PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrCABOMETYX™
cabozantinib tablets

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

Antineoplastic
ATC Code: L01XE26

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RECENT MAJOR LABEL CHANGES

WARNINGS AND PRECAUTIONS (7)	05-2020
PATIENT MEDICATION INFORMATION	05-2020

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Renal Cell Carcinoma (RCC)
CABOMETYX (cabozantinib) is indicated for the treatment of advanced RCC:

- In treatment-naïve adults with intermediate or poor risk.
- In adult patients who have received prior vascular endothelial growth factor (VEGF)-targeted therapy.

Hepatocellular Carcinoma (HCC)
CABOMETYX is indicated for the treatment of patients with HCC who have been previously treated with sorafenib.

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

Management of suspected adverse drug reactions may require temporary treatment interruption and/or dose reduction of CABOMETYX therapy. When dose reduction is necessary, it is recommended to reduce to 40 mg daily, and then to 20 mg daily. Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities. Dose reductions are recommended for events that, if persistent, could become serious or intolerable.

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)*. Patients with mild or moderate hepatic impairment should be closely monitored.

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	Dosage Form /	Non-medicinal Ingredients

Administration	Strength/Composition	
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).

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

Cardiovascular
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. In the pivotal HCC study (XL184-309), portal vein thrombosis was observed in 1% (including one fatal event) of CABOMETYX-treated patients. Patients with a history of portal vein invasion appeared to be at higher risk of developing portal vein thrombosis. Arterial thromboembolism occurred in 3% of CABOMETYX-treated HCC patients; most frequently occurred cerebrovascular accident (1% CABOMETYX vs 0% placebo) including one fatal event. In addition, two other subjects in the CABOMETYX arm had Grade 5 arterial thrombotic AEs and two had Grade 5 venous/mixed thrombotic AEs.

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

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. In the pivotal HCC study, hypertension events were reported in 30% (16% Grade ≥ 3) of CABOMETYX-treated patients.

Serious cases of artery dissection have been reported in patients using VEGF receptor tyrosine kinase inhibitors (VEGFR TKIs), including CABOMETYX, with or without hypertension.

Blood pressure should be well controlled prior to initiating CABOMETYX. Monitor blood pressure prior to initiation and regularly during CABOMETYX treatment. Reduce the dose of 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% of RCC 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% of patients treated with CABOMETYX. Grade 3 diarrhea was reported in 11% 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 interruption or reduction, or permanent discontinuation of CABOMETYX should be considered in case of persistent or recurrent significant GI adverse reactions. Dose modification due to diarrhea occurred in 26% of RCC patients previously treated with VEGF-targeted therapy (*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% (including 0.6% anal fistula) of CABOMETYX-treated patients and GI perforations were reported in 1% of patients treated with CABOMETYX. In the pivotal HCC study, fistulas occurred in 2% of CABOMETYX- treated patients including a fatal case of esophagobronchial fistula. 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. In two pivotal RCC studies (XL184-308 and A031203), the incidence of Grade ≥ 3 hemorrhagic events was 3%. 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.

In the pivotal HCC study, fatal hemorrhagic events were reported at a higher incidence with CABOMETYX than with placebo (1% vs 0%). Predisposing risk factors for severe hemorrhage in the advanced HCC population may include tumour invasion of major blood vessels and the presence of underlying liver cirrhosis resulting in oesophageal varices, portal hypertension, and thrombocytopenia. The study excluded patients with concomitant anticoagulation treatment or antiplatelet agents. Subjects with untreated, or incompletely treated, varices with bleeding or high risk for bleeding were also excluded from this study.

Thrombocytopenia

In the pivotal HCC study, thrombocytopenia (11%) and decreased platelets (10%) were reported with CABOMETYX. Platelet levels should be monitored during CABOMETYX treatment and the dose modified according to the severity of the thrombocytopenia.

Hepatic/Biliary/Pancreatic

Hepatotoxicity

In RCC patients previously treated with VEGF-targeted therapy (XL184-308), increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were reported in 24% and 26% CABOMETYX-treated RCC patients respectively (see *ADVERSE REACTIONS*). Grade 3 or higher ALT and AST increases were also observed in 3% and 2% of RCC 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.

Hepatic Encephalopathy

In the pivotal HCC study, hepatic encephalopathy was reported more frequently in the CABOMETYX arm (4%) than in the placebo arm (1%). CABOMETYX has been associated with diarrhea, vomiting, decreased appetite and electrolyte abnormalities. In HCC patients with compromised livers, these non-hepatic effects may be precipitating factors for the development of hepatic encephalopathy. Patients should be monitored for signs and symptoms of hepatic encephalopathy.

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.

Osteonecrosis
Events of osteonecrosis of the jaw (ONJ) have been observed with CABOMETYX. An oral examination should be performed prior to initiation of CABOMETYX and periodically during therapy. Patients should be advised regarding oral hygiene practice. For invasive dental procedures, CABOMETYX treatment should be held at least 28 days prior to scheduled surgery, if possible. Caution should be used in patients receiving agents associated with ONJ, such as bisphosphonates. Withhold CABOMETYX for development of ONJ until complete resolution.

