

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

^{Pr}CABOMETYX™
cabozantinib tablets

Tablets, 20 mg, 40 mg, 60 mg cabozantinib (as cabozantinib (S)-malate), Oral

Antineoplastic
ATC Code: L01XE26

Ipsen Biopharmaceuticals Canada Inc.
5060 Spectrum Way, 5th Floor
Mississauga, ON L4W 5N5

Date of Preparation:
September 13, 2018

Submission Control No: 206230

CABOMETYX is a trademark of Exelixis Inc., used under license by Ipsen Biopharmaceuticals Canada Inc.

TABLE OF CONTENTS

TABLE OF CONTENTS.....	2
PART I: HEALTH PROFESSIONAL INFORMATION.....	4
1 INDICATIONS.....	4
1.1 Pediatrics.....	4
1.2 Geriatrics.....	4
2 CONTRAINDICATIONS.....	4
3 SERIOUS WARNINGS AND PRECAUTIONS	5
4 DOSAGE AND ADMINISTRATION.....	5
4.1 Recommended Dose and Dosage Adjustment	5
4.2 Administration	6
4.3 Missed Dose.....	6
5 OVERDOSAGE	6
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING	7
7 WARNINGS AND PRECAUTIONS	7
7.1 Special Populations	11
7.1.1 Pregnant Women	11
7.1.2 Breast-feeding	12
7.1.3 Pediatrics	12
7.1.4 Geriatrics (65 years of age)	12
8 ADVERSE REACTIONS.....	12
8.1 Adverse Reaction Overview	12
8.2 Clinical Trial Adverse Reactions	13
8.3 Less Common Clinical Trial Adverse Reactions (2%).....	14
8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data	15
9 DRUG INTERACTIONS.....	15
9.1 Overview.....	15
9.2 Drug-Drug Interactions	16
9.3 QTc Interval-Prolonging Drugs	17
10 ACTION AND CLINICAL PHARMACOLOGY.....	18
10.1 Mechanism of Action	18
10.2 Pharmacodynamics.....	18
10.3 Pharmacokinetics.....	19
11 STORAGE, STABILITY AND DISPOSAL.....	20
12 PHARMACEUTICAL INFORMATION.....	21
13 CLINICAL TRIALS	22
13.1 Trial Design and Study Demographics	22
13.2 Study Results	22

14	NON-CLINICAL TOXICOLOGY	26
	PATIENT MEDICATION INFORMATION	28

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CABOMETYX (cabozantinib) is indicated for:

- the treatment of adult patients with advanced renal cell carcinoma (RCC) who have received prior vascular endothelial growth factor (VEGF)-targeted therapy.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with no differences in safety or effectiveness.

2 CONTRAINDICATIONS

CABOMETYX (cabozantinib) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).

3 SERIOUS WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Treatment with CABOMETYX (cabozantinib) should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.

CABOMETYX has not been studied in patients with cardiac impairment.

CABOMETYX has not been studied in patients with severe renal impairment.

CABOMETYX has not been studied in patients with severe hepatic impairment.

The following are clinically significant adverse events:

- Thromboembolism, including deaths (see [WARNINGS AND PRECAUTIONS, Cardiovascular](#))
- Hypertension and hypertensive crisis (see [WARNINGS AND PRECAUTIONS, Cardiovascular](#))
- Gastrointestinal perforations and fistulas, including deaths (see [WARNINGS AND PRECAUTIONS, Gastrointestinal](#))
- Hemorrhage, including deaths (see [WARNINGS AND PRECAUTIONS, Hematologic](#))
- Hepatotoxicity (see [WARNINGS AND PRECAUTIONS, Hepatic](#))
- Reversible Posterior Leukoencephalopathy Syndrome (see [WARNINGS AND PRECAUTIONS, Neurologic](#))
- Wound complications (see [WARNINGS AND PRECAUTIONS, Peri-Operative Considerations](#))

4 DOSAGE AND ADMINISTRATION

4.1 Recommended Dose and Dosage Adjustment

The recommended daily dose of CABOMETYX (cabozantinib) is 60 mg. Continue treatment until patient no longer experiences clinical benefit or experiences unacceptable toxicity.

For Patients Undergoing Surgery

Stop treatment with CABOMETYX at least 28 days prior to scheduled surgery, including dental surgery (see [WARNINGS AND PRECAUTIONS, Peri-Operative Considerations](#)).

For Adverse Reactions

Withhold CABOMETYX for NCI CTCAE Grade 4 adverse reactions, and for Grade 3 or intolerable Grade 2 adverse reactions that cannot be managed with a dose reduction, interruption or supportive care.

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

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 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 [ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics](#)).

In Patients with Renal Impairment

CABOMETYX should be used with caution in patients with mild or moderate renal impairment. CABOMETYX is not recommended for use in patients with severe renal impairment as safety and efficacy have not been established in this population (see [ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics](#)).

Health Canada has not authorized an indication for pediatric use.

4.2 Administration

Swallow CABOMETYX tablets whole. Do not crush CABOMETYX tablets.

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.

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

4.3 Missed Dose

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

5 OVERDOSAGE

There is no specific treatment for CABOMETYX (cabozantinib) overdose and possible symptoms of overdose have not been established.

In the event of suspected overdose, CABOMETYX should be withheld and supportive care instituted. Liver function tests, serum electrolytes and metabolic clinical laboratory parameters should be monitored at least weekly or as deemed clinically appropriate to assess any possible changing trends. Blood pressure and ECG monitoring are recommended. Adverse reactions associated with overdose are to be treated symptomatically.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet 20 mg, 40 mg, 60 mg cabozantinib as cabozantinib (S)-malate	Colloidal Silicon Dioxide, Croscarmellose Sodium, Hydroxypropyl Cellulose, Hypromellose 2910, Iron Oxide Yellow, Lactose Anhydrous, Magnesium Stearate, Microcrystalline Cellulose, Titanium Dioxide and Triacetin.

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.

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.

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.

7 WARNINGS AND PRECAUTIONS

General

As most events can occur early in the course of treatment, the physician should evaluate the patient closely during the first eight weeks of treatment to determine if dose modifications are warranted. Events that generally have early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, palmar-plantar erythrodysesthesia syndrome (PPES), proteinuria, and gastrointestinal (GI) events (abdominal pain, mucosal inflammation, constipation, diarrhea, vomiting).

Dose reductions and dose interruptions due to an adverse event (AE) occurred in 59.8% and 70%, respectively, of cabozantinib-treated patients in the pivotal clinical trial. Two dose reductions were required in 19.3% of patients. The median time to first dose reduction was 55 days, and to first dose interruption was 38 days.

Carcinogenesis and Mutagenesis

There are no human data on carcinogenesis and mutagenesis. Based on non-clinical findings, the long-term carcinogenic potential of CABOMETYX is unknown (see [NON-CLINICAL TOXICOLOGY, Carcinogenicity](#)).

