Monitor blood pressure prior to initiation and regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy. Discontinue CABOMETYX if there is evidence of hypertensive crisis or severe hypertension despite optimal medical management.

5.5 Diarrhea

In RCC studies, diarrhea occurred in 74% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 11% of patients treated with CABOMETYX. Withhold CABOMETYX in patients who develop intolerable Grade 2 diarrhea or Grade 3-4 diarrhea that cannot be managed with standard antidiarrheal treatments until improvement to Grade 1; resume CABOMETYX at a reduced dose.

5.6 Palmar-Plantar Erythrodysesthesia

In RCC studies, palmar-plantar erythrodysesthesia (PPE) occurred in 42% of patients treated with CABOMETYX. Grade 3 PPE occurred in 8% of patients treated with CABOMETYX. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPE or Grade 3 PPE until improvement to Grade 1; resume CABOMETYX at a reduced dose.

5.7 Reversible Posterior Leukoencephalopathy Syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in the cabozantinib clinical program. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

5.8 Embryo-fetal Toxicity

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

6 ADVERSE REACTIONS

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

- Hemorrhage *[see Warnings and Precautions (5.1)]*
- GI Perforations and Fistulas *[see Warnings and Precautions (5.2)]*
- Thrombotic Events *[see Warnings and Precautions (5.3)]*
- Hypertension and Hypertensive Crisis *[see Warnings and Precautions (5.4)]*
- Diarrhea *[see Warnings and Precautions (5.5)]*
- Palmar-plantar erythrodysesthesia *[see Warnings and Precautions (5.6)]*
- Reversible Posterior Leukoencephalopathy Syndrome *[see Warnings and Precautions (5.7)]*

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.

METEOR

The safety of CABOMETYX was evaluated in METEOR, a randomized, open-label trial in which 331 patients with advanced renal cell carcinoma received 60 mg CABOMETYX and 322 patients received 10 mg everolimus administered 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)]*. The median duration of treatment was 7.6 months (range 0.3 – 20.5) for patients receiving CABOMETYX and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

Adverse reactions which occurred in ≥ 25% of CABOMETYX-treated patients included, in order of decreasing frequency: 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, lymphocytes decreased, anemia, hypokalemia, and GGT increased.

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

Table 1. Adverse Reactions Occurring in ≥ 10% Patients Who Received CABOMETYX in METEOR

Adverse Reaction	**CABOMETYX (n=331)[1]**		**Everolimus (n=322)**	
	All Grades[2]	**Grade 3-4**	**All Grades[2]**	**Grade 3-4**
	Percentage (%) of Patients			
Gastrointestinal Disorders				
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 Disorders and Administration Site Conditions				
Fatigue	56	9	47	7
Mucosal inflammation	19	<1	23	3
Asthenia	19	4	16	2
Metabolism and Nutrition Disorders				
Decreased appetite	46	3	34	<1
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia	42	8	6	<1
Rash [4]	23	<1	43	<1
Dry skin	11	0	10	0
Vascular Disorders				
Hypertension [5]	39	16	8	3
Investigations				
Weight decreased	31	2	12	0

Adverse Reaction	CABOMETYX (n=331) [1]		Everolimus (n=322)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Nervous System Disorders				
Dysgeusia	24	0	9	0
Headache	11	<1	12	<1
Dizziness	11	0	7	0
Endocrine Disorders				
Hypothyroidism	21	0	<1	<1
Respiratory, Thoracic, and Mediastinal Disorders				
Dysphonia	20	<1	4	0
Dyspnea	19	3	29	4
Cough	18	<1	33	<1
Blood and Lymphatic Disorders				
Anemia	17	5	38	16
Musculoskeletal and Connective Tissue Disorders				
Pain in extremity	14	1	8	<1
Muscle spasms	13	0	5	0
Arthralgia	11	<1	14	1
Renal and Urinary Disorders				
Proteinuria	12	2	9	<1

[1] One subject randomized to everolimus received cabozantinib.
[2] National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0
[3] Includes PT terms abdominal pain, abdominal pain upper, and abdominal pain lower
[4] Includes PT 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 PT terms hypertension, blood pressure increased, hypertensive crisis, blood pressure fluctuation

