This leaflet format has been determined by the Ministry of Health and the content has been checked and approved in November 2018

PHYSICIAN'S PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

CABOMETYX 20 mg
CABOMETYX 40 mg
CABOMETYX 60 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CABOMETYX 20 mg
Each film-coated tablet contains cabozantinib (*S*)-malate equivalent to 20 mg cabozantinib.

Excipients with known effect
Each film-coated tablet contains 15.54 mg lactose.

CABOMETYX 40 mg
Each film-coated tablet contains cabozantinib (S)-malate equivalent to 40 mg cabozantinib.

Excipients with known effect
Each film-coated tablet contains 31.07 mg lactose.

CABOMETYX 60 mg
Each film-coated tablet contains cabozantinib (S)-malate equivalent to 60 mg cabozantinib.

Excipients with known effect
Each film-coated tablet contains 46.61 mg lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

CABOMETYX 20 mg
The tablets are yellow round with no score, and identified with "XL" on one side and "20" on the other side of the tablet.

CABOMETYX 40 mg
The tablets are yellow triangle shaped with no score, and identified with "XL" on one side and "40" on the other side of the tablet.

CABOMETYX 60 mg
The tablets are yellow oval shaped with no score, and identified with "XL" on one side and "60" on the other side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CABOMETYX is indicated for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy

CABOMETYX is indicated for the treatment of advanced clear cell renal cell carcinoma in treatment-naïve adults with intermediate or poor risk per IMDC criteria (see section 5.1)

4.2 Posology and method of administration

Therapy with CABOMETYX should be initiated by a physician experienced in the administration of anticancer medicinal products.

Posology

The recommended dose of CABOMETYX is 60 mg once daily. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

Management of suspected adverse drug reactions may require temporary treatment interruption and/or dose reduction of CABOMETYX therapy (see Table 1). 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.

If a patient misses a dose, the missed dose should not be taken if it is less than 12 hours before the next dose.

Table 1: Recommended CABOMETYX dose modifications for adverse reactions

Adverse reaction and severity	**Treatment Modification**
Grade 1 and Grade 2 adverse reactions which are tolerable and easily managed	Dose adjustment is usually not required. Consider adding supportive care as indicated.
Grade 2 adverse reactions which are intolerable and cannot be managed with a dose reduction or supportive care	Interrupt treatment until the adverse reaction resolves to Grade ≤1. Add supportive care as indicated. Consider re-initiating at a reduced dose.
Grade 3 adverse reactions (except clinically nonrelevant laboratory abnormalities)	Interrupt treatment until the adverse reaction resolves to Grade ≤1. Add supportive care as indicated. Re-initiate at a reduced dose.
Grade 4 adverse reactions (except clinically nonrelevant laboratory abnormalities)	Interrupt treatment. Institute appropriate medical care. If adverse reaction resolves to Grade ≤1, re-initiate at a reduced dose. If adverse reaction does not resolve, permanently discontinue CABOMETYX.

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4)

Concomitant medicinal products
Concomitant medicinal products that are strong inhibitors of CYP3A4 should be used with caution, and chronic use of concomitant medicinal products that are strong inducers of CYP3A4 should be avoided (see sections 4.4 and 4.5).

Selection of an alternative concomitant medicinal product with no or minimal potential to induce or inhibit CYP3A4 should be considered.

Special populations

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

Race
There is little experience with cabozantinib in non-White patients.

Patients with renal impairment
Cabozantinib should be used with caution in patients with mild or moderate renal impairment. Cabozantinib is not recommended for use in patients with severe renal impairment as safety and efficacy have not been established in this population.

Patients with hepatic impairment
In patients with mild or moderate hepatic impairment the recommended dose is 40 mg once daily. Patients should be monitored for adverse events and dose adjustment or treatment interruption should be considered as needed (see section 4.2). Cabozantinib is not recommended for use in patients with severe hepatic impairment as safety and efficacy have not been established in this population.

Patients with cardiac impairment
There is limited data in patients with cardiac impairment. No specific dosing recommendations can be made.
Paediatric population
The safety and efficacy of cabozantinib in children and adolescents aged <18 years have not yet been established. No data are available.