Cardiovascular

Thrombotic Events

Venous thromboembolism was reported in 7.3% of patients treated with CABOMETYX. Pulmonary embolism occurred in 3.9% of CABOMETYX-treated patients. Events of arterial thromboembolism have been observed in 0.9% of patients treated with CABOMETYX. Fatal thrombotic events occurred in the CABOMETYX clinical program.

Use CABOMETYX with caution in patients who are at risk for, or who have a history of these

events. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or any other clinically significant arterial thromboembolic complication (see [DOSAGE AND ADMINISTRATION](#)).

Hypertension and Hypertensive Crisis

Hypertension and hypertensive crisis have been observed in 37.0% (15.0% Grade ≥ 3) and 0.6% of patients treated with CABOMETYX respectively. Blood pressure should be well-controlled prior to initiating CABOMETYX. During treatment with CABOMETYX, monitor all patients regularly for hypertension. Withhold CABOMETYX for hypertension that is not adequately controlled by 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 in the case of hypertensive crisis or severe hypertension despite optimal medical management (see [DOSAGE AND ADMINISTRATION](#)).

Prolongation of QT interval

CABOMETYX causes a prolongation of the QTc interval (see [ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology](#)). QTc prolongation may lead to an increased risk of ventricular arrhythmias including torsade de pointes. Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death. Hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to initiating or continuing CABOMETYX administration.

Particular care should be exercised when administering CABOMETYX to patients who are taking other medicinal products known to prolong the QTc interval (see [DRUG INTERACTIONS](#)) or who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug.

Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender, age ≥ 65 years, baseline prolongation of the QT/QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years of age; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease); history of arrhythmias; electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders); bradycardia; acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma); diabetes mellitus; and autonomic neuropathy.

Monitor electrocardiogram and electrolytes regularly. Permanently discontinue CABOMETYX in patients who develop torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia.

When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug. Patients should be advised to contact their healthcare provider immediately to report any new chest pain or discomfort,

changes in heartbeat, palpitations, dizziness, lightheadedness, fainting, or changes in or new use of other medications.

Heart Rate Decrease and PR Interval Prolongation

CABOMETYX causes a decrease in heart rate and a prolongation of the PR interval (see [ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology](#)). Caution should be observed in patients with a low heart rate at baseline (< 60 beats per minute), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, or congestive heart failure. Concomitant medications that result in a decrease in heart rate and/or PR interval prolongation should be avoided to the extent possible during treatment with CABOMETYX (see [DRUG INTERACTIONS](#)).

Driving and Operating Machinery

Adverse events such as fatigue, dizziness and weakness occurred in CABOMETYX-treated patients. Caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Endocrine

Thyroid dysfunction

Hypothyroidism occurred in 21.0% of patients treated with CABOMETYX.

Monitoring for thyroid function before initiation of, and periodically throughout, treatment with CABOMETYX is recommended. Hypothyroidism should be treated according to standard medical practice to maintain euthyroid state.

Gastrointestinal (GI)

Diarrhea

Diarrhea occurred in 74.0% of patients treated with CABOMETYX. Grade 3 diarrhea was reported in 11.0% of CABOMETYX-treated patients. Withhold CABOMETYX in patients that 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. Dose modification due to diarrhea occurred in 26.0% of patients (see [DOSAGE AND ADMINISTRATION](#)).

GI Perforation and Fistulas

Serious GI perforations and fistulas, sometimes fatal, have been observed with CABOMETYX. Fistulas were reported in 1.2% (including 0.6% anal fistula) of CABOMETYX-treated patients and GI perforations were reported in 0.9% of patients treated with CABOMETYX. Patients who have inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, peritonitis, diverticulitis, or appendicitis), have tumour infiltration in the GI tract, or have complications from prior GI surgery (particularly when associated with delayed or incomplete healing) should be carefully evaluated before initiating CABOMETYX therapy. Persistent or recurring diarrhea while on treatment may be a risk factor for the development of anal fistula. Monitor patients for symptoms of fistulas and perforations. Discontinue CABOMETYX in patients who experience a GI perforation or a fistula that cannot be adequately managed (see [DOSAGE AND ADMINISTRATION](#)).

Hematologic

Hemorrhage

Severe hemorrhage, sometimes fatal, occurred with CABOMETYX. The incidence of Grade ≥ 3 hemorrhagic events was 2.1%. Discontinue CABOMETYX in patients who experience severe hemorrhage (see [DOSAGE AND ADMINISTRATION](#)).

Patients who have a history of severe bleeding prior to treatment initiation should be carefully evaluated before initiating CABOMETYX therapy. CABOMETYX should not be administered to patients that have or are at risk for severe hemorrhage.

Hepatic/Biliary/Pancreatic

Hepatotoxicity

Increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were reported in 16.0% and 18.0% of CABOMETYX-treated patients respectively. Greater than Grade 3 ALT and AST increases were observed in 2.4% and 1.8% of subjects treated with CABOMETYX. Fatal hepatic failure has occurred in the CABOMETYX clinical program. Hepatitis, hepatic failure and hepatic encephalopathy have been reported in the post market setting.

Monitoring of ALT, AST and bilirubin before initiation of, and periodically throughout treatment with CABOMETYX is recommended.

Monitoring and Laboratory Tests

Cardiac Safety Monitoring

Patients receiving CABOMETYX should be monitored for heart rate and blood pressure. ECG evaluations should be performed prior to initiating therapy and periodically during treatment to monitor for QTc and PR interval prolongation (see WARNINGS AND PRECAUTIONS, Cardiovascular; ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology).

Electrolyte Monitoring

Electrolyte levels (calcium, potassium, and magnesium) should be assessed at baseline and monitored regularly during treatment with CABOMETYX, particularly in patients at risk for these electrolyte abnormalities (see WARNINGS AND PRECAUTIONS, Cardiovascular; DRUG INTERACTIONS). Hypocalcemia, hypokalemia, and hypomagnesemia should be corrected prior to initiating or continuing CABOMETYX administration.

Liver Function

Monitoring of ALT, AST and bilirubin before initiation of, and periodically throughout treatment with CABOMETYX is recommended.

Thyroid Function

Monitoring for thyroid function before initiation of, and periodically throughout, treatment with CABOMETYX is recommended. Hypothyroidism should be treated according to standard medical practice to maintain euthyroid state.

Neurologic

Reversible Posterior Leukoencephalopathy Syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS), also known as Posterior Reversible Encephalopathy Syndrome (PRES), has been observed with CABOMETYX. This syndrome should be considered in any patient presenting with multiple symptoms, including seizures, headache, visual disturbances, confusion or altered mental function. CABOMETYX

treatment should be discontinued in patients with RPLS (see [DOSAGE AND ADMINISTRATION](#)).

