ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CABOMETYX 20 mg film-coated tablets
CABOMETYX 40 mg film-coated tablets
CABOMETYX 60 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Renal cell carcinoma (RCC)
CABOMETYX is indicated as monotherapy for advanced renal cell carcinoma
- as first-line treatment of adult patients with intermediate or poor risk (see section 5.1),
- in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy (see section 5.1).

CABOMETYX, in combination with nivolumab, is indicated for the first-line treatment of advanced renal cell carcinoma in adults (see section 5.1).

Hepatocellular carcinoma (HCC)
CABOMETYX is indicated as monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib.

Differentiated thyroid carcinoma (DTC)
CABOMETYX is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy.

Neuroendocrine Tumours (NET)
CABOMETYX is indicated for the treatment of adult patients with unresectable or metastatic, well differentiated extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours who have progressed following at least one prior systemic therapy other than somatostatin analogues.

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
CABOMETYX tablets and cabozantinib capsules are not bioequivalent and should not be used interchangeably (see section 5.2).

CABOMETYX as monotherapy
For RCC, HCC, DTC and NET, 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.

CABOMETYX in combination with nivolumab in first-line advanced RCC
The recommended dose of CABOMETYX is 40 mg once daily in combination with nivolumab solution for infusion administered intravenously at either 240 mg every 2 weeks or 480 mg every 4 weeks, **or** with nivolumab solution for injection administered subcutaneously at either 600 mg every 2 weeks or 1200 mg every 4 weeks. The treatment should continue until disease progression or unacceptable toxicity. Nivolumab should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression (see the Summary of Product Characteristics (SmPC) for posology of nivolumab).

Treatment modification
Management of suspected adverse drug reactions may require temporary treatment interruption and/or dose reduction (see Table 1). When dose reduction is necessary in monotherapy, it is recommended to reduce to 40 mg daily, and then to 20 mg daily.

When CABOMETYX is administered in combination with nivolumab, it is recommended to reduce the dose to 20 mg of CABOMETYX once daily, and then to 20 mg every other day (refer to the nivolumab SmPC for recommended treatment modification for nivolumab).

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. Add 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 the treatment.
Liver enzymes elevations for RCC patients treated with CABOMETYX in combination with nivolumab	
ALT or AST > 3 times ULN but ≤10 times ULN without concurrent total bilirubin ≥ 2 times ULN	Interrupt CABOMETYX and nivolumab until these adverse reactions resolves to Grade ≤1 Corticosteroid therapy may be considered if immune-mediated reaction is suspected (refer to nivolumab SmPC). Re-initiate with a single medicine or sequential re-initiating with both medicines after recovery may be considered. If re-initiating with nivolumab, refer to nivolumab SmPC.

ALT or AST > 10 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN	Permanently discontinue CABOMETYX and nivolumab. Corticosteroid therapy may be considered if immune-mediated reaction is suspected (refer to nivolumab SmPC).

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

Race
No dose adjustment is necessary based on ethnicity (see section 5.2)

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.

Hepatic impairment
In patients with mild hepatic impairment no dose adjustment is required. Since only limited data are available for patients with moderate hepatic impairment (Child Pugh B), no dosing recommendation can be provided. Close monitoring of overall safety is recommended in these patients (see sections 4.4 and 5.2). There is no clinical experience in patients with severe hepatic impairment (Child Pugh C), so cabozantinib is not recommended for use in these patients (see section 5.2).

Cardiac impairment
There are 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. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

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 adverse reactions 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. Adverse reactions 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).

Management of suspected adverse reactions may require temporary interruption or dose reduction of cabozantinib therapy (see section 4.2):

Dose reductions and dose interruptions due to an adverse event (AE) occurred in 46-67% and 70-84%, respectively, of cabozantinib-treated patients in the pivotal monotherapy clinical trials in RCC (METEOR, CABOSUN), HCC (CELESTIAL), DTC (COSMIC-311) and NET (CABINET). Two dose reductions were required in 9.4%-33% of patients. The median time to first dose reduction was 38-106 days and to first dose interruption was 28-68 days.

When cabozantinib is given in combination with nivolumab in first-line advanced RCC, dose reduction and dose interruption of cabozantinib due to an AE occurred in 54.1% and 73.4% of patients in the clinical trial (CA2099ER). Two dose reductions were required in 9.4% of patients. The median time to first dose reduction was 106 days, and to first dose interruption was 68 days.