Method of administration
CABOMETYX is for oral use. The tablets should be swallowed whole and not crushed. Patients should be instructed to not eat anything for at least 2 hours before, through 1 hour after, taking CABOMETYX.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 hypocalcaemia, hypokalaemia, thrombocytopenia, hypertension, palmar-plantar erythrodysaesthesia syndrome (PPES), proteinuria, and gastrointestinal (GI) events (abdominal pain, mucosal inflammation, constipation, diarrhoea, vomiting).

In renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy, dose reductions and dose interruptions due to an AE occurred in 59.8% and 70%, respectively, of cabozantinib-treated patients in the pivotal clinical trial (METEOR). 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.

In treatment-naïve clear cell renal cell carcinoma, dose reductions and dose interruptions occurred in 46% and 73%, respectively, of cabozantinib-treated patients in the clinical trial (CABOSUN).

Perforations and fistulas
Serious gastrointestinal (GI) perforations and fistulas, sometimes fatal, have been observed with cabozantinib. 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 cabozantinib therapy and subsequently they should be monitored closely for symptoms of perforations and fistulas including abscesses and sepsis. Persistent or recurring diarrhoea while on treatment may be a risk factor for the development of anal fistula. Cabozantinib should be discontinued in patients who experience a GI perforation or a fistula that cannot be adequately managed.

Thromboembolic events
Events of venous thromboembolism, including pulmonary embolism, and events of arterial thromboembolism have been observed with cabozantinib. Cabozantinib should be used with caution in patients who are at risk for, or who have a history of, these events. Cabozantinib should be discontinued in patients who develop an acute myocardial infarction or any other clinically significant arterial thromboembolic complication.

Haemorrhage
Severe haemorrhage has been observed with cabozantinib. Patients who have a history of severe bleeding prior to treatment initiation should be carefully evaluated before initiating cabozantinib therapy. Cabozantinib should not be administered to patients that have or are at risk for severe haemorrhage.

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

Hypertension
Hypertension has been observed with cabozantinib. Blood pressure should be well-controlled prior to initiating cabozantinib. During treatment with cabozantinib, all patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensives, the cabozantinib dose should be reduced. Cabozantinib should be discontinued if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of cabozantinib. In case of hypertensive crisis, cabozantinib should be discontinued.

Palmar-plantar erythrodysaesthesia syndrome
Palmar-plantar erythrodysaesthesia syndrome (PPES) has been observed with cabozantinib. When PPES is severe, interruption of treatment with cabozantinib should be considered. Cabozantinib should be restarted with a lower dose when PPES has been resolved to grade 1.

Proteinuria
Proteinuria has been observed with cabozantinib. Urine protein should be monitored regularly during cabozantinib treatment. Cabozantinib should be discontinued in patients who develop nephrotic syndrome.

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

Prolongation of QT interval
Cabozantinib should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using cabozantinib, periodic monitoring with on-treatment ECGs and electrolytes (serum calcium, potassium, and magnesium) should be considered.

CYP3A4 inducers and inhibitors
Cabozantinib is a CYP3A4 substrate. Concurrent administration of cabozantinib with the strong CYP3A4 inhibitor ketoconazole resulted in an increase in cabozantinib plasma exposure. Caution is required when administering cabozantinib with agents that are strong CYP3A4 inhibitors. Concurrent administration of cabozantinib with the strong CYP3A4 inducer rifampicin resulted in a decrease in cabozantinib plasma exposure. Therefore chronic administration of agents that are strong CYP3A4 inducers with cabozantinib should be avoided (see sections 4.2 and 4.5).

P-glycoprotein substrates
Cabozantinib was an inhibitor (IC_{50} = 7.0 μM), but not a substrate, of P-glycoprotein (P-gp) transport activities in a bi-directional assay system using MDCK-MDR1 cells. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. Subjects should be cautioned regarding taking a P-gp substrate (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib (see section 4.5).