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
In RCC patients previously treated with VEGF-targeted therapy (XL184-308) wound complications have been observed in 2% 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
In RCC patients previously treated with VEGF-targeted therapy (XL184-308), proteinuria had been observed in 12% of patients treated with CABOMETYX. Grade 3 or higher occurred in 2% of CABOMETYX treated patients. In HCC patients treated with CABOMETYX, the rate of proteinuria was 4% (2% Grade ≥3). 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 NONCLINCIAL TOXICOLOGY*).

Skin

Palmar-Plantar Erythrodysesthesia Syndrome

In the pivotal clinical trial in previously treated RCC patients (XL184-308), palmar-plantar erythrodysesthesia syndrome (PPES) had been observed in 42% of patients treated with CABOMETYX. Grade 3 PPES occurred in 8% of CABOMETYX-treated patients. Dose modifications due to PPES occurred in 16% of patients. The rate of PPES in HCC CABOMETYX-treated patients was 46% (17% Grade 3); a dose modification rate was 28%. 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.

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 most common adverse reactions (in ≥ 25% of patients) included: diarrhea, fatigue, hypertension, decreased appetite, palmar-plantar erythrodysesthesia syndrome (PPES), nausea, weight decreased, AST increased, ALT increased, dysgeusia, platelet count decreased, stomatitis, anemia, vomiting, dyspepsia and constipation.

Within 30 days of the last dose administration, 4 treatment-naïve RCC patients died (gastrointestinal perforation n=2; acute renal failure n=1 and clinical deterioration n=1).

Serious adverse events (SAEs), other than renal cell carcinoma reported in ≥ 1% of RCC patients were hypertension, diarrhea, embolism, PPES, dehydration, decreased weight, decreased appetite, hypophosphatemia, hypotension, lung infection, nausea, acute renal failure, skin ulcer, stomatitis, syncope, pulmonary embolism, ALT increased, hyponatremia, vomiting, fatigue and hypomagnesemia. SAEs reported in ≥ 1% of HCC patients were hepatic encephalopathy, asthenia, abdominal pain, fatigue, PPES, diarrhea, hyponatremia and thrombocytopenia.

Grade 3-4 adverse events (AEs) and laboratory abnormalities reported in ≥ 5% of RCC patients were hypertension, diarrhea, PPES, fatigue, hyponatremia, hypophosphatemia, embolism, ALT increased, anemia, decreased appetite, hypotension, pain and stomatitis. Grade 3-4 AEs and laboratory abnormalities which occurred in ≥ 5% of HCC patients were PPES, hypertension, AST increased, fatigue, diarrhea, asthenia and decreased appetite.

Adverse reactions led to permanent discontinuation of CABOMETYX treatment in 10% of RCC patients previously treated with VEGF-targeted therapy. The most frequent adverse reactions leading to permanent discontinuation were decreased appetite (2%) and fatigue (1%).

Adverse reactions requiring dose reductions occurred in 60% of RCC patients previously treated with VEGF-targeted therapy. Two dose reductions were required in 19% of patients. Twenty percent CABOMETYX (20%) of patients received 20 mg CABOMETYX as their lowest dose. The median time to first dose reduction was 55 days, and to first dose interruption was 38 days. The most frequent adverse reactions leading to dose reduction were: diarrhea (16%), PPES (11%), fatigue (10%), and hypertension (8%). In the pivotal clinical trial in previously treated HCC patients, dose reductions and dose interruptions occurred in 62% and 84%, respectively, of CABOMETYX-treated patients. Two dose reductions were required in 33% of patients. The median time to first dose reduction was 38 days, and to first dose interruption was 28 days. Closer monitoring is advised in patients with mild or moderate hepatic impairment.

Adverse reactions led to CABOMETYX treatment interruptions in 70% of RCC patients previously treated with VEGF-targeted therapy. The most frequent adverse reactions leading to treatment interruptions were: diarrhea (22%), PPES (14%) and fatigue (12%). In the treatment-naïve RCC study (A031203), dose modifications (reduction or interruption) were reported for 81% of subjects in the CABOMETYX arm and 76% of subjects in the sunitinib arm. There was a longer duration of exposure in the CABOMETYX arm compared with the sunitinib arm (median: 6.5 months vs 3.1 months). Dose reductions (46% CABOMETYX vs 35% sunitinib) and dose interruptions (73% vs 71%) were frequent with both agents, indicating that dose modifications were effectively used to manage side effects. Twenty-one percent (21%) of subjects in the CABOMETYX arm and 22% in the sunitinib arm discontinued study treatment due to an AE.

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.

XL184-308
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.

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.