Peri-Operative Considerations

Wound Complications

Wound complications have been observed in 2.4% of patients treated with CABOMETYX. CABOMETYX treatment should be stopped at least 28 days prior to scheduled surgery, including dental surgery, if possible. The decision to resume CABOMETYX therapy after surgery should be based on clinical judgment of adequate wound healing. CABOMETYX should be discontinued in patients with wound healing complications requiring medical intervention.

Renal

Proteinuria

Proteinuria has been observed in 12.0% of patients treated with CABOMETYX. Grade 3 or 4 proteinuria occurred in 2.4% of CABOMETYX-treated patients. Monitor urine protein regularly during CABOMETYX treatment. Discontinue CABOMETYX in patients who develop nephrotic syndrome (see [DOSAGE AND ADMINISTRATION](#)).

Sexual Health

Reproduction

Women of childbearing potential must be advised to avoid pregnancy while on CABOMETYX. Female partners of male patients taking CABOMETYX must also avoid pregnancy. Effective methods of contraception should be used by male and female patients and their partners during therapy, and for at least 4 months after completing therapy. Because oral contraceptives might possibly not be considered as “effective methods of contraception”, they should be used together with another method, such as a barrier method (see [DRUG INTERACTIONS](#)).

Fertility

There are no data on human fertility. Based on non-clinical safety findings, male and female fertility may be compromised by treatment with CABOMETYX. Both men and women should be advised to seek advice and consider fertility preservation before treatment (see [NONCLINICAL TOXICOLOGY](#)).

Skin

Palmar-Plantar Erythrodysesthesia Syndrome

Palmar-plantar erythrodysesthesia syndrome (PPES) has been observed in 42.0% of patients treated with CABOMETYX. Grade 3 PPES occurred in 8.2% of CABOMETYX-treated patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPES or Grade 3 PPES until improvement to Grade 1; resume CABOMETYX at a reduced dose. Dose modifications due to PPES occurred in 16.0% of patients.

7.1 Special Populations

7.1.1 Pregnant Women

There are no studies in pregnant women using CABOMETYX. Studies in animals have shown embryo-foetal and teratogenic effects at exposures below those occurring clinically at the recommended dose. The potential risk for humans is unknown. CABOMETYX should not be used during pregnancy unless the clinical condition of the woman requires treatment with CABOMETYX.

Embryo-fetal development studies were performed in rats and rabbits. In rats, cabozantinib caused post-implantation loss, fetal edema, cleft palate/lip, dermal aplasia and kinked or rudimentary tail. In rabbits, cabozantinib produced fetal soft tissue changes (reduced spleen size, small or missing intermediate lung lobe) and increased fetal incidence of total malformations. NOAEL for embryo-fetal toxicity and teratogenic findings were below human clinical exposure levels at intended therapeutic dose (see [DRUG INTERACTIONS, ACTION AND CLINICAL PHARMACOLOGY, Mechanism of Action](#)).

7.1.2 Breast-feeding

It is not known whether cabozantinib and/or its metabolites are excreted in human milk. Because of the potential harm to the infant, mothers should discontinue breast-feeding during treatment with CABOMETYX, and for at least 4 months after completing therapy.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics (> 65 years of age)

No specific dose adjustment for the use of CABOMETYX in older people (≥ 65 years) is recommended.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of CABOMETYX (cabozantinib) was evaluated in 331 patients with advanced renal cell carcinoma who received 60 mg CABOMETYX.

The most common adverse reactions (in $\geq 25\%$ of patients) included: diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia syndrome (PPES), hypertension, vomiting, weight decreased, and constipation (see *Table 2*). Serious adverse reactions (in $\geq 1\%$ of patients) were diarrhea (1.8%), fatigue (1.2%), pulmonary embolism (1.5%) and hypomagnesemia (1.2%).

Grade 3-4 adverse reactions and laboratory abnormalities which occurred in $\geq 5\%$ of patients were hypertension, diarrhea, fatigue, palmar-plantar erythrodysesthesia syndrome, hyponatremia, hypophosphatemia, hypomagnesemia, lymphocytes decreased, anemia, hypokalemia, and GGT increased (see *Table 3*).

Interruption of CABOMETYX treatment was allowed at the discretion of the investigator. If treatment was interrupted due to adverse reactions for more than 6 weeks, CABOMETYX was discontinued. Adverse reactions led to permanent discontinuation of CABOMETYX treatment in 9.7% of patients. The most frequent adverse reactions leading to permanent discontinuation were decreased appetite (1.8%) and fatigue (1.2%).

Adverse reactions requiring dose reductions occurred in 60.0% of patients. Twenty percent

(20.0%) of patients received 20 mg CABOMETYX as their lowest dose. The most frequent adverse reactions leading to dose reduction were: diarrhea (16.0%), PPES (11.0%), fatigue (10.0%), and hypertension (7.6%).

Adverse reactions led to CABOMETYX treatment interruptions in 70.0% of patients. The most frequent adverse reactions leading to treatment interruptions were: diarrhea (22%), PPES (14%) and fatigue (12%).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of CABOMETYX was evaluated in a randomized (1:1), open-label, multicenter, active comparator-controlled Phase 3 study (XL184-308) 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. 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.

Table 2: Adverse Reactions Occurring in ≥ 10% Patients Who Received CABOMETYX

	CABOMETYX n = 331¹ (%)		Everolimus n = 332 (%)	
	All Grades ²	Grade 3-4	All Grades ²	Grade 3-4
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 syndrome	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
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				
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				
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				

Grade 3 or 4 AEs occurring in CABOMETYX-treated patients at a rate higher than what was seen in patients receiving everolimus (and not included in Table 2 or 3) were: hypokalemia, lipase increased, pleural effusion, pulmonary embolism, hypocalcemia, blood bilirubin increased and syncope.

8.3 Less Common Clinical Trial Adverse Reactions (2%)

Gastrointestinal: pancreatitis

Hepatobiliary Disorders: hepatitis cholestatic

Musculoskeletal Disorders: osteonecrosis of the jaw

Nervous System Disorders: convulsion

Skin and Subcutaneous Tissue Disorders: wound complications

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 3: Laboratory Abnormalities Occurring in ≥ 25% Patients Who Received CABOMETYX

Test	CABOMETYX n = 331 (%)		Everolimus n = 332 (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
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				

9 DRUG INTERACTIONS

9.1 Overview

CABOMETYX (cabozantinib) is a substrate of CYP3A4, and also a moderate inhibitor of the multidrug efflux pump P-glycoprotein (P-gp). Therefore, absorption and subsequent elimination of cabozantinib may be influenced by products that affect CYP3A4 and/or P-gp.