MRP2 inhibitors
Administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations. Therefore, concomitant use of MRP2 inhibitors (e.g. cyclosporine, efavirenz, emtricitabine) should be approached with caution (see section 4.5).

Excipient related warnings
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on cabozantinib

CYP3A4 inhibitors and inducers
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%. Therefore co-administration of strong CYP3A4 inhibitors (e.g., ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) with cabozantinib should be approached with caution.

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.

Gastric pH modifying agents
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
In vitro data demonstrate that cabozantinib is a substrate of MRP2. Therefore, administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations.

Bile salt-sequestering agents
Bile salt-sequestering agents such as cholestyramine and cholestagel may interact with cabozantinib and may impact absorption (or reabsorption) resulting in potentially decreased exposure (see section 5.2). The clinical significance of these potential interactions is unknown.

Effect of cabozantinib on other medicinal products
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.
Because of high plasma protein binding levels of cabozantinib (section 5.2) a plasma protein displacement interaction with warfarin may be possible. In case of such combination, INR values should be monitored.

P-glycoprotein substrates
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. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. Subjects should be cautioned regarding taking a P-gp substrate (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
Women of childbearing potential must be advised to avoid pregnancy while on cabozantinib. Female partners of male patients taking cabozantinib 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 section 4.5).

Pregnancy
There are no studies in pregnant women using cabozantinib. Studies in animals have shown embryo-foetal and teratogenic effects (see section 5.3). The potential risk for humans is unknown. Cabozantinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with cabozantinib.

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 cabozantinib, and for at least 4 months after completing therapy.

Fertility
There are no data on human fertility. Based on non-clinical safety findings, male and female fertility may be compromised by treatment with cabozantinib (see section 5.3). Both men and women should be advised to seek advice and consider fertility preservation before treatment.

4.7 Effects on ability to drive and use machines

Cabozantinib has minor influence on the ability to drive and use machines. Adverse reactions such as fatigue and weakness have been associated with cabozantinib. Therefore, caution should be recommended when driving or operating machines.

4.8 Undesirable effects

Summary of safety profile

The most common serious adverse drug reactions are hypertension, diarrhoea, palmar-plantar erythrodysaesthesia syndrome (PPES), pulmonary embolism, fatigue and hypomagnesaemia.

The most frequent adverse reactions of any grade (experienced by at least 25% of patients) included diarrhoea, hypertension, fatigue, AST increased, ALT increased, nausea, decreased appetite, PPES, dysgeusia, platelet count decreased, stomatitis, anaemia, vomiting, weight decreased, dyspepsia, and constipation. Hypertension was observed more frequently in the treatment naïve RCC population (67%) compared to RCC patients following prior VEGF-targeted therapy (37%).

Tabulated list of adverse reactions
Adverse reactions are listed in Table 2 according to MedDRA System Organ Class and frequency categories. Frequencies are based on all grades and defined as: very common (≥1/10), common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); not known. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse drug reactions (ADRs) reported with cabozantinib in advanced RCC

MedDRA System Organ Class	Very Common	Common	Uncommon	Not Known
Infections and infestations		abscess		
Blood and lymphatic disorders	anaemia, lymphopenia, neutropenia, thrombocytopenia			
Endocrine disorders	hypothyroidism			
Metabolism and nutrition disorders	dehydration, decreased appetite, hyperglycaemia, hypoglycaemia hypophosphataemia, hypoalbuminaemia, hypomagnesaemia, hyponatraemia, hypokalaemia, hyperkalaemia, hypocalcaemia, hyperbilirubinemia.			
Nervous system disorders	peripheral sensory neuropathy, dysgeusia, headache, dizziness		convulsion	cerebrovascular accident
Ear and labyrinth disorders		tinnitus		