Table 2: Adverse Reactions Occurring in ≥ 10% of RCC Patients Previously Treated with VEGF-Targeted Therapy in Study XL184-308

	CABOMETYX n = 331[1] (%)		**Everolimus n = 332 (%)**	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
Blood and Lymphatic Disorders				
Anemia	17	5	38	16
Endocrine Disorders				
Hypothyroidism	21	0	<1	<1

	CABOMETYX n = 331[1] (%)		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
Constipation	25	<1	19	<1
Abdominal pain[3]	23	4	13	2
Stomatitis	22	2	24	2
Dyspepsia	12	<1	5	0
General Disorders and Administration Site Conditions				
Fatigue	56	9	47	7
Asthenia	19	4	16	2
Mucosal inflammation	19	<1	23	3
Investigations				
Weight decreased	31	2	12	0
Metabolism and Nutrition Disorders				
Decreased Appetite	46	3	34	<1
Musculoskeletal and Connective Tissue				
Pain in extremity	14	1	8	<1
Muscle spasms	13	0	5	0
Arthralgia	11	<1	14	1
Nervous System Disorders				
Dysgeusia	24	0	9	0
Headache	11	<1	12	<1
Dizziness	11	0	7	0
Renal and Urinary Disorders				
Proteinuria	12	2	9	<1
Respiratory, Thoracic, and Mediastinal				
Dysphonia	20	<1	4	0
Dyspnea	19	3	29	4
Cough	18	<1	33	<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

	CABOMETYX n = 331[1] (%)		Everolimus n = 332 (%)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
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 5) were: hypokalemia, lipase increased, pleural effusion, pulmonary embolism, hypocalcemia, blood bilirubin increased and syncope.

A031203
The safety of CABOMETYX was evaluated in a randomized (1:1), open-label, multicenter, active comparator-controlled phase 2 study (A031203) in which 79 patients with advanced renal cell carcinoma received 60 mg CABOMETYX and 78 patients received 50 mg sunitinib taken once daily (4 weeks on treatment followed by 2 weeks off), until disease progression or unacceptable toxicity. 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.

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.

Table 3: Adverse Reactions Occurring in ≥ 10% of Treatment-Naïve RCC Patients in Study A031203

	CABOMETYX n = 78 (%)		Sunitinib n = 72 (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Blood and Lymphatic Disorders				
Anemia	33	1	46	3
Endocrine Disorders				
Hypothyroidism	23	0	6	0

	CABOMETYX n = 78 (%)		Sunitinib n = 72 (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Gastrointestinal Disorders				
Diarrhea	73	10	54	11
Stomatitis	37	5	29	6
Nausea	32	3	39	4
Dyspepsia	27	0	17	0
Vomiting	23	1	22	3
Dry Mouth	19	0	13	0
Constipation	18	1	15	0
Abdominal pain	13	0	11	4
Oral pain	10	0	8	0
General Disorders and Administration Site Conditions				
Fatigue	64	6	68	17
Pain	13	5	6	0
Investigations				
AST increased	60	3	31	3
ALT increased	55	5	28	0
Platelet count decreased	38	1	61	11
Weight decreased	32	4	17	0
Blood creatinine increased	24	3	21	3
Hypophosphatemia	23	9	17	7
Hypomagnesemia	22	3	11	0
Hyperglycemia	21	0	15	6
Hypoalbuminemia	19	0	17	0
Hypocalcemia	18	3	15	0
Hypokalemia	15	1	7	0
Neutrophil count decreased	15	0	35	4
Hyponatremia	14	9	22	8
Blood bilirubin increased	14	0	7	1
Lymphocyte count decreased	13	1	18	6
Blood ALP increased	13	0	13	1
White blood cell count decreased	12	0	35	3
Metabolism and Nutrition Disorders				
Decreased Appetite	47	5	32	1
Dehydration	12	4	10	1
Edema Peripheral	8	0	14	0
Musculoskeletal and Connective Tissue				
Back pain	10	4	6	0
Pain in extremity	10	3	10	0
Arthralgia	10	1	7	0
Muscular Weakness	4	0	17	1

	CABOMETYX n = 78 (%)		Sunitinib n = 72 (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Nervous System Disorders				
Dysgeusia	41	0	29	0
Dizziness	22	1	22	0
Headache	12	1	17	1
Insomnia	10	0	8	0
Peripheral Sensory Neuropathy	10	1	6	0
Renal and Urinary Disorders				
Proteinuria	6	3	14	1
Respiratory, Thoracic, and Mediastinal				
Dysphonia	22	1	1	0
Dyspnea	17	1	19	6
Cough	12	0	7	0
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia syndrome	42	8	33	4
Dry Skin	19	0	8	0
Alopecia	18	0	3	0
Rash Maculo-Papular	15	0	13	3
Dermatitis Acneiform	15	0	3	0
Vascular Disorders				
Hypertension	67	28	44	21
Embolism	12	8	1	0
Hypotension	10	5	4	1
Epistaxis	10	0	4	0

XL184-309
The safety of CABOMETYX was evaluated in a randomized (2:1), double-blind, controlled study vs. placebo in 704 subjects with hepatocellular carcinoma who had received prior sorafenib therapy. The randomized subjects received CABOMETYX 60 mg once daily (n=467) or matching placebo (n=237).The median duration of treatment was 3.8 months (range 0.1-37.3) for patients receiving CABOMETYX and 2.0 months (range 0.0-27.2) for patients receiving placebo. Dose modification rates due to AEs were 88% vs 39% with CABOMETYX vs placebo. The median average daily dose for CABOMETYX was 36 mg.