In vitro, cabozantinib is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

9.2 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4: Established or Potential Drug-Drug Interactions

CABOMETYX	Source of Evidence	Effect	Clinical comment
CYP3A4 inhibitors	CT	Administration of the strong CYP3A4 inhibitor ketoconazole (400 mg daily for 27 days) to healthy volunteers decreased cabozantinib clearance (by 29%) and increased single-dose plasma cabozantinib exposure (AUC) by 38%.	Co-administration of strong CYP3A4 inhibitors (e.g., ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) with cabozantinib should be approached with caution. Increased CABOMETYX exposure may increase the risk of exposure-related toxicity and the selection of an alternative agent should be considered.
CYP3A4 inducers	CT	Administration of the strong CYP3A4 inducer rifampicin (600 mg daily for 31 days) to healthy volunteers increased cabozantinib clearance (4.3-fold) and decreased single-dose plasma cabozantinib exposure (AUC) by 77%.	Chronic co-administration of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing St. John's Wort [<i>Hypericum perforatum</i>]) with cabozantinib should therefore be avoided and alternative agents should be considered as the efficacy of CABOMETYX may be substantially reduced.
Gastric pH modifying agents	CT	Co-administration of proton pump inhibitor (PPI) esomeprazole (40 mg daily for 6 days) with a single dose of 100 mg cabozantinib to healthy volunteers resulted in no clinically-significant effect on plasma cabozantinib exposure (AUC).	No dose adjustment is indicated when gastric pH modifying agents (i.e., PPIs, H2 receptor antagonists, and antacids) are co-administered with cabozantinib.
MRP2 inhibitors	CT	<i>In vitro</i> data demonstrate that cabozantinib is a substrate of MRP2.	Administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations.
Bile salt-sequestering agents	T	Bile salt-sequestering agents such as cholestyramine and cholestagel may interact with cabozantinib and may impact absorption (or reabsorption) resulting in potentially decreased exposure	The clinical significance of these potential interactions is unknown.

CABOMETYX	Source of Evidence	Effect	Clinical comment
Contraceptive steroids	T	The effect of cabozantinib on the pharmacokinetics of contraceptive steroids has not been investigated.	As unchanged contraceptive effect may not be guaranteed, an additional contraceptive method, such as a barrier method, is recommended.
Warfarin	T	Because of high plasma protein binding levels of cabozantinib, a plasma protein displacement interaction with warfarin may be possible.	INR values should be monitored.
P-glycoprotein substrates (P-gp)	CT	Cabozantinib was an inhibitor (IC ₅₀ = 7.0 µM), but not a substrate, of P-gp transport activities in a bi-directional assay system using MDCK-MDR1 cells.	Cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.3 QTc Interval-Prolonging Drugs

The concomitant use of CABOMETYX with QTc interval-prolonging drugs should be avoided to the extent possible (see [WARNINGS AND PRECAUTIONS, Cardiovascular, Monitoring and Laboratory Tests](#) and [ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology](#)).

Drugs that have been associated with QT interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc interval prolongation and/or torsade de pointes: Class IA antiarrhythmics; Class III antiarrhythmics; Class 1C antiarrhythmics; antipsychotics; antidepressants; opioids; macrolide antibiotics and analogues; quinolone antibiotics; pentamidine; antimalarials; azole antifungals; domperidone; 5-hydroxytryptamine (5-HT)₃ receptor antagonists; kinase inhibitors; arsenic trioxide; histone deacetylase inhibitors; beta-2 adrenoceptor agonists.

Drugs that Decrease Heart Rate and/or Prolong the PR Interval

CABOMETYX results in a decrease in heart rate and an increase in the PR interval (see [WARNINGS AND PRECAUTIONS, Cardiovascular, Monitoring and Laboratory Tests](#) and [ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology](#)). Caution should be observed if CABOMETYX is used concomitantly with other drugs that lower heart rate and/or prolong the PR interval, including, but not limited to, antiarrhythmics, beta adrenoceptor antagonists, non-dihydropyridine calcium channel blockers, digitalis glycosides, cholinesterase inhibitors, sphingosine-1 phosphate receptor modulators, HIV protease inhibitors, alpha₂-adrenoceptor agonists, and I_f blockers.

Drugs that Affect Electrolytes

Caution should be observed if CABOMETYX is administered with drugs that can deplete electrolyte levels.

Drugs that can reduce electrolyte levels include, but are not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high-dose corticosteroids and proton pump inhibitors.

The above lists of potentially interacting drugs are not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QTc interval, decrease heart rate and/or prolong the PR interval, or decrease electrolytes, as well as for older drugs for which these effects have recently been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Cabozantinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodeling, drug resistance, and metastatic progression of cancer. Cabozantinib was evaluated for its inhibitory activity against a variety of kinases and was identified as an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors. In addition, cabozantinib inhibits other tyrosine kinases including the GAS6 receptor (AXL), RET, ROS1, TYRO3, MER, the stem cell factor receptor (KIT), TRKB, Fms-like tyrosine kinase-3 (FLT3), and TIE-2.

10.2 Pharmacodynamics

Pharmacodynamic effects Cabozantinib exhibited dose-related tumour growth inhibition, tumour regression, and/or inhibited metastasis in a broad range of preclinical tumour models.

Cardiac Electrophysiology

In a placebo-controlled clinical trial in patients with medullary thyroid cancer receiving the cabozantinib 138 mg once-daily capsule (N=214) or placebo (N=109), serial ECGs were collected on Day 1 and during steady-state treatment on Day 29. During steady-state cabozantinib treatment, prolongation of the QTcF and PR intervals and a reduction in heart rate were observed. An increase from baseline in corrected QT interval by Fridericia (QTcF) of 10 – 15 ms was observed on Day 29 (but not on Day 1). The maximum differences from placebo in the mean change from baseline on Day 29 were 10.9 ms (90% CI 8.0, 13.9) for the QTcF interval, 6.2 ms (90% CI 3.4, 9.0) for the PR interval, and -6.7 bpm (90% CI -8.6, -4.7) for heart rate. No cabozantinib-treated subjects in this study were observed to have QTcF >500 ms, nor did any cabozantinib-treated subjects in the RCC study (at a dose of 60 mg).

The mean C_{max} (1510 ng/mL) of cabozantinib achieved on Day 29 in this study in patients with medullary thyroid cancer receiving once daily dosing with the 138 mg capsule was comparable to the mean steady-state C_{max} (1230 ng/mL) in patients with renal cell carcinoma receiving once-daily dosing with the 60 mg tablet.

10.3 Pharmacokinetics

Table 5: Summary of Pharmacokinetic parameters

Parameters	Mean*	90% Confidence Interval (CI)
Apparent clearance CL/F (L/h)	2.23	2.13 – 2.34
Apparent volume of distribution (central compartment) Vc/F (L)	81.45	68.5 – 96.8
Apparent terminal half-life (h)**	99	

*: mean values based on population PK analysis

**: parameter derived from CL/F and Vc/F, therefore no 90% CI available

Absorption: Following oral administration of cabozantinib, peak cabozantinib plasma concentrations are reached at 3 to 4 hours post-dose. Plasma-concentration time profiles show a second absorption peak approximately 24 hours after administration, which suggests that cabozantinib may undergo enterohepatic recirculation.