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

Table 2. Laboratory Abnormalities Occurring in ≥ 25% Patients Who Received CABOMETYX in METEOR

Test	CABOMETYX (n=331)		Everolimus (n=322)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	Percentage (%) of Patients			
Chemistry				
AST increased	74	3	40	<1
ALT increased	68	3	32	<1
Creatinine increased	58	<1	71	0
Triglycerides increased	53	4	73	13
Hypophosphatemia	48	8	36	5
Hyperglycemia	37	2	59	8
Hypoalbuminemia	36	2	28	<1
ALP increased	35	2	29	1
Hypomagnesemia	31	7	4	<1
Hyponatremia	30	8	26	6
GGT increased	27	5	43	9
Hematology				
White blood cells decreased	35	<1	31	<1
Absolute neutrophil count decreased	31	2	17	<1
Hemoglobin decreased	31	4	71	17
Lymphocytes decreased	25	7	39	12
Platelets decreased	25	<1	27	<1

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.
National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0

CABOSUN

The safety of CABOMETYX was evaluated in CABOSUN, a randomized, open-label trial in patients with advanced renal cell carcinoma, in which 78 patients received 60 mg CABOMETYX daily and 72 patients received 50 mg sunitinib taken once daily (4 weeks on treatment followed by 2 weeks off), until disease progression or unacceptable toxicity *[see Clinical Studies (14)]*. The median duration of treatment was 6.5 months (range 0.2 – 28.7) for patients receiving CABOMETYX 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 CABOMETYX and 6 deaths in patients treated with sunitinib. Of the 4 patients treated with CABOMETYX, two patients died due to gastrointestinal perforation, one patient had acute renal failure, and one 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 CABOMETYX were hypertension, diarrhea, hyponatremia, hypophosphatemia, PPE, fatigue, ALT increased, decreased appetite, stomatitis, pain, hypotension, and syncope.

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

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

	CABOMETYX (n = 78)	**Sunitinib (n = 72)**
	Grade 3-4[1]	**Grade 3-4**[1]
	Percentage (%) of Patients	
Patients with any Grade 3-4 Adverse Reaction	68	65
Gastrointestinal Disorders		
Diarrhea	10	11
Stomatitis	5	6
Nausea	3	4
Vomiting	1	3
Constipation	1	0
General Disorders and Administration Site Conditions		
Fatigue	6	17
Pain	5	0
Metabolism and Nutrition Disorders		
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 Skin Disorders		
Palmar-plantar erythrodysesthesia	8	4
Skin ulcer	3	0
Vascular Disorders		
Hypertension[3]	28	21
Hypotension	5	1
Angiopathy	1	1
Investigations		
ALT increased[2]	5	0
Weight decreased	4	0
AST increased[2]	3	3
Blood creatinine increased[2]	3	3
Lymphocyte count decreased[2]	1	6
Platelet count decreased[2]	1	11
Nervous System Disorders		
Syncope	5	0

	CABOMETYX (n = 78)	Sunitinib (n = 72)
	Grade 3-4[1]	Grade 3-4[1]
	Percentage (%) of Patients	
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	1	6
Dysphonia	1	0
Blood and Lymphatic Disorders		
Anemia	1	3
Psychiatric Disorders		
Depression	4	0
Confusional state	1	1
Infections and Infestations		
Lung infection	4	0
Musculoskeletal and Connective Tissue Disorders		
Back pain	4	0
Bone pain	3	1
Pain in extremity	3	0
Arthralgia	1	0
Renal and Urinary Disorders		
Renal failure acute	4	1
Proteinuria	3	1

ALT, alanine aminotransferase; AST, aspartate aminotransferase

[1] National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0

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

[3] Includes PT term hypertension

7 DRUG INTERACTIONS

Table 4. Clinically Significant Drug Interactions Involving Drugs that Affect Cabozantinib