There was a higher rate in the CABOMETYX group of treatment discontinuation due to AEs (CABOMETYX 21% vs placebo 5%), including AEs related to study treatment (16% vs 3%). Overall rate of Grade ≥3 AEs was higher with CABOMETYX (68% vs 36%) as was the rate of SAEs (50% vs 37%). Grade 5 AEs that were considered to be treatment-related occurred in 6 patients receiving CABOMETYX (esophagobronchial fistula, hepatic failure, hepatorenal syndrome, portal-vein thrombosis, upper gastrointestinal hemorrhage, pulmonary embolism) and in 1 patient in the placebo group (hepatic failure).

Table 4: Adverse Reactions Occurring in ≥ 10% of HCC Patients in Study XL184-309

	CABOMETYX n = 467 (%)		Placebo n = 237 (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Gastrointestinal Disorders				
Diarrhea	54	10	19	2
Nausea	31	2	18	2
Vomiting	26	0	12	3
Constipation	19	0	19	0
Abdominal Pain	18	2	25	4
Stomatitis	13	2	2	0
Abdominal Pain Upper	13	1	13	0
Dyspepsia	10	0	3	0
General Disorders and Administration Site Conditions				
Fatigue	45	10	30	4
Asthenia	22	7	8	2
Mucosal inflammation	14	2	2	0
Pyrexia	14	0	10	0
Hepatobiliary Disorders				
Ascites	12	4	13	5
Investigations				
AST Increased	22	12	11	7
ALT Increased	17	5	6	2
Weight decreased	17	1	6	0
Hypoalbuminemia	12	0	5	0
Thrombocytopenia	11	3	0	0
Metabolism and Nutrition Disorders				
Decreased Appetite	48	6	18	0
Musculoskeletal and Connective Tissue				
Back pain	10	1	10	0
Nervous System Disorders				
Edema Peripheral	13	1	14	1
Dysgeusia	12	0	2	0
Headache	11	0	7	0
Insomnia	10	0	7	0
Dizziness	10	0	6	0
Respiratory, Thoracic, and Mediastinal				
Dysphonia	19	1	2	0
Cough	13	0	11	0
Dyspnea	12	3	10	0
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia syndrome	46	17	5	0
Rash	12	0	6	0
Vascular Disorders				
Hypertension	29	16	6	2

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 5: Laboratory Abnormalities Occurring in ≥ 25% Patients Who Received CABOMETYX in Study XL184-308

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

In HCC patients, the most frequent (≥ 25%) treatment-emergent laboratory abnormalities (all grades) reported in the CABOMETYX arm were: LDH increased, ALT increased, AST increased, albumin decreased, glucose increased, ALP increased, sodium decreased, total bilirubin increased, GGT increased, phosphate decreased, platelets decreased, white blood cell count decreased, absolute neutrophil count decreased, lymphocytes decreased, hemoglobin decreased and hemoglobin increased.

8.5 Post-Market Adverse Drug Reactions

Vascular disorders: Artery dissection and artery aneurysm (including rupture) have been reported in association with VEGFR TKIs.

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 6: 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 [Hypericum perforatum]) with cabozantinib should therefore be avoided and alternative agents should be considered as the efficacy of CABOMETYX may be substantially reduced.

CABOMETYX	Source of Evidence	Effect	Clinical comment
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	*In vitro* 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.
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 (IC50 = 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, alpha$_2$-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 has a distinct mechanism of action with primary inhibition targets of MET (hepatocyte growth factor receptor protein), VEGF (vascular endothelial growth factor) receptors and GAS6 receptor (AXL). VEGF, MET and AXL receptors are involved in tumour progression and drug resistance in RCC. In addition, cabozantinib inhibits other tyrosine kinases including RET, ROS1, TYRO3, MER, the stem cell factor receptor (KIT), TRKB, Fms-like tyrosine kinase-3 (FLT3), and TIE-2.

10.2 Pharmacodynamics

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 7: 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 (≥ 99.7%). Based on the population pharmacokinetic (PK) model, the volume of distribution (Vz) is approximately 319 L (SE: ± 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 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.

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 ($AUC_{0\text{-inf}}$) increased by 81% and 63% in subjects with mild and moderate hepatic impairment, respectively (90% CI for $AUC_{0\text{-}inf}$: 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 $AUC_{0\text{-}inf}$ were 19% and 30% higher, for subjects with mild renal impairment (90% CI for C_{max} 91.60% to 155.51%; $AUC_{0\text{-}inf}$ 98.79% to 171.26%) and 2% and 6-7% higher (90% CI for C_{max} 78.64% to 133.52%; $AUC_{0\text{-}inf}$ 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 (cabozantinib) at room temperature (15°C to 25°C).