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

A high-fat meal increased C_{max} and AUC values (by 41% and 57%, respectively) relative to fasted conditions in healthy volunteers administered a single 140 mg oral cabozantinib dose. There is no information on the precise food-effect when taken 1 hour after administration of cabozantinib.

Distribution: Cabozantinib is highly protein bound *in vitro* in human plasma ($\geq 99.7\%$). Based on the population pharmacokinetic (PK) model, the volume of distribution (V_z) is approximately 319 L (SE: $\pm 2.7\%$). Protein binding was not altered in subjects with mild or moderately impaired renal or hepatic function.

Metabolism: Cabozantinib was metabolized *in vivo*. Four metabolites were present in plasma at exposures (AUC) greater than 10% of parent: XL184-N-oxide, XL184 amide cleavage product, XL184 monohydroxy sulfate, and 6-desmethyl amide cleavage product sulfate. Two non-conjugated metabolites (XL184-N-oxide and XL184 amide cleavage product), which possess $<1\%$ of the on-target kinase inhibition potency of parent cabozantinib, each represent $<10\%$ of total drug-related plasma exposure.

Cabozantinib is a substrate for CYP3A4 metabolism *in vitro*, as a neutralizing antibody to CYP3A4 inhibited formation of metabolite XL184 N-oxide by $>80\%$ in a NADPH-catalyzed human liver microsomal (HLM) incubation; in contrast, neutralizing antibodies to CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation. A neutralizing antibody to CYP2C9 showed a minimal effect on cabozantinib metabolite formation (i.e. a $<20\%$ reduction).

Elimination: In a population PK analysis of cabozantinib using data collected from 318 patients with RCC and 63 normal healthy volunteers following oral administration of doses of 60 mg, 40 mg, and 20 mg, the plasma terminal half-life of cabozantinib is approximately 99 hours. Mean clearance (CL/F) at steady-state was estimated to be 2.2 L/hr. Within a 48-day collection period

after a single dose of ¹⁴C-cabozantinib in healthy volunteers, approximately 81% of the total administered radioactivity was recovered with 54% in faeces and 27% in urine.

Special Populations and Conditions

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 m² 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/1.73m²) as estimated by MDRD equation or renal impairment requiring dialysis.

Pediatrics: The pharmacokinetics of cabozantinib has not been studied in the pediatric population (see [WARNINGS AND PRECAUTIONS, Special Populations](#)).

Ethnic origin: A population PK analysis did not identify clinically relevant differences in PK of cabozantinib based on race.

Hepatic Insufficiency: Cabozantinib exposure (AUC_{0-inf}) increased by 81% and 63% in subjects with mild and moderate hepatic impairment, respectively (90% CI for AUC_{0-inf}: 121.44% to 270.34% for mild and 107.37% to 246.67% for moderate). Patients with severe hepatic impairment have not been studied.

Renal Insufficiency: Ratios of geometric LS mean for plasma cabozantinib, C_{max} and AUC_{0-inf} were 19% and 30% higher, for subjects with mild renal impairment (90% CI for C_{max} 91.60% to 155.51%; AUC_{0-inf} 98.79% to 171.26%) and 2% and 6-7% higher (90% CI for C_{max} 78.64% to 133.52%; AUC_{0-inf} 79.61% to 140.11%), for subjects with moderate renal impairment compared to subjects with normal renal function. Patients with severe renal impairment have not been studied.

11 STORAGE, STABILITY AND DISPOSAL

Store CABOMETYX at room temperature (15°C to 25°C).

Keep out of sight and reach of children.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

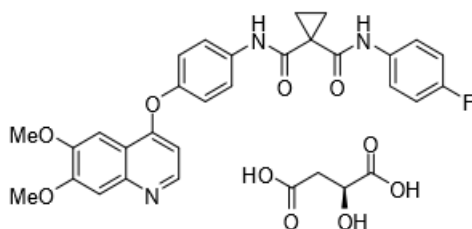
Drug Substance

Proper/Common name: cabozantinib (S)-malate

Chemical name: N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate.

Molecular formula and molecular mass: $C_{28}H_{24}FN_3O_5 \cdot C_4H_6O_5$
635.6 Daltons as malate salt

Structural formula:



Physicochemical properties: Cabozantinib (S)-malate was found to exist in two neat, closely related solid forms (N-1 and N-2) that have similar properties.

Physical Description: white to off-white solid

Solubility: 0.03 mg/mL in water
0.3 mg/mL in methyl ethyl ketone

pH: ~100mcg/mL at pH 3; practically insoluble above pH 4

pKa: 6.32

Partition coefficient: log D50 = 3.88; log P = 5.15

Melting Point: N-1 ~186.50C; N-2 ~185.40C; Amorphous Tg ~900C>

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

Table 6: Summary of patient demographics for clinical trials in Renal Cell Carcinoma

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
XL 184-308 (METEOR)	Open label, active-controlled, randomized 2-arm Phase 3 study	CABOMETYX (60 mg) daily, oral	N=330	62.5 (32, 86)	77%M
		everolimus (10 mg) daily, oral	N=328	62.0 (31, 84)	73%M

The safety and efficacy of CABOMETYX (cabozantinib) were evaluated in a randomized, open-label, multicenter Phase 3 study. Patients (N=658) with advanced Renal Cell Carcinoma (RCC) with a clear cell component who had previously received at least 1 prior VEGF receptor tyrosine kinase inhibitor (VEGFR TKI) were randomized (1:1) to receive CABOMETYX (N=330) or everolimus (N=328). Patients could have received other prior therapies, including cytokines, and antibodies targeting VEGF, the programmed death 1 (PD-1) receptor, or its ligands. Patients with treated brain metastases were allowed. Progression-free survival (PFS) was assessed by a blinded independent radiology review committee, and the primary analysis was conducted among the first 375 subjects randomized. Secondary efficacy endpoints were objective response rate (ORR) and overall survival (OS). Tumor assessments were conducted every 8 weeks for the first 12 months, then every 12 weeks thereafter.

The baseline demographic and disease characteristics were similar between the CABOMETYX and everolimus arms. The majority of the patients were male (75%), with a median age of 62 years. Seventy-one percent (71%) received only one prior VEGFR TKI; 41% of patients received sunitinib as their only prior VEGFR TKI. According to the Memorial Sloan Kettering Cancer Center criteria for prognostic risk category, 46% were favorable (0 risk factors), 42% were intermediate (1 risk factor), and 13% were 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 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.

The main efficacy outcomes measure was progression-free survival (PFS) assessed by 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.