MedDRA System Organ Class	Very Common	Common	Uncommon	Not Known
Cardiac disorders				myocardial infarction
Vascular disorders	hypertension	venous thrombosis arterial thrombosis		
Respiratory, thoracic, and mediastinal disorders	dysphonia, dyspnoea, cough	pulmonary embolism		
Gastrointestinal disorders	diarrhoea, nausea, vomiting, stomatitis, constipation, abdominal pain, dyspepsia, oral pain, dry mouth	pancreatitis, abdominal pain upper, gastro-oesophageal reflux disease, haemorrhoids	anal fistula	
Hepatobiliary disorders			hepatitis cholestatic	
Skin and subcutaneous tissue disorders	palmar-plantar erythrodysaesthesia syndrome, dermatitis acneiform, rash, rash maculopapular, dry skin, alopecia, hair colour change	pruritus		
Musculoskeletal and connective tissue disorders	pain in extremity, muscle spasms, arthralgia		osteonecrosis of the jaw	
Renal and urinary disorders	proteinuria			
General disorders and administration site conditions	fatigue, mucosal inflammation, asthenia	peripheral oedema		

MedDRA System Organ Class	Very Common	Common	Uncommon	Not Known
Investigations	weight decreased, serum ALT, AST, and ALP increased, blood bilirubin increased, creatinine increased, triglycerides increased, white blood cell decreased, GGT increased, amylase increased, blood cholesterol increased, lipase increased			
Injury, poisoning and procedural complications		wound complication		

Description of selected adverse reactions
Data for the following reactions are based on patients who received Cabometyx 60 mg qd po in the pivotal studies in RCC following prior VEGF-targeted therapy and in treatment-naïve RCC (section 5.1).

Gastrointestinal (GI) perforation
In the study in RCC following prior VEGF-targeted therapy (METEOR), GI perforations were reported in 0.9% (3/331) of cabozantinib-treated RCC patients. Events were Grade 2 or 3. Median time to onset was 10.0 weeks.
In the treatment-naïve RCC study (CABOSUN), GI perforations were reported in 2.6% (2/78) of cabozantinib-treated patients. Events were Grade 4 and 5.

Fatal perforations have occurred in the cabozantinib clinical program.
Fistulas
In the study in RCC following prior VEGF-targeted therapy (METEOR), fistulas were reported in 1.2% (4/331) of cabozantinib-treated patients, and included anal fistulas in 0.6% (2/331) cabozantinib-treated patients. One event was Grade 3; the remainder was Grade 2. Median time to onset was 30.3 weeks.
In the treatment-naïve RCC study (CABOSUN), no cases of fistulas were reported.

Haemorrhage
In the study in RCC following prior VEGF-targeted therapy (METEOR), the incidence of severe haemorrhagic events (Grade ≥ 3) was 2.1% (7/331) in cabozantinib-treated RCC patients. Median time to onset was 20.9 weeks.

In the treatment-naïve RCC study (CABOSUN), the incidence of severe haemorrhagic events (Grade ≥ 3) was 5.1% (4/78) in cabozantinib-treated RCC patients.

Fatal haemorrhages have occurred in the cabozantinib clinical program.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
No cases of RPLS were reported in the METEOR or CABOSUN studies, but RPLS has been reported in other clinical studies with cabozantinib.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/ or by email (mailto:adr@MOH.HEALTH.GOV.IL).

4.9 Overdose

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

In the event of suspected overdose, cabozantinib should be withheld and supportive care instituted. Metabolic clinical laboratory parameters should be monitored at least weekly or as deemed clinically appropriate to assess any possible changing trends. Adverse reactions associated with overdose are to be treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agent, protein kinase inhibitor, ATC code: L01XE26.

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.

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
An increase from baseline in corrected QT interval by Fridericia (QTcF) of 10 – 15 ms on Day 29 (but not on Day 1) following initiation of cabozantinib treatment (at a dose of 140 mg qd) was observed in a controlled clinical study in medullary thyroid cancer patients. This effect was not associated with a change in cardiac wave form morphology or new rhythms. No cabozantinib-treated subjects in this study had a confirmed QTcF >500 ms, nor did any cabozantinib-treated subjects in the RCC studies (at a dose of 60 mg).

Clinical efficacy and safety

Clinical data in renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy

The safety and efficacy of CABOMETYX for the treatment of renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy were evaluated in a randomized, open-label, multicenter Phase 3 study (METEOR). Patients (N=658) with advanced 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.