Keep out of sight and reach of children.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

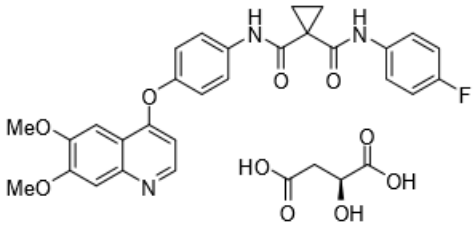
Drug Substance

Proper/Common name: cabozantinib (*S*)-malate

Chemical name: N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4fluorophenyl)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 8: Summary of patient demographics for clinical trials in RCC and HCC

Study #	Trial design	Dosage, route of administration	Study subjects (n)	Mean age (Range)	Sex
XL184-308 (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
A031203 (CABOSUN)	Open label, active-controlled, randomized 2-arm phase 2 study	CABOMETYX (60 mg) daily, oral	N=79	62.0 (40, 82)	84%M
		sunitinib (50 mg) daily, oral	N=78	63.6 (31, 87)	57%M
XL184-309 (CELESTIAL)	Double-blind, placebo-controlled, randomized 2-arm phase 3 study	CABOMETYX (60 mg) daily, oral	N=467	64.0 (22, 86)	81%M
		Placebo daily, oral	N=237	64.0 (24, 86)	85%M

XL184-308
The safety and efficacy of CABOMETYX (cabozantinib) were evaluated in a randomized, open-label, multicenter Phase 3 study (METEOR). 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.

Statistically significant improvement in PFS was demonstrated for CABOMETYX compared to everolimus (Figure 1 and Table 9). 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 10).

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)

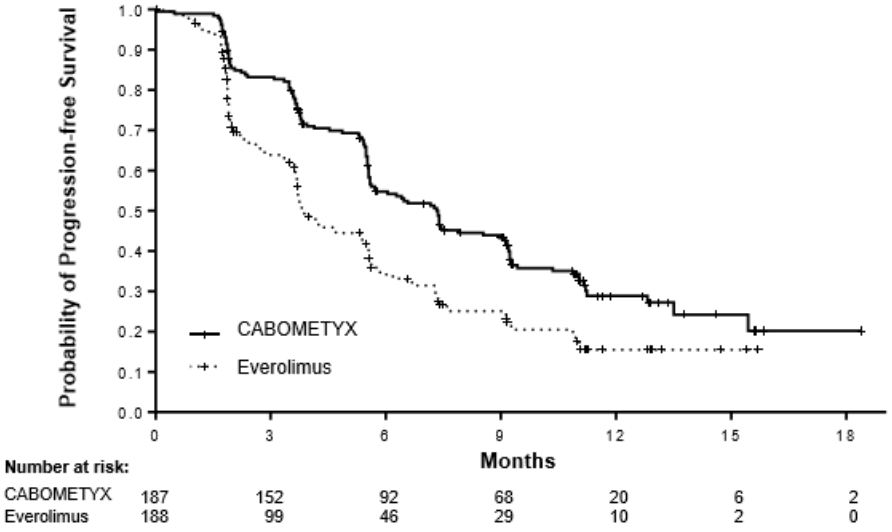


Table 9: Progression-Free Survival (First 375 randomized)

	Primary PFS analysis Population	
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)

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

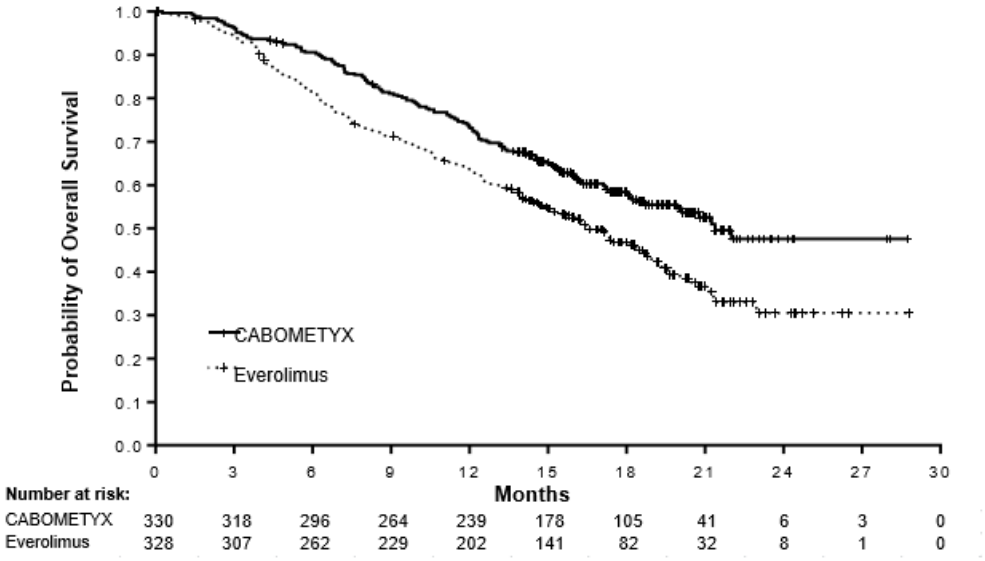


Table 10: Final Overall Survival Rate (ITT)

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 11: 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

A031203

The safety and efficacy of CABOMETYX for the treatment of treatment-naïve renal cell carcinoma were evaluated in a randomized, open-label, multicenter study (CABOSUN). Patients (N=157) with previously untreated, locally advanced or metastatic RCC with a clear cell component were randomized (1:1) to receive CABOMETYX (N=79) or sunitinib (N=78). Patients had 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). Approximately 75% of patients had a nephrectomy prior to onset of treatment.