13.2 Study Results

Statistically significant improvement in PFS was demonstrated for CABOMETYX compared to everolimus (Figure 1 and Table 5). A planned interim analysis of OS was conducted at the time of the PFS analysis and did not reach the interim boundary for statistical significance (HR=0.68

[0.51, 0.90], $p=0.006$). In a subsequent unplanned interim analysis of OS, a statistically significant improvement was demonstrated for patients randomized to CABOMETYX as compared with everolimus (median of 21.4 months vs. 16.5 months; HR=0.66 [95% CI: 0.53, 0.83], $p=0.0003$; Figure 2). The follow-up supplemental analysis demonstrated a statistically significant difference in OS for patients randomized to CABOMETYX as compared with everolimus; (median 21.4 months vs. 17.1 months; HR= 0.70 (95% CI: 0.58, 0.85; p -value = 0.0002; Table 6).

Exploratory analyses of PFS and OS in the ITT population have also shown consistent results in favour of CABOMETYX compared to everolimus across different subgroups according to age (<65 vs. ≥ 65 , sex, MSKCC risk group (favourable, intermediate, poor), ECOG status (0 vs. 1), time from diagnosis to randomisation (<1 year vs. ≥ 1 year), tumour MET status (high vs. low vs. unknown), bone metastases (absence vs. presence), visceral metastases (absence vs. presence), visceral and bone metastases (absence vs. presence), number of prior VEGFR-TKIs (1 vs. ≥ 2), duration of first VEGFR-TKI (≤ 6 months vs. >6 months).

Figure 1: Progression-free survival (first 375 randomized)

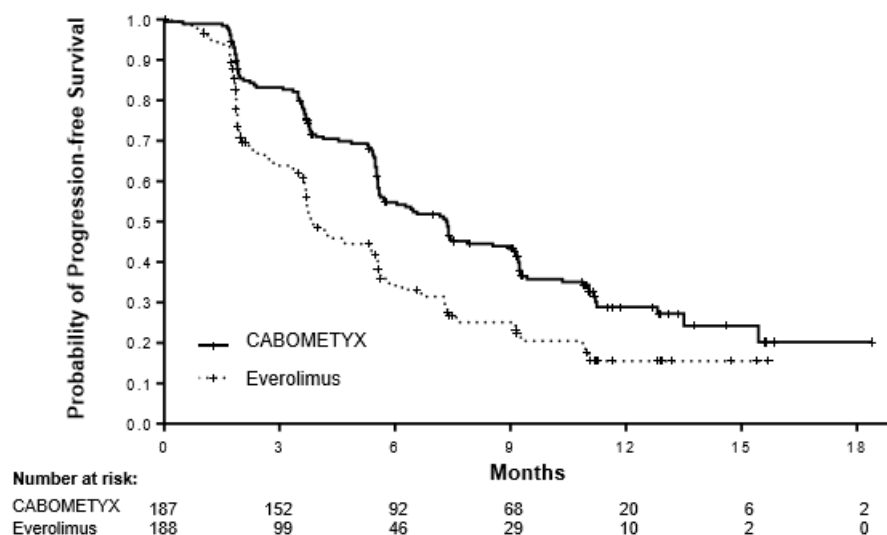


Table 7: Progression-Free Survival (First 375 randomized)

Endpoint	Primary PFS analysis Population	
	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), $p<0.0001$	

¹stratified 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 IIRS data)

The PFS analysis was repeated in the ITT population (658 subjects), and results were similar to those obtained for the primary PFS analysis population.

Figure 2: Kaplan-Meier curve of overall survival

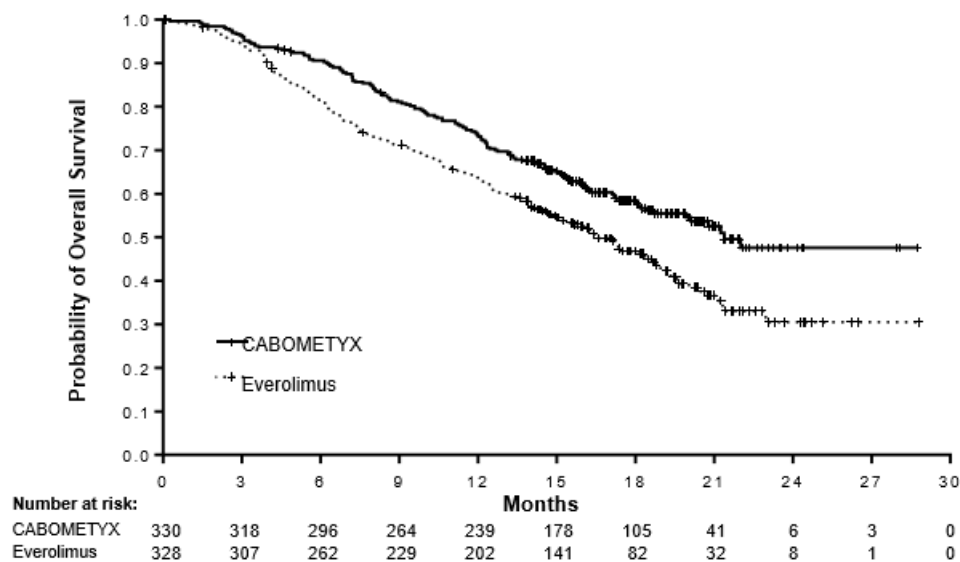


Table 8: Final Overall Survival Rate (ITT)

Endpoint	CABOMETYX	Everolimus
Number (%) of Subjects	330	328
Censored	132 (40)	96 (29)
Death	198 (60)	232 (71)
Duration of overall survival (months)		
Median (95% CI)	21.4 (18.6, 23.5)	17.1 (14.9, 18.9)
25th percentile, 75th percentile	11.5, NE	7.5, 29.5
Range	0.26, 37.8+	0.07+, 35.5+
p-value (stratified log-rank test) ^a	0.0002	
Hazard ratio (95% CI; stratified) ^b	0.70 (0.58, 0.85)	
p-value (unstratified log-rank test)	0.0006	
Hazard ratio (95% CI; unstratified)	0.72 (0.59, 0.87)	

+ indicates a censored observation; CI, confidence interval; ITT, intent-to-treat; IxRS, interactive record system; NE, not estimable; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

^a Stratification factors (based on IxRS) were prior VEGFR-targeting TKI therapy: 1 vs 2 or more, and Memorial Sloan-Kettering Cancer Center prognostic criteria (0 vs 1 vs 2 or 3).

^b Estimated using the Cox proportional hazard model adjusted for stratification factors. A hazard ratio <1 indicates overall survival in favor of cabozantinib.