Strong CYP3A4 Inhibitors	
Clinical Implications:	• Concomitant use of CABOMETYX with a strong CYP3A4 inhibitor increased the exposure of cabozantinib compared to the use of CABOMETYX alone *[see Clinical Pharmacology (12.3)]*. • Increased cabozantinib exposure may increase the risk of exposure-related toxicity.
Prevention or Management:	Reduce the dosage of CABOMETYX if concomitant use with strong CYP3A4 inhibitors cannot be avoided *[see Dosage and Administration (2.2)]*.
Examples:	Boceprevir, clarithromycin, conivaptan, grapefruit juice[a], indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, and voriconazole
Strong CYP3A4 Inducers	
Clinical Implications:	• Concomitant use of CABOMETYX with a strong CYP3A4 inducer decreased the exposure of cabozantinib compared to the use of CABOMETYX alone *[see Clinical Pharmacology (12.3)]*. • Decreased cabozantinib exposure may lead to reduced efficacy.
Prevention or Management:	Increase the dosage of CABOMETYX if concomitant use with strong CYP3A4 inducers cannot be avoided *[see Dosage and Administration (2.2)]*.
Examples:	Rifampin, phenytoin, carbamazepine, phenobarbital, rifabutin, rifapentine, and St. John's Wort[b]

[a] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).
[b] The effect of St. John's Wort varies widely and is preparation-dependent

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data in pregnant women to inform the drug-associated risk. In animal developmental and reproductive toxicology studies administration of cabozantinib to pregnant rats and rabbits during organogenesis resulted in embryofetal lethality and structural anomalies at exposures that were below those occurring clinically at the recommended dose *[see Nonclinical Toxicology (13.1)]*. Advise pregnant women or women of childbearing potential of the potential hazard to a fetus.

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

Data

Animal Data

In an embryo-fetal development study in pregnant rats, daily oral administration of cabozantinib throughout organogenesis caused increased embryo-fetal lethality compared to controls at a dose of 0.03 mg/kg (approximately 0.12-fold of human 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 infant, or milk production. Because of the potential for serious adverse reactions in a breastfed infant from CABOMETYX, advise a lactating woman not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

CABOMETYX can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

Infertility

Females and Males

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

8.4 Pediatric Use

The safety and effectiveness of CABOMETYX in pediatric patients have not been established.

Juvenile Animal Data

Juvenile rats were administered cabozantinib daily at doses of 1 or 2 mg/kg/day from Postnatal Day 12 (comparable to less than 2 years in humans) through Postnatal Day 35 or 70. Mortalities occurred at doses equal and greater than 1 mg/kg/day (approximately 0.16 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 the 2 mg/kg dose level (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 RCC studies, 41% of patients treated with CABOMETYX were age 65 years and older, and 8% of patients were 75 years and older.

Grade 3-4 adverse reactions occurred in 73% of patients age 65 years and older, and in 76% of patients 75 years and older. No overall differences in safety or efficacy were observed between older and younger patients.

8.6 Hepatic Impairment

Increased exposure to cabozantinib has been observed in patients with mild to moderate hepatic impairment. Reduce the CABOMETYX dose in patients with mild (Child-Pugh score (C-P) A) or moderate (C-P B) hepatic impairment. CABOMETYX is not recommended for use in patients

with severe hepatic impairment *[see Dosage and Administration (2.2), and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

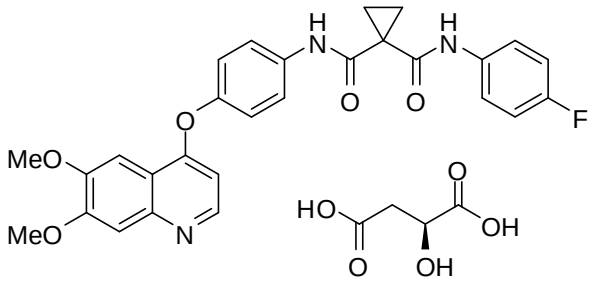
Dosage adjustment is not required in patients with mild or moderate renal impairment. There is no experience with CABOMETYX in patients with severe renal impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

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

11 DESCRIPTION

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



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

CABOMETYX (cabozantinib) tablets for oral use are supplied as film-coated tablets containing 20 mg, 40 mg, or 60 mg of cabozantinib, which is equivalent to 25 mg, 51 mg, or 76 mg of cabozantinib (*S*)-malate, respectively. CABOMETYX also contains the following inactive ingredients: microcrystalline cellulose, lactose anhydrous, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.