Hepatotoxicity
Abnormalities of liver function tests (increases in alanine aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin) have been frequently observed in patients treated with cabozantinib. It is recommended to perform liver function tests (ALT, AST and bilirubin) before initiation of cabozantinib treatment and to monitor closely during treatment. For patients with worsening of liver function tests considered related to cabozantinib treatment (i.e. where no alternative cause is evident), the dose modification advice in Table 1 should be followed (see section 4.2).
When cabozantinib is given in combination with nivolumab, higher frequencies of Grades 3 and 4 ALT and AST elevations have been reported relative to cabozantinib monotherapy in patients with advanced RCC (see section 4.8). Liver enzymes should be monitored before initiation of and periodically throughout treatment. Medical management guidelines for both medicines should be followed (see section 4.2 and refer to the SmPC for nivolumab).
Rare instances of vanishing bile duct syndrome have been reported. All cases have occurred in patients who have received immune checkpoint inhibitors, either before or concurrently with cabozantinib treatment.
Cabozantinib is eliminated mainly via the hepatic route. Closer monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment (see also sections 4.2 and 5.2). A higher relative proportion of patients with moderate hepatic impairment (Child-Pugh B) developed hepatic encephalopathy with cabozantinib treatment. Cabozantinib is not recommended for use in patients with severe hepatic impairment (Child-Pugh C, see section 4.2).

Hepatic encephalopathy
In the HCC study (CELESTIAL), hepatic encephalopathy was reported more frequently in the cabozantinib than the placebo arm. Cabozantinib has been associated with diarrhoea, 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.

Perforations and fistulas
Serious 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.

Gastrointestinal (GI) disorders
Diarrhoea, nausea/vomiting, decreased appetite, and stomatitis/oral pain were some of the most commonly reported GI events (see section 4.8). Prompt medical management, including supportive care with antiemetics, antidiarrhoeals, or antacids, should be instituted to prevent dehydration, electrolyte imbalances and weight loss. Dose interruption or reduction, or permanent discontinuation of cabozantinib should be considered in case of persistent or recurrent significant GI adverse reactions (see Table 1).

Thromboembolic events
Events of venous thromboembolism, including pulmonary embolism, and arterial thromboembolism, sometimes fatal, 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.
In the HCC study (CELESTIAL), portal vein thrombosis was observed with cabozantinib, including one fatal event. Patients with a history of portal vein invasion appeared to be at higher risk of developing portal vein thrombosis. Cabozantinib should be discontinued in patients who develop an acute myocardial infarction or any other clinically significant thromboembolic complication.
In the CABINET study, the frequency VTE was higher in the pNET cohort (19%) compared to epNET cohort (3.8%) in participants who received cabozantinib.

Haemorrhage
Severe haemorrhage, sometimes fatal, 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.
In the HCC study (CELESTIAL), fatal haemorrhagic events were reported at a higher incidence with cabozantinib than placebo. Predisposing risk factors for severe haemorrhage 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 CELESTIAL 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.
The study of cabozantinib in combination with nivolumab in first-line advanced RCC (CA2099ER) excluded patients with anticoagulants at therapeutic doses.

Aneurysms and artery dissections
The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating cabozantinib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Thrombocytopenia
In the HCC study (CELESTIAL), in the DTC study (COSMIC-311) and in the NET study (CABINET), thrombocytopenia and decreased platelets were reported. Platelet levels should be monitored during cabozantinib treatment and the dose modified according to the severity of the thrombocytopenia (see Table 1).

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 or invasive dental procedures, 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, including hypertensive crisis has been observed with cabozantinib. Blood pressure should be well-controlled prior to initiating cabozantinib. After cabozantinib initiation, blood pressure should be monitored early and regularly and treated as needed with appropriate antihypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensives, the cabozantinib treatment should be interrupted until blood pressure is controlled, after which cabozantinib can be resumed at a reduced dose. 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.

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

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.

Posterior reversible encephalopathy syndrome
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 PRES.

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.

Thyroid dysfunction
Baseline laboratory measurement of thyroid function is recommended in all patients. Patients with pre-existing hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of cabozantinib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction during cabozantinib treatment. Thyroid function should be

monitored periodically throughout treatment with cabozantinib. Patients who develop thyroid dysfunction should be treated as per standard medical practice.

Biochemical laboratory test abnormalities
Cabozantinib has been associated with an increased incidence of electrolyte abnormalities (including hypo- and hyperkalaemia, hypomagnesaemia, hypocalcaemia, hyponatraemia). Hypocalcaemia has been observed with cabozantinib at a higher frequency and/or increased severity (including Grade 3 and 4) in patients with thyroid cancer compared to patients with other cancers. It is recommended to monitor biochemical parameters during cabozantinib treatment and to institute appropriate replacement therapy according to standard clinical practice if required. Cases of hepatic encephalopathy in HCC patients can be attributed to the development of electrolyte disturbances. Dose interruption or reduction, or permanent discontinuation of cabozantinib should be considered in case of persistent or recurrent significant abnormalities (see Table 1).

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. cyclosporin, efavirenz, emtricitabine) should be approached with caution (see section 4.5).

Excipient
Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

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 colestyramine 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.
The effect of cabozantinib on the pharmacokinetics of warfarin has not been investigated. An 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 Pgp transport activities in a bidirectional assay system using MDCK-MDR1 cells. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of Pgp. Subjects should be cautioned regarding taking a Pgp 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

Cabozantinib as monotherapy
Summary of safety profile
The most common serious adverse drug reactions in the RCC population (≥1% incidence) are pneumonia, abdominal pain, diarrhoea, nausea, hypertension, embolism, hyponatraemia, pulmonary embolism, vomiting, dehydration, fatigue, asthenia, decreased appetite, deep vein thrombosis, dizziness, hypomagnesaemia and palmar-plantar erythrodysaesthesia syndrome (PPES).