Table 9: Summary of ORR findings per independent radiology committee review (IRC) and investigator review

	Primary Analysis ORR Intent-to-Treat Population (IRC)		ORR per Investigator Review Intent-To-Treat Population	
Endpoint	CABOMETYX	Everolimus	CABOMETYX	Everolimus
	N = 330	N = 328	N = 330	N = 328
ORR (partial responses only) (95% CI)	17% (13%, 22%)	3% (2%, 6%)	24% (19%, 29%)	4% (2%, 7%)
p-value ¹	p<0.0001		p<0.0001	
Partial Response	17%	3%	24%	4%
Median time to First Response, months (95% CI)	1.91 (1.6, 11.0)	2.14 (1.9, 9.20)	1.91 (1.3, 9.8)	3.50 (1.8, 5.6)
Stable Disease as Best Response	65%	62%	63%	63%
Progressive Disease as Best Response	12%	27%	9%	27%

¹ chi-squared test

14 NON-CLINICAL TOXICOLOGY

Single dose toxicity

Toxicity associated with single oral doses of cabozantinib in rats (100, 300 and 900 mg/kg) was characterized by dose-dependent clinical signs, clinical chemistry parameter changes reflective of possible hepatotoxicity, and hematologic parameters indicative of possible hematopoietic tissue toxicity. Histopathologic changes in gastrointestinal (GI) tract tissues, bone marrow, lymphoid tissue, and male and female reproductive tissues were considered cabozantinib-related. Minimal evidence of cabozantinib-related toxicity was observed in dogs administered single oral doses up to 2000 mg/kg (dose range: 30-2000 mg/kg/day).

Repeat dose toxicity

Repeat dose toxicity studies were performed in mice (4 weeks at 5, 15 and 50 mg/kg/day), rats (2 and 6 months at 0.1-15 mg/kg/day) and dogs (6 months at 0.2-30 mg/kg). Target organs for toxicity were lymphoid tissues, bone marrow, GI tract, kidney, adrenal and reproductive tract tissues. The no observed adverse effect level (NOAEL) yielded plasma exposures estimated to be below human clinical exposure levels at intended therapeutic dose (≥ 0.4 -fold, ≥ 0.2 -fold and $< 1\%$, for mice, rats and dogs, respectively).

Genotoxicity

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.

Carcinogenicity

Cabozantinib was not carcinogenic in a 26-week carcinogenicity study in rasH2 transgenic mice (2, 5 and 15 mg/kg/day).

During a 104-week carcinogenic study, Cabozantinib was daily administered at 0.1, 0.3 and 1.0 mg/kg/day in Sprague-Dawley rats. Cabozantinib-related neoplastic findings consisted of an increased incidence of benign pheochromocytoma, alone or in combination with malignant pheochromocytoma/complex malignant pheochromocytoma, of the adrenal medulla in males administered ≥ 0.1 mg/kg/day and females administered ≥ 0.3 mg/kg/day. In addition, increased incidence of hyperplasia of the adrenal medulla also occurred in females administered ≥ 0.1 mg/kg/day.

Reproductive and developmental toxicity

In reproductive and developmental toxicity studies, cabozantinib administration was associated with: reduced fertility in male and female rats (1, 2.5 and 5 mg/kg/day); embryotoxicity in rats (0.01, 0.03 and 0.1 mg/kg/day); fetal soft-tissue malformations (small spleen, missing lung lobe) in rabbits (0.3, 1 and 3.0 mg/kg/day); fetal skeletal malformations (cleft palate and kinked/rudimentary tail) at embryotoxic doses in rats (dose range: 0.03-7.5 mg/kg); and no fetal external or skeletal malformations in rabbits (0.3, 1.0 and 3.0 mg/kg/day). These effects were observed at exposures that were significantly lower than the human exposure at the therapeutic dose.

Target organs for toxicity in rat juvenile studies (dose range: 0.3-3 mg/kg/day) were bone, bone marrow, GI tract, lymphoid and reproductive organs. At the NOAEL (0.3 mg/kg/day) plasma exposures are estimated to be approximately 0.1-fold of the mean clinical exposure.

Phototoxicity in vitro studies

Cabozantinib was negative in an in vitro Balb/c mouse 3T3 fibroblast phototoxicity bioassay.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

^{Pr}**CABOMETYX™** **cabozantinib tablets**

Read this carefully before you start taking **CABOMETYX** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CABOMETYX**.

Serious Warnings and Precautions

CABOMETYX should only be prescribed and used under the supervision of a healthcare professional experienced in drugs to treat cancer.

Serious side-effects with **CABOMETYX** can include:

- Life-threatening blood clots
- High blood pressure. Blood pressure can be severely high and could cause stroke (hypertensive crisis).
- Life-threatening tear in your stomach or intestinal wall (**perforation**) or abnormal connection between 2 parts of your body (**fistula**)
- Life-threatening bleeding
- Life-threatening liver injury
- A condition called **posterior reversible leukoencephalopathy syndrome**
- Abnormal wound healing

CABOMETYX has not been studied in patients with heart problems or severe kidney or liver problems.

What is **CABOMETYX used for?**

CABOMETYX is used to treat adults with a type of advanced kidney cancer called renal cell carcinoma who have had previous treatment with a specific type of cancer medication.

How does **CABOMETYX work?**

CABOMETYX is a multi-kinase inhibitor. It works by blocking the action of proteins called receptor tyrosine kinases (RTKs). RTKs are involved in cell growth and the development of new blood vessels. These proteins can be present in high amounts in cancer cells. By blocking their action, **CABOMETYX** can slow down how fast the tumour grows, help to block the blood supply that the cancer needs and may increase the length of time before the cancer gets worse.

What are the ingredients in **CABOMETYX?**

Medicinal ingredient: cabozantinib (S)-malate

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hypromellose 2910, iron oxide yellow, lactose anhydrous, magnesium stearate, microcrystalline cellulose, titanium dioxide and triacetin

CABOMETYX comes in the following dosage forms:

Tablets: 20 mg, 40 mg, 60 mg cabozantinib (as cabozantinib (S)-malate)

Do not use CABOMETYX if:

You are allergic to cabozantinib or any other ingredients in this medicine including lactose anhydrous.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CABOMETYX. Talk about any health conditions or problems you may have, including if you:

- have high blood pressure
- have heart disease
- have diarrhea
- have any unusual bleeding
- plan to have any surgery, including dental surgery. You should stop treatment with CABOMETYX at least 28 days before any scheduled surgery.
- have liver or kidney disease, including increased amounts of protein in your urine
- have inflammatory bowel disease (for example Crohn's disease or ulcerative colitis, diverticulitis, or appendicitis)
- have had a blood clot in the leg or lungs, stroke, or heart attack
- have any heart disorder, including an irregular heartbeat, prolongation of the QT interval or a family history of QT prolongation or sudden cardiac death at less than 50 years of age
- have thyroid problems
- are pregnant, or plan to become pregnant. Avoid getting pregnant while taking CABOMETYX, as it can harm your unborn baby.
 - Female patients who are able to become pregnant, should use effective methods of birth control during treatment and for 4 months after your last 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 a male patient with a female partner who is able to become pregnant. Your female partner should avoid getting pregnant while you are taking CABOMETYX.
 - Effective birth control should be used during treatment with CABOMETYX and for 4 months after your last dose.
 - Tell your healthcare professional right away if your partner becomes pregnant while you are receiving treatment with CABOMETYX.
- 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 last dose of CABOMETYX.