A statistically significant improvement in PFS was demonstrated for CABOMETYX compared to everolimus (Figure 1 and Table 3). 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 (202 events, 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 (320 events, median of 21.4 months vs. 16.5 months; HR=0.66 [0.53, 0.83], p=0.0003; Figure 2). Comparable results for OS were observed with a follow-up analysis (descriptive) at 430 events.

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).

Objective response rate findings are summarized in Table 4.

Figure 1: Kaplan Meier curve for progression-free survival by independent radiology review committee, in RCC subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy (first 375 subjects randomized)

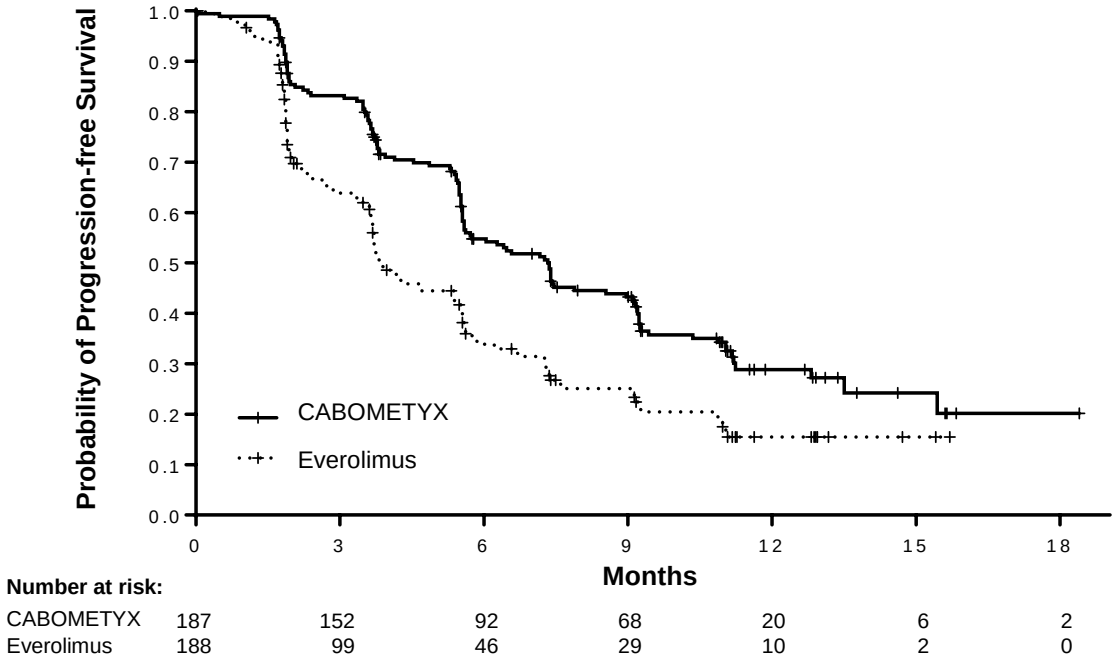


Table 3: Summary of PFS findings by independent radiology review committee in RCC subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy

	Primary PFS analysis Population		**Intent-To-Treat Population**	
Endpoint	**CABOMETYX**	**Everolimus**	**CABOMETYX**	**Everolimus**
	N = 187	N = 188	N = 330	N = 328
Median PFS (95% CI), months	7.4 (5.6, 9.1)	3.8 (3.7, 5.4)	7.4 (6.6, 9.1)	3.9 (3.7, 5.1)
HR (95% CI), p-value[1]	0.58 (0.45, 0.74), p<0.0001		0.51 (0.41, 0.62), p<0.0001	

[1] stratified log-rank test

Figure 2: Kaplan-Meier curve of overall survival in RCC subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy

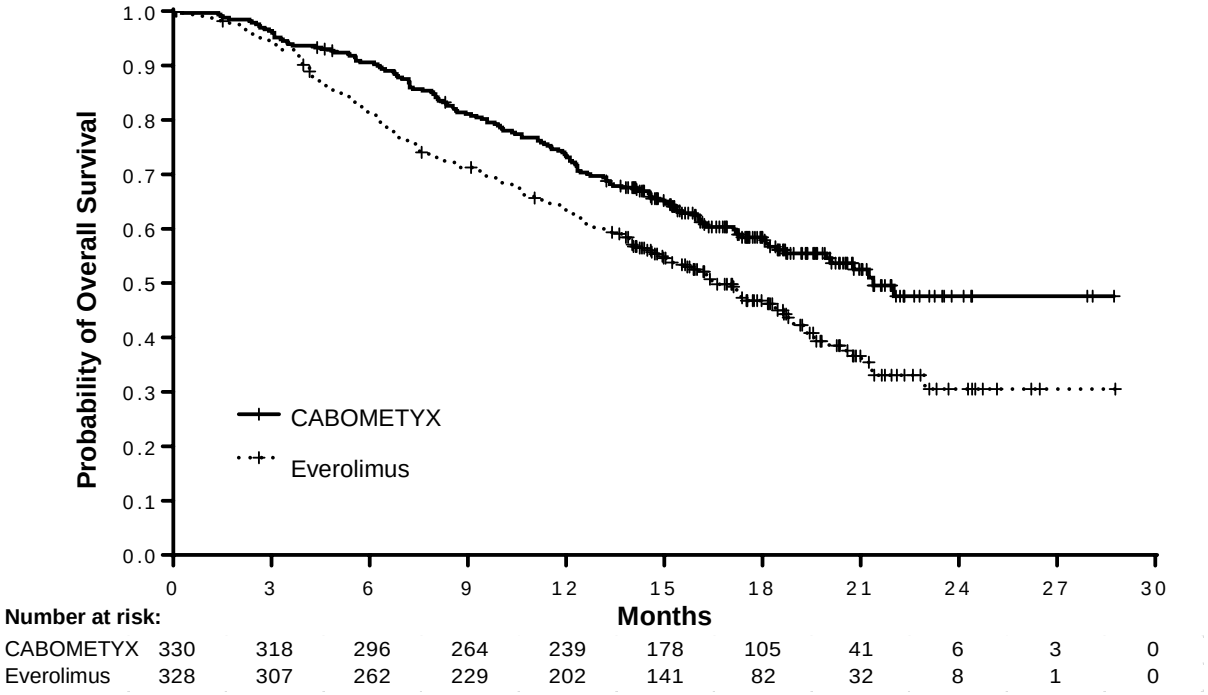


Table 4: Summary of ORR findings per independent radiology committee review (IRC) and investigator review, in RCC subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy

	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, 9.2)	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

Clinical data in treatment-naïve clear cell renal cell carcinoma

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.
For intermediate risk disease, one or two of the following risk factors were met, while for poor risk, three or more factors were met: time from diagnosis of RCC to systemic treatment < 1 year, Hgb < LLN, Corrected calcium > ULN, KPS < 80%, Neutrophil count > ULN and Platelet count > ULN.

The primary endpoint was PFS. Secondary efficacy endpoints were objective response rate (ORR) and overall survival (OS). Tumor assessments were conducted every 12 weeks.

The baseline demographic and disease characteristics were similar between the CABOMETYX and sunitinib arms. The majority of the patients were male (78%) 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.