The film coating contains hypromellose, titanium dioxide, triacetin, and iron oxide yellow.

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

The exposure-response or –safety relationship for cabozantinib is unknown.

Cardiac Electrophysiology

The effect of orally administered cabozantinib on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled study in patients with medullary thyroid cancer administered a dose of 140 mg. A mean increase in QTcF of 10 - 15 ms was observed at 4 weeks after initiating cabozantinib. A concentration-QTc relationship could not be definitively established. Changes in cardiac wave form morphology or new rhythms were not observed. No cabozantinib-treated patients in this study had a confirmed QTcF > 500 ms nor did any cabozantinib-treated patients in the RCC study (at a dose of 60 mg).

12.3 Pharmacokinetics

Repeat daily dosing of cabozantinib at 140 mg for 19 days resulted in 4- to 5-fold mean cabozantinib accumulation (based on AUC) compared to a single dose administration; steady state was achieved by Day 15.

Absorption

Following oral administration of cabozantinib, median time to peak cabozantinib plasma concentrations (T_{max}) ranged from 3 to 4 hours post-dose.

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

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

Distribution

The oral volume of distribution (V_z/F) of cabozantinib is approximately 319 L. Cabozantinib is highly protein bound in human plasma (≥ 99.7%).

Elimination

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

Metabolism

Cabozantinib is a substrate of CYP3A4 *in vitro.*

Excretion

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

Specific Populations

The following patient characteristics did not result in a clinically relevant difference in the pharmacokinetics of cabozantinib: age (32-86 years), sex, race (Whites and non-Whites), or mild to moderate renal impairment (eGFR greater than or equal to 30 mL/min/1.73 m^2 as estimated by MDRD (modification of diet in renal disease equation)). The pharmacokinetics of cabozantinib is unknown in patients with worse than moderate renal impairment (eGFR less than 29 mL/min/1.73m^2) as estimated by MDRD equation or renal impairment requiring dialysis.

Hepatic Impairment

Cabozantinib exposure ($AUC_{0\text{-}inf}$) increased by 81% and 63%, respectively, in patients with mild (C-P A) and moderate (C-P B) hepatic impairment. Patients with severe hepatic impairment have not been studied *[see Dosage and Administration (2.2), Use in Specific Populations (8.6)]*.

Pediatric Population

The pharmacokinetics of cabozantinib has not been studied in the pediatric population *[see Use in Specific Populations (8.4)]*.

Drug Interactions

CYP3A4 Inhibition on Cabozantinib

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

CYP3A4 Induction on Cabozantinib

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

Cabozantinib on CYP2C8 substrates

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

Gastric pH modifying agents on Cabozantinib

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

In vitro Studies

Metabolic Pathways

Inhibition of CYP3A4 reduced the formation of the oxidative metabolite by > 80%. Inhibition of CYP2C9 had a minimal effect on cabozantinib metabolite formation (i.e., a <20% reduction). Inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation.

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

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

Drug Transporter Systems

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of cabozantinib has been evaluated in two species: rasH2 transgenic mice and Sprague-Dawley rats. In the 2-year rat carcinogenicity study, once daily oral administration of cabozantinib resulted in a statistically significant increase in the incidence of malignant/complex malignant pheochromocytoma in combination with benign pheochromocytoma or in benign pheochromocytoma alone in male rats at a dose of 1 mg/kg (approximately 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.

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

Based on nonclinical findings, male and female fertility may be impaired by treatment with CABOMETYX. 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

METEOR

METEOR (NCT01865747) was a randomized (1:1), open-label, multicenter study of CABOMETYX 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 (N=658) were randomized to receive CABOMETYX (N=330) administered orally at 60 mg daily or everolimus (N=328) administered orally at 10 mg 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 CABOMETYX compared to everolimus (Figures 1 and 2 and Tables 5 and 6).