The baseline demographic and disease characteristics were similar between the CABOMETYX and sunitinib arms. The majority of the patients treated with CABOMETYX were male (84%) with a median age of 62 years. Patient distribution by IMDC risk groups was 81% intermediate (1-2 risk factors) and 19% poor (≥3 risk factors). Most patients (87%) had ECOG performance status of 0 or 1; 13% had an ECOG performance status of 2. Thirty-six percent (36%) of patients had bone metastases.

The primary efficacy endpoint was PFS retrospectively assessed by a blinded Independent Radiology Committee (IRC). Secondary efficacy endpoints were objective response rate (ORR) and overall survival (OS). Tumor assessments were conducted every 12 weeks.

A statistically significant improvement in PFS as retrospectively assessed by an IRC was demonstrated for CABOMETYX compared to sunitinib (Figure 3 and Table 12). The results from the Investigator determined analysis and IRC-determined analysis of PFS were consistent.

Based on exploratory subgroup analyses, patients with a positive MET status showed a favorable effect in PFS (HR: 0.32; 95% CI: 0.16 – 0.63) and OS (HR: 0.31; 95% CI: 0.14 – 0.69) with CABOMETYX when compared with sunitinib. However, when comparing CABOMETYX to sunitinib in patients with MET negative status the numerical benefit seen in the PFS (HR: 0.67; 95% CI: 0.37 - 1.3) did not translate into the prolongation of the OS (HR: 1.34; 95% CI: 0.67 - 2.70), and a negative trend of OS treatment effect was found. The study was not powered for the OS analysis.

Objective response rate (ORR) findings are summarized in Table 12.

Figure 3: Kaplan Meier Curve for Progression-Free Survival by IRC in Treatment-Naïve RCC Subjects

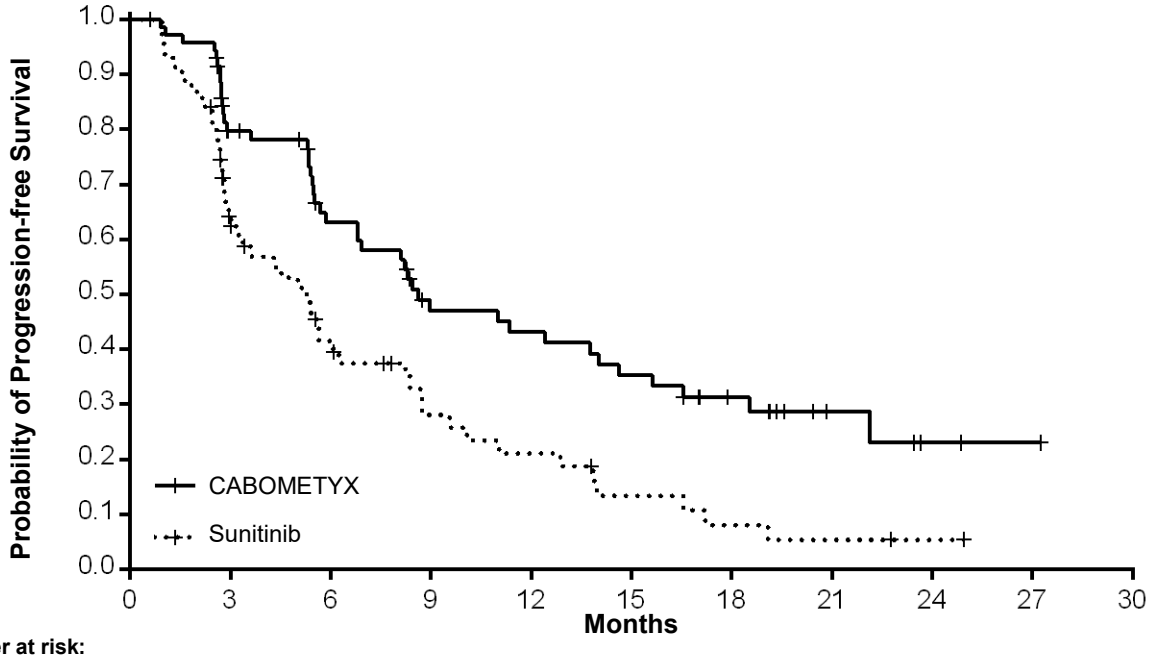


Table 12: Efficacy Results in Treatment-Naïve RCC Subjects (ITT population)

	CABOMETYX (N=79)	**Sunitinib (N=78)**
Progression-free survival (PFS) by IRC		
Median PFS in months (95% CI)	8.6 (6.8, 14.0)	5.3 (3.0, 8.2)
HR (95% CI); stratified[a, b]	0.48 (0.31, 0.74)	
Two-sided log-rank p-value: stratified [b]	p=0.0008	
Objective Response Rate n (%) by IRC		
Complete responses	0	0
Partial responses	16 (20)	7 (9)
ORR (partial responses only)	16 (20)	7 (9)
Stable disease	43 (54)	30 (38)
Progressive Disease	14 (18)	23 (29)

[a]Stratification factors per IxRS comprise IMDC risk categories (intermediate risk, poor risk and bone metastasis (yes, no)

[b]Estimated using the Cox proportional hazard model adjusted for stratification factors per IxRS. Hazard ratio < 1 indicates PFS in favor of cabozantinib