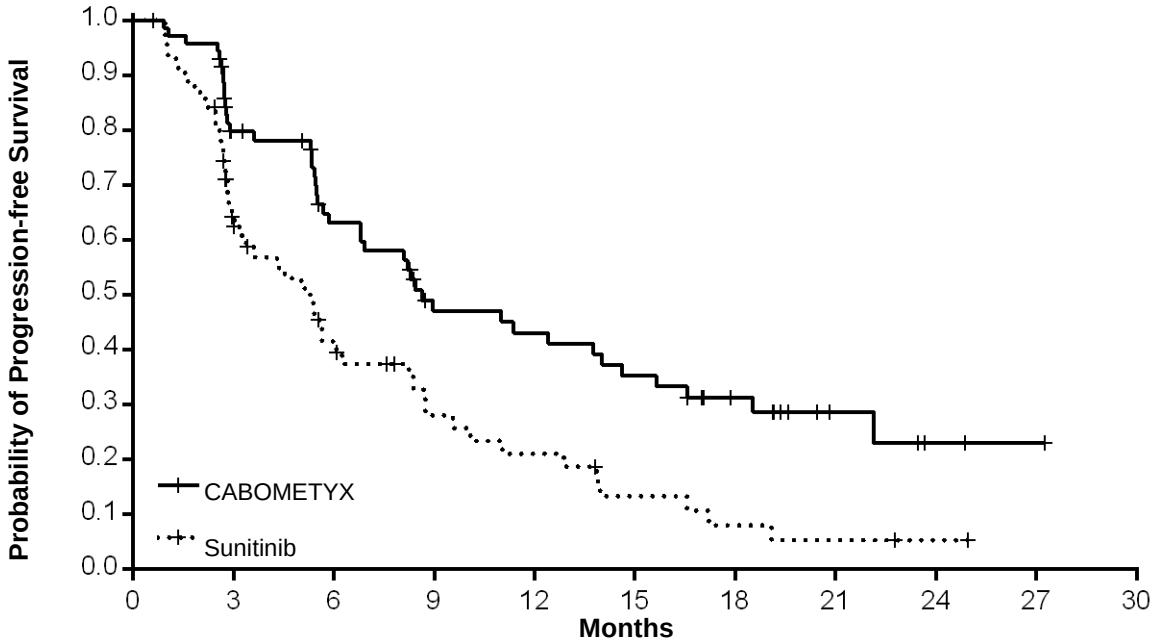
A statistically significant improvement in PFS as retrospectively assessed by a blinded Independent Radiology Committee (IRC) was demonstrated for CABOMETYX compared to sunitinib (Figure 3 and Table 5). The results from the Investigator determined analysis and IRC-determined analysis of PFS were consistent.

Patients with both positive and negative MET status showed a favourable effect with CABOMETYX compared to sunitinib, with greater activity in patients with a positive MET status compared to patients with a negative MET status (HR=0.32 (0.16, 0.63) vs 0.67 (0.37, 1.23)) respectively.

CABOMETYX treatment was associated with a trend for longer survival compared to sunitinib (Table 5). The study was not powered for the OS analysis and the data are immature.

Objective response rate (ORR) findings are summarized in Table 5.

Figure 3: Kaplan Meier curve for progression-free survival by IRC in treatment-naïve clear cell RCC subjects



Number at risk:

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

Table 5: Efficacy results in treatment-naïve RCC subjects (ITT population, CABOSUN)

	CABOMETYX (N=79)	Sunitinib (N=78)
Progression-free survival (PFS) by IRC [a]		
Median PFS in months (95% CI)	8.6 (6.2, 14.0)	5.3 (3.0, 8.2)
HR (95% CI); stratified [b,c]	0.48 (0.32, 0.73)	
Two-sided log-rank p-value: stratified [b]	p=0.0005	
Progression-free survival (PFS) by Investigator		
Median PFS in months (95% CI)	8.3 (6.5, 12.4)	5.4 (3.4, 8.2)
HR (95% CI); stratified [b,c]	0.56 (0.37, 0.83)	
Two-sided log-rank p-value: stratified [b]	p=0.0042	
Overall Survival		
Median OS in months (95% CI)	30.3 (14.6, NE)	21.0 (16.3, 27.0)
HR (95% CI); stratified [b,c]	0.74 (0.47, 1.14)	
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)
Objective Response Rate n (%) by Investigator		
Complete responses	1 (1)	0
Partial responses	25 (32)	9 (12)
ORR (partial responses only)	26 (33)	9 (12)
Stable disease	34 (43)	29 (37)
Progressive Disease	14 (18)	19 (24)

[a] in accord with EU censoring
[b] Stratification factors per IxRS comprise IMDC risk categories (intermediate risk, poor risk and bone metastasis (yes, no)
[c] Estimated using the Cox proportional hazard model adjusted for stratification factors per IxRS. Hazard ratio < 1 indicates progression-free survival in favor of cabozantinib

5.2 Pharmacokinetic properties

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 moderately increased C_{max} and AUC values (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.