Figure 1: Progression-Free Survival in METEOR (First 375 Randomized)

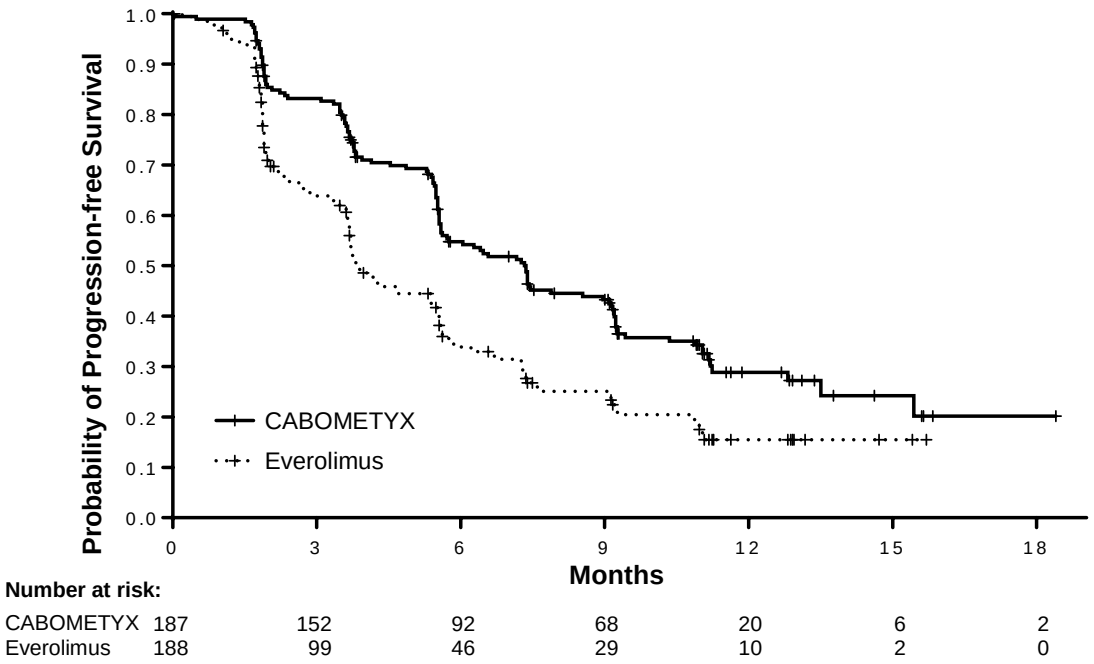


Table 5: Progression-Free Survival in METEOR (First 375 Randomized)

Endpoint	CABOMETYX	Everolimus
	N = 187	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 2: Overall Survival in METEOR (ITT)