XL184-309

The safety and efficacy of CABOMETYX were evaluated in a randomized, placebo-controlled,

double-blind study of CABOMETYX 60 mg once daily in subjects with advanced HCC who had received prior sorafenib. The study randomized a total of 707 patients, 470 to receive CABOMETYX and 237 to receive placebo. The median age was 64 years (range 22 to 86 years), 81% were male, 56% were White and 34% were Asian. Baseline ECOG performance status was 0 (52%) or 1 (48%). Etiology of HCC was HBV in 39% of patients and HCV in 28% of patients, and etiology was attributed to causes other than HBV or HCV in 40% of patients. Macroscopic vascular invasion or extra-hepatic tumor spread was present in 78% of patients. The majority of patients (98% and 99% in the CABOMETIX and placebo arms, respectively) had Child-Pugh A liver disease. All (100%) patients received prior sorafenib and 28% received two prior systemic therapy regimens. Randomization was stratified by etiology of disease (HBV [with or without HCV], HCV [without HBV], or other), geographic region (Asia, other regions) and by presence of extrahepatic spread of disease and/or macrovascular invasions (Yes, No).

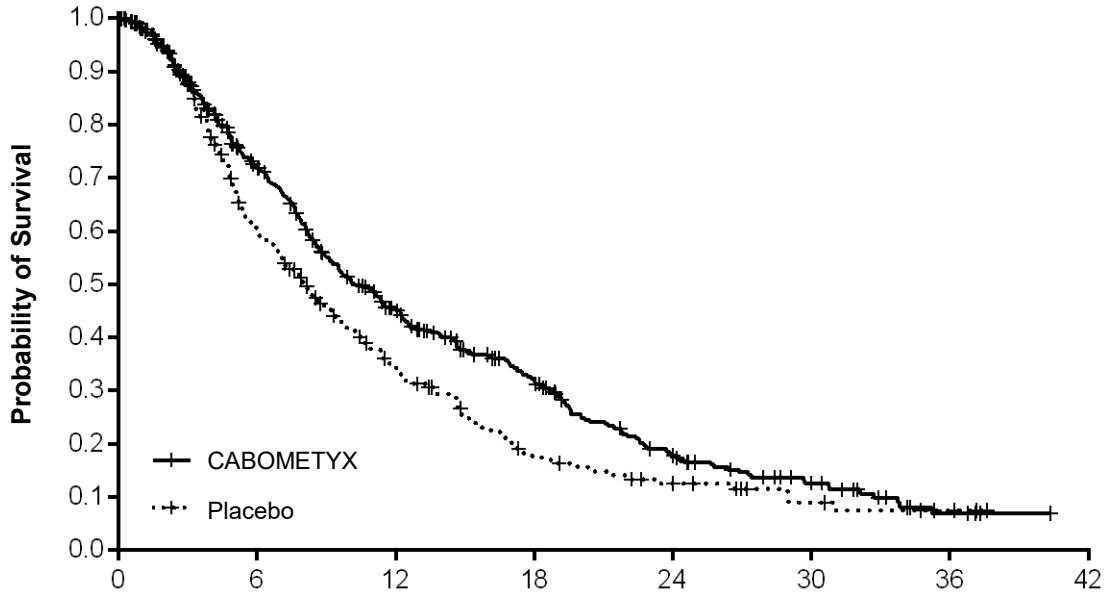
The primary endpoint was duration of OS and secondary endpoints were duration of Investigator-determined PFS and ORR per RECIST 1.1. The analysis of the primary endpoint (OS) was based on a second planned interim analysis prespecified to be performed at approximately the 75% information fraction (i.e., at approximately 466 deaths). The median duration of follow up was 22.9 months. The primary analysis demonstrated a statistically significant improvement in duration of OS for subjects in the CABOMETYX arm compared with the placebo arm: the HR, adjusted for stratification factors, was 0.76 (95% CI: 0.63, 0.92; p-value =0.0049).

Table 13: Efficacy Results in HCC (ITT population, CELESTIAL)

	CABOMETYX (N=470)	**Placebo (N=237)**
Overall Survival		
Median OS (95% CI), months	10.2 (9.1, 12.0)	8.0 (6.8, 9.4)
HR (95% CI)[1,2]	0.76 (0.63, 0.92)	
p-value[1]	p=0.0049	
Progression-free survival (PFS)[3]		
Median PFS in months (95% CI)	5.2 (4.0, 5.5)	1.9 (1.9, 1.9)
HR (95% CI)[1]	0.44 (0.36, 0.52)	
p-value[1]	p<0.0001	
Kaplan-Meier landmark estimates of percent of subjects event-free at 3 months		
% (95% CI)	67.0% (62.2%, 71.3%)	33.3% (27.1%, 39.7%)
Objective Response Rate n (%)[3]		
Complete responses (CR)	0	0
Partial responses (PR)	18 (4)	1 (0.4)
ORR (CR+PR)	18 (4)	1 (0.4)
p-value[1,4]	p=0.0086	
Stable disease	282 (60)	78 (33)
Progressive Disease	98 (21)	131 (55)