Bioequivalence could not be demonstrated between the cabozantinib capsule and tablet formulations following a single 140 mg dose in healthy subjects. A 19% increase in the C_{max} of the tablet formulation (CABOMETYX) compared to the capsule formulation (COMETRIQ) was observed. A less than 10% difference in the AUC was observed between cabozantinib tablet (CABOMETYX) and capsule (COMETRIQ) formulations.

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

Biotransformation
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 (ie, 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 ^{14}C-cabozantinib in healthy volunteers, approximately 81% of the total administered radioactivity was recovered with 54% in faeces and 27% in urine.

Pharmacokinetics in special patient populations

Renal impairment
Results from a study in patients with renal impairment indicate that the 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.

Hepatic impairment
Results from a study in patients with hepatic impairment indicate that 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.

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

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

In rat and dog repeat-dose toxicity studies up to 6 months duration, target organs for toxicity were GI tract, bone marrow, lymphoid tissues, kidney, adrenal and reproductive tract tissues. The no observed adverse effect level (NOAEL) for these findings were below human clinical exposure levels at intended therapeutic dose.

Cabozantinib has shown no mutagenic or clastogenic potential in a standard battery of genotoxicity assays. The carcinogenic potential of cabozantinib has been evaluated in two species: rasH2 transgenic mice and

Sprague-Dawley rats. In the 2-year rat carcinogenicity study, 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 both sexes at exposures well below the intended exposure in humans. The clinical relevance of the observed neoplastic lesions in rats is uncertain, but likely to be low.
Cabozantinib was not carcinogenic in the rasH2 mouse model at a slightly higher exposure than the intended human therapeutic exposure.

Fertility studies in rats have shown reduced male and female fertility. Further, hypospermatogenesis was observed in male dogs at exposure levels below human clinical exposure levels at intended therapeutic dose.

Embryo-foetal development studies were performed in rats and rabbits. In rats, cabozantinib caused postimplantation loss, foetal oedema, cleft palate/lip, dermal aplasia and kinked or rudimentary tail. In rabbits, cabozantinib produced foetal soft tissue changes (reduced spleen size, small or missing intermediate lung lobe) and increased foetal incidence of total malformations. NOAEL for embryo-foetal toxicity and teratogenic findings were below human clinical exposure levels at intended therapeutic dose.

Juvenile rats (comparable to a >2 year old pediatric population) administered cabozantinib showed increased WBC parameters, decreased haematopoiesis, pubescent/immature female reproductive system (without delayed vaginal opening), tooth abnormalities, reduced bone mineral content and density, liver pigmentation and lymph node lymphoid hyperplasia. Findings in uterus/ovaries and decreased haematopoiesis appeared to be transient, while effects on bone parameters and liver pigmentation were sustained. Juvenile rats (correlating to a <2 year pediatric population) showed similar treatment-related findings, but appeared to be more sensitive to cabozantinib-related toxicity at comparable dose levels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet content
Microcrystalline Cellulose
Lactose Anhydrous
Croscarmellose Sodium
Hydroxypropyl Cellulose
Magnesium stearate
Colloidal Silicon Dioxide (Anhydrous)

Film-coating
Opadry®yellow Components:
Hypromellose (HPMC) 2910
Titanium Dioxide (E171)
Triacetin
Iron Oxide Yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

HDPE bottle with a polypropylene child-resistant closure and three silica gel dessicant canisters. Each bottle contains 30 film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Ipsen Pharma
65 quai Georges Gorse
92100 Boulogne-Billancourt
France

8. IMPORTER AND LICENSE HOLDER

Medison Pharma Ltd.
10 Hashiloach St., P.O.B 7090, Petach Tikva

9. REGISTRATION NUMBERS

CABOMETYX 20 mg: 160-99-35263-00
CABOMETYX 40 mg: 161-01-35264-00
CABOMETYX 60 mg: 161-02-35265-00