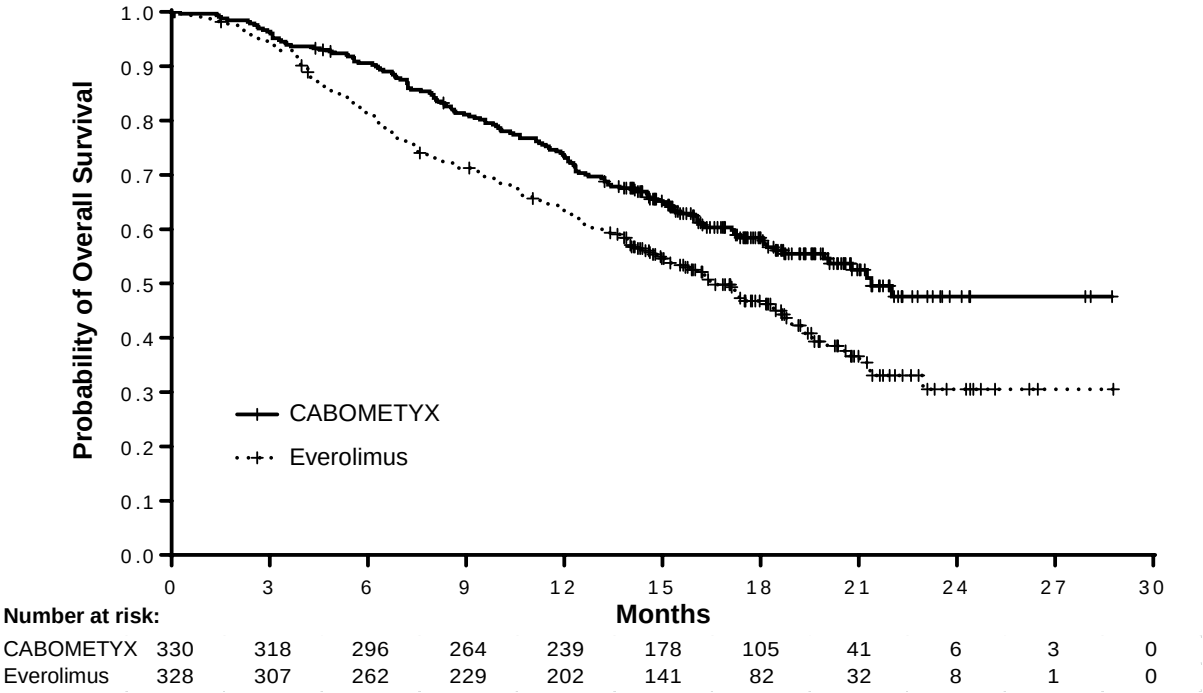


Table 6. Overall Survival and Objective Response Rate in METEOR (ITT)

Endpoint	CABOMETYX	Everolimus
	N = 330	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

CABOSUN

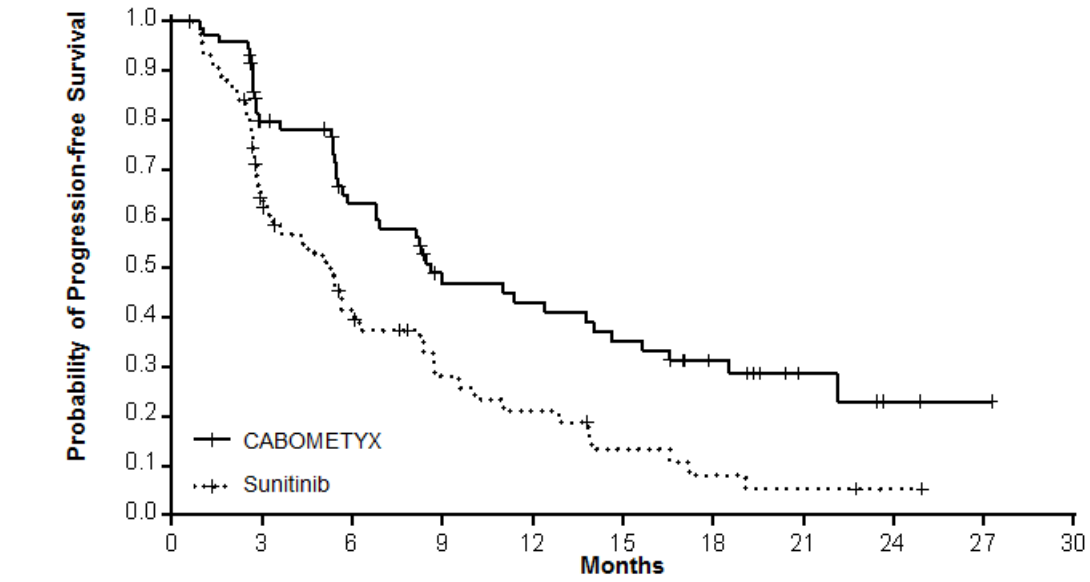
CABOSUN (NCT01835158) was a randomized (1:1), open-label, multicenter study of CABOMETYX versus sunitinib conducted in patients with advanced RCC who had not received prior therapy. Patients were randomized to receive CABOMETYX (N=79) 60 mg orally daily or sunitinib (N=78) 50 mg orally daily (4 weeks 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 CABOMETYX compared to sunitinib (Figure 3, Table 7). The OS results are presented in Figure 4 and Table 7; ORR results are presented in Table 7.