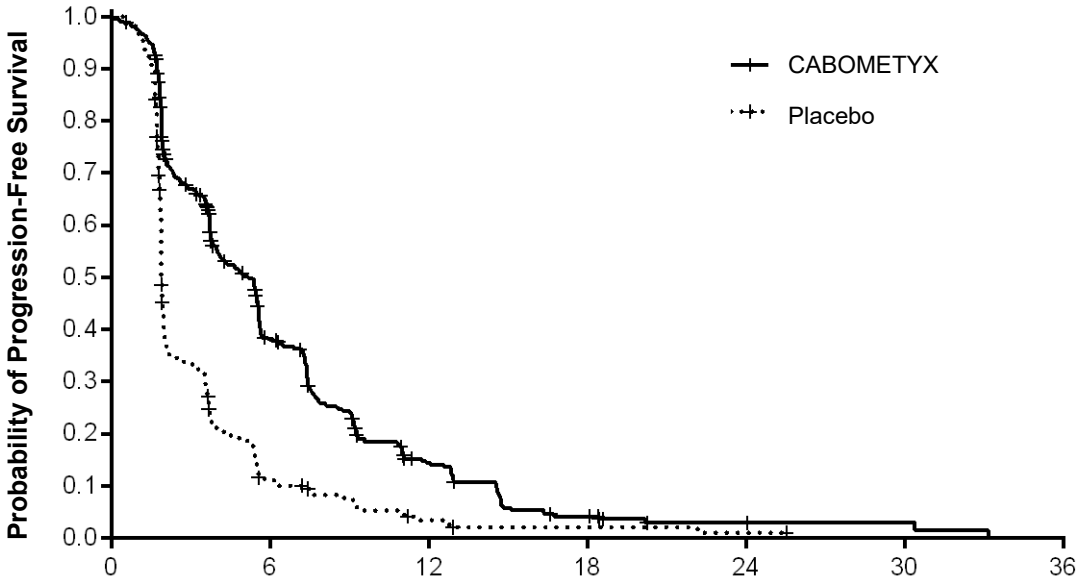
[1] 2-sided stratified log-rank test with etiology of disease (HBV [with or without HCV], HCV [without HBV], or Other), geographic region (Asia, Other Regions), and presence of extrahepatic spread of disease and/or macrovascular invasion (Yes, No) as stratification factors (per IVRS data)
[2] Estimated using the Cox proportional-hazard model
[3] As assessed by investigator per RECIST 1.1
[4] Stratified Cochran-Mantel-Haenszel (CMH) test

Figure 4: Kaplan-Meier Curve of Overall Survival (CELESTIAL)



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

Figure 5: Kaplan Meier Curve for Progression-Free Survival (CELESTIAL)



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

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

PrCABOMETYX™
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. Some of these patients may have had no previous treatment for their disease. Others may have been treated with medicines that block the growth of blood vessels (anti-angiogenic therapies).
- a type of liver cancer called hepatocellular carcinoma. These patients will have been previously treated with a medication called sorafenib.

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 and its complications, including separation of the layers of an artery wall (artery dissection)
- 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, lungs or liver, 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
- 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, such as cholestyramin and cholestagel
- Medicines that may lengthen the QT-interval of your heart, such as certain drugs to treat heart conditions, psychosis, depression, pain, infections and other conditions
- Medicines that may affect the levels of electrolytes in your body, such as 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 adjust your dose or stop treatment for some time (then resume at the same or a lower 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 and mouth
- Fatigue, insomnia
- Weakness
- Headache
- Fever
- Dizziness, fainting
- Pain in arms, legs and joints, muscle spasms
- Shortness of breath
- Difficulty in speaking, hoarseness
- Cough
- Hair loss
- Swelling in lower legs or hands
- Weakness or numbness in hands or feet

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		
Ascites (fluid in the abdomen): abdominal pain, feeling of fullness, flat or pushed out navel, weight increase, shortness of breath		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 gland): changes in heart rate, appetite or weight, tiredness, constipation, feeling cold, dry skin, swelling at front of neck		X	
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		
Proteinuria (too much protein in your urine): swelling of the hands, feet, face	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		
Dehydration (condition that happens when you lose more fluid than you take in): thirst, headache, loss of appetite, tiredness, weakness, decreased urine, dark urine	X		
Thrombocytopenia (low level of platelets in the blood): bruising easily, bleeding gums, nosebleeds, more bleeding than expected.	X		
Hepatic encephalopathy (worsening brain function due to liver issues): change in alertness, confusion, mood or personality changes, disorientation, changes in sleep patterns, loss of consciousness, coma		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 flow from the liver): yellow skin or eyes	X		
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): pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth		X	
Wound complication: a wound that does not heal		X	
VERY RARE		X	

Artery Dissection (separation of the layers of an artery wall): sudden severe pain in the back, chest or abdomen			
Artery Aneurysm (a bulge in the wall of any artery including in the chest, arms, legs, heart, and brain): symptoms will differ by the site. They can be cough, coughing up blood, strong pain high in your neck or in your back when you didn't hurt yourself, problems swallowing, hoarse voice, unusual pulsing in your chest or abdomen.		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); 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: May 7, 2020