Driving and using machines: Before you do tasks which may require special attention, wait until you know how you respond to CABOMETYX. If you feel dizzy, weak, or tired, do not drive or use tools or machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CABOMETYX:

- Medicines that treat fungal infections, such as itraconazole, ketoconazole, and posaconazole
- Medicines used to treat bacterial infections (antibiotics) such as erythromycin, clarithromycin, and rifampicin
- Allergy medicines such as fexofenadine and ranolazine
- Medicines used to treat epilepsy or fits such as phenytoin, carbamazepine, and phenobarbital
- Herbal preparations containing St. John's Wort (*Hypericum perforatum*), sometimes used for treating depression or depression-related conditions such as anxiety
- Medicines used to thin the blood, such as warfarin, dabigatran, etexilate
- Medicines to treat high blood pressure or other heart conditions, such as ambrisentan, aliskeren, talinolol, digoxin, and tolvaptan
- Medicines for diabetes, such as saxagliptin and sitagliptin
- Medicines used to treat gout, such as colchicine
- Medicines used to treat HIV or AIDS, such as efavirenz, ritonavir, maraviroc and emtricitabine
- Medicines used to lower high cholesterol in the blood or to remove substances called bile acids from your body (cholestyramin, cholestagel)
- Medicines that may lengthen the QT-interval of your heart (examples include certain drugs to treat heart conditions, psychosis, depression, pain, infections and other conditions)
- Medicines that may affect the levels of electrolytes in your body (examples include certain diuretics, laxatives, enemas and corticosteroids)

How to take CABOMETYX:

- Always take CABOMETYX exactly as your healthcare professional tells you to take it.
- Take CABOMETYX once a day on an empty stomach. Do not eat for at least 2 hours before and at least 1 hour after taking the dose.
- Swallow tablets whole with a full glass (at least 8 ounces) of water.
- **Do not** crush tablets.
- Take your medicine at about the same time each day.
- Do not drink grapefruit juice or eat grapefruit while taking CABOMETYX. Do not take supplements that contain grapefruit while taking CABOMETYX.

Usual adult dose:

60 mg tablet, once a day. Your healthcare professional will decide on the right dose for you.

Your doctor may interrupt or adjust your dose. This may happen if you:

- have surgery.
- have problems with your liver.
- have certain side effects while taking CABOMETYX.

Overdose:

If you think you have taken too much CABOMETYX, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose and your next dose is in:

- less than 12 hours, take your next dose at its scheduled 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 are possible side effects from using CABOMETYX?

These are not all the possible side effects you may feel when taking CABOMETYX. If you experience any side effects not listed here, contact your healthcare professional.

- Stomach upset, including diarrhea, nausea, vomiting, constipation, indigestion, and abdominal pain
- Decreased appetite
- Weight loss
- Altered sense of taste
- Heartburn (bringing up stomach acid)
- Redness, swelling or pain in the mouth or throat
- Rash or redness of the skin
- Dry skin
- Fatigue
- Weakness
- Headache
- Dizziness, fainting
- Pain in arms, legs and joints, muscle spasms
- Shortness of breath
- Difficulty in speaking, hoarseness
- Cough

CABOMETYX can cause abnormal blood and urine test results. Your healthcare professional will decide when to perform blood or urine tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON Hand-foot skin reaction: redness, blisters, pain in the palms of the hands or soles of the feet	X		
Hypertension (high blood pressure): headaches, vision problems, nausea and vomiting	X		
Anemia (low levels of red blood cells): fatigue, having pale skin, shortness of breath, loss of energy or weakness	X		
Hypothyroidism (underactive thyroid)		X	

gland): changes in heartrate, appetite or weight, tiredness, constipation, feeling cold, dry skin, swelling at front of neck			
Hyponatremia (low level of sodium in your blood): loss of energy, tiredness, muscle weakness or cramps, seizures	X		
Hypophosphatemia (low level of phosphate in the blood): muscle weakness, coma, bone pain and fractures	X		
Hypomagnesemia (low level of magnesium in the blood): nausea, vomiting, weakness, muscle spasms, tremors	X		
Hypokalemia (low level of potassium in the blood): muscle weakness, cramping	X		
Decreased lymphocytes (low level of white blood cells): swollen lymph nodes, painful swollen joints and rash	X		
COMMON Thromboembolism (blood clot in a vein or artery): pain or tenderness or swelling in your arm or leg, skin that is red or warm, coldness, tingling or numbness, pale skin, muscle pain or spasms, weakness			X
Severe hemorrhage (bleeding): vomiting blood, black stools, bloody urine, headache, coughing up blood			X
Gastrointestinal perforation (tear in your stomach or intestinal wall): abdominal pain, feeling sick, vomiting, constipation, fever			X
Hypocalcemia (low level of calcium in the blood): numbness and tingling in the hands, feet or lips, muscle cramping or spasms, lightheadedness, slow heartbeat	X		
UNCOMMON Convulsion: Fits (seizures), headaches, confusion, or struggling to focus			X
Anal fistula (abnormal connection between the anus and another part of your body): pain and swelling around the anus, pain with bowel movements, bleeding, bloody or foul smelling discharge from the anus, fever, chills	X		
Pancreatitis (inflammation of the pancreas): abdominal pain that lasts or gets worse when you lie down, nausea, vomiting	X		
Liver injury: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, itching, bruising, weight loss			X
Hepatitis cholestatic (decrease in bile	X		

flow from the liver): yellow skin or eyes			
Pulmonary Embolism (blood clot in the lungs): sharp chest pain, coughing up blood, sudden shortness of breath			X
Pleural effusion (build-up of fluid around the lung): chest pain, dry cough, fever, difficulty breathing, shortness of breath			X
Osteonecrosis (bone damage in the jaw): jaw pain		X	
Wound complication: a wound that does not heal		X	
UNKNOWN QT Prolongation (an abnormal heart signal): irregular heartbeat, fainting, loss of consciousness			X
Reversible posterior leukoencephalopathy syndrome: headache, confusion, seizures (fits), visual problems			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at 15°C to 25°C. Keep out of reach and sight of children.

If you want more information about CABOMETYX:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](https://www.canada.ca/en/health-canada.html) (<https://www.canada.ca/en/health-canada.html>); the manufacturer's website at www.ipsen.ca or by calling 1-855-215-2288.

This leaflet was prepared by Ipsen Biopharmaceuticals Canada Inc.

Last Revised: September 13, 2018