Figure 3: Progression-Free Survival in CABOSUN (ITT)



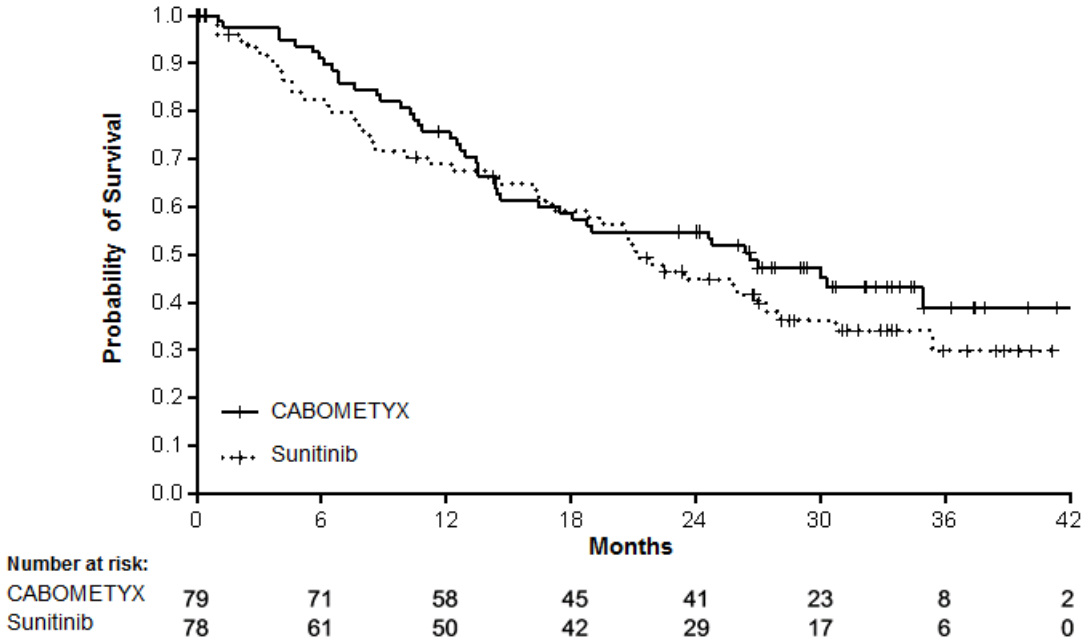
Number at risk:											
CABOMETYX	79	51	37	24	22	18	12	5	2	1	0
Sunitinib	78	36	21	12	9	5	3	2	1	0	0

Table 7. Progression-free Survival, Overall Survival and Objective Response Rate in CABOSUN (ITT)

Endpoint	CABOMETYX	Sunitinib
	N = 79	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 4: Overall Survival in CABOSUN (ITT)



16 HOW SUPPLIED/STORAGE AND HANDLING

CABOMETYX tablets are supplied as follows:

60 mg tablets are yellow film-coated, oval shaped with no score, debossed with “XL” on one side and “60” on the other side of the tablet; available in bottles of 30 tablets:
NDC 42388-023-26

40 mg tablets are yellow film-coated, triangle shaped with no score, debossed with “XL” on one side and “40” on the other side of the tablet; available in bottles of 30 tablets:
NDC 42388-025-26

20 mg tablets are yellow film-coated, round shaped with no score, debossed with “XL” on one side and “20” on the other side of the tablet; available in bottles of 30 tablets:
NDC 42388-024-26

Store CABOMETYX 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).

Inform patients of the following:

- 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 (5.1)]*.
- Gastrointestinal disorders: Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during CABOMETYX treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistula have been reported in patients taking CABOMETYX *[see Warnings and Precautions (5.2)]*.
- Thrombotic Events: Venous and arterial thrombotic events have been reported. Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolus have been reported. Advise patients to contact their health care provider if new onset of dyspnea, chest pain, or localized limb edema occurs *[see Warnings and Precautions (5.3)]*.
- Hypertension: 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 (5.4)]*.
- 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 (5.5)]*.

- Palmar-plantar erythrodysesthesia: Advise patients to contact their healthcare provider for progressive or intolerable rash *[see Warnings and Precautions (5.6)]*.
- Wound healing: Patients should be advised to contact their healthcare provider before any planned surgeries, including dental surgery *[see Dosage and Administration (2.2)]*.
- Drug interactions: Advise patients to inform their healthcare provider of all prescription or nonprescription medication or herbal products that they are taking.
- Embryo-fetal toxicity: Advise females of reproductive potential of the potential risk to a fetus. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with CABOMETYX *[see Warnings and Precautions (5.8), Use in Specific Populations (8.1)]*.
- Females of reproductive potential: Advise patients of reproductive potential to use effective contraception during treatment with CABOMETYX and for at least four months after the final dose of CABOMETYX *[Use in Specific Populations (8.3)]*.
- Lactation: Advise women not to breastfeed during treatment with CABOMETYX and for 4 months following the last dose *[Use in Specific Populations (8.2)]*.
- Important Administration Information

- Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking CABOMETYX. Instruct patients to not crush CABOMETYX tablets and to take CABOMETYX tablets with a full glass (at least 8 ounces) of water.
- Advise patients not to consume grapefruits or grapefruit juice while taking CABOMETYX.

  [see Dosage and Administration (2.1)]

Manufactured for Exelixis, Inc. South San Francisco, CA 94080

PATIENT INFORMATION
CABOMETYX® (Ka-boe-met-iks)
cabozantinib
tablets

What is CABOMETYX?

CABOMETYX is a prescription medicine used to treat people with advanced kidney cancer (renal cell carcinoma).

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

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

- have any unusual bleeding
- have high blood pressure
- plan to have any surgery, including dental surgery. You should stop treatment with CABOMETYX at least 28 days before any scheduled surgery.
- have liver problems
- are pregnant, or plan to become pregnant. CABOMETYX can harm your unborn baby. If you are able to become pregnant, you should use effective birth control during treatment and for 4 months after your final dose of CABOMETYX. Talk to your healthcare provider about birth control methods that may be right for you. If you become pregnant or think you are pregnant, tell your healthcare provider right away.
- are breastfeeding or plan to breastfeed. It is not known if CABOMETYX passes into your breast milk. Do not breastfeed during treatment and for 4 months after your final dose of CABOMETYX.

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

How should I take CABOMETYX?

- Take CABOMETYX exactly as your healthcare provider tells you to take it.
- **Do not** take CABOMETYX with food. **Do not** eat for at least 2 hours before and at least 1 hour after taking CABOMETYX.
- Swallow CABOMETYX tablets whole with a full glass (at least 8 ounces) of water.
- **Do not** crush CABOMETYX tablets.
- If you miss a dose and your next dose is in:
  - less than 12 hours, take your next dose at the normal time. Do not make up the missed dose.
  - 12 hours or more, take the missed dose as soon as you remember. Take your next dose at the normal time.

What should I avoid while taking CABOMETYX?

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

What are the possible side effects of CABOMETYX?

CABOMETYX may cause serious side effects, including:

- **severe bleeding (hemorrhage).** Tell your healthcare provider right away if you get any signs of bleeding during treatment with CABOMETYX, 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).
- **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 CABOMETYX and sometimes can be severe. Your healthcare provider will check your blood pressure before starting CABOMETYX and during treatment with CABOMETYX. If needed, your healthcare provider may prescribe medicine to treat your high blood pressure.
- **diarrhea.** Diarrhea is common with CABOMETYX 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 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.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** A condition called reversible posterior leukoencephalopathy syndrome can happen during treatment with CABOMETYX. Tell your healthcare provider right away if you have headaches, seizures, confusion, changes in vision, or problems thinking.

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

The most common side effects of CABOMETYX are:

- tiredness
- nausea
- decreased appetite
- weight loss
- vomiting
- altered sense of taste
- inflamed and sore mouth

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

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

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

How should I store CABOMETYX?

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

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

General information about CABOMETYX.

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

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

What are the ingredients in CABOMETYX?

Active ingredient: cabozantinib

Inactive ingredients: microcrystalline cellulose, lactose anhydrous, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The film coating contains hypromellose, titanium dioxide, triacetin, and iron oxide yellow.

Manufactured for Exelixis, Inc. South San Francisco, CA 94080

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

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 12/2017