The most common serious adverse drug reactions in the HCC population (≥1% incidence) are hepatic encephalopathy, asthenia, fatigue, PPES, diarrhoea, hyponatraemia, vomiting, abdominal pain and thrombocytopenia.

The most common serious adverse drug reactions in the DTC population (≥1% incidence) are diarrhoea, pleural effusion, pneumonia, pulmonary embolism, hypertension, anaemia, deep vein thrombosis, hypocalcaemia, osteonecrosis of jaw, pain, PPES, vomiting and renal impairment.

The most common serious adverse drug reactions in the NET population (≥1% incidence) are hypertension, fatigue, pulmonary embolism, vomiting, diarrhoea, nausea and embolism.

The most frequent adverse reactions of any grade (experienced by at least 25% of patients) in the RCC, HCC, DTC and NET populations were diarrhoea, fatigue, nausea, decreased appetite, PPES and hypertension.

Tabulated list of adverse reactions
Adverse reactions reported in the pooled dataset for patients treated with cabozantinib monotherapy in RCC, HCC, DTC and NET (n=1355) or reported after post-marketing use of cabozantinib are listed in Table 2. The adverse reactions are listed by 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 (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse drug reactions (ADRs) reported in clinical trials or after post-marketing use in patients treated with cabozantinib in monotherapy

Infections and infestations	
Common	abscess, pneumonia
Blood and lymphatic disorders	
Very common	anaemia, thrombocytopenia

Common	neutropenia, lymphopenia
Endocrine disorders	
Very common	hypothyroidism[*]
Metabolism and nutrition disorders	
Very common	decreased appetite, hypomagnesaemia, hypokalaemia, hypoalbuminaemia, hypocalcaemia
Common	dehydration, hypophosphataemia, hyponatraemia, hyperkalaemia, hyperbilirubinemia, hyperglycaemia, hypoglycaemia
Nervous system disorders	
Very common	dysgeusia, headache, dizziness
Common	peripheral neuropathy[a]
Uncommon	convulsion, cerebrovascular accident, posterior reversible encephalopathy syndrome
Ear and labyrinth disorders	
Common	tinnitus
Cardiac disorders	
Uncommon	acute myocardial infarction
Vascular disorders	
Very common	hypertension, haemorrhage[b*]
Common	venous thrombosis[c], hypotension, embolism
Uncommon	hypertensive crisis, arterial thrombosis, embolism arterial
Not known	aneurysms and artery dissections
Respiratory, thoracic, and mediastinal disorders	
Very common	dysphonia, dyspnoea, cough
Common	pulmonary embolism, rhinitis allergic
Uncommon	pneumothorax
Gastrointestinal disorders	
Very common	diarrhoea[*], nausea, vomiting, stomatitis, constipation, abdominal pain, dyspepsia
Common	gastrointestinal perforation[*g], pancreatitis, fistula[*], gastroesophageal reflux disease, haemorrhoids, oral pain, dry mouth, dysphagia, flatulence
Uncommon	glossodynia
Hepatobiliary disorders	
Common	hepatic encephalopathy[*]
Uncommon	hepatitis cholestatic
Skin and subcutaneous tissue disorders	
Very common	palmar-plantar erythrodysaesthesia syndrome, rash[f]
Common	pruritus, alopecia, dry skin, hair colour change, hyperkeratosis, erythema
Not known	cutaneous vasculitis
Musculoskeletal and connective tissue disorders	
Very common	pain in extremity, arthralgia
Common	muscle spasms
Uncommon	osteonecrosis of the jaw
Renal and urinary disorders	
Common	proteinuria
General disorders and administration site conditions	
Very common	fatigue, mucosal inflammation, asthenia, peripheral oedema
Investigations[d]	
Very Common	weight decreased, serum ALT increased, AST increased, blood alkaline phosphatase increased
Common	GGT increased, blood creatinine increased, amylase increased, lipase increased, blood cholesterol increased, blood triglycerides increased, white blood cell count decreased

Injury, poisoning and procedural complications	
Uncommon	wound complications[e]

[*]See section 4.8 Description of selected adverse reactions for further characterisation.
[a] including polyneuropathy; peripheral neuropathy is mainly sensory
[b] Including epistaxis as the most commonly reported adverse reaction
[c]All venous thrombosis including deep vein thrombosis
[d] Based on reported adverse reactions
[e] Impaired healing, incision site complication and wound dehiscence
[f] Rash is a composite term which includes dermatitis, dermatitis acneiform, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic and drug eruption.
[g] Fatal cases have been reported

Cabozantinib in combination with nivolumab in first-line advanced RCC

Summary of safety profile

When cabozantinib is administered in combination with nivolumab, refer to the SmPC for nivolumab prior to initiation of treatment. For additional information on the safety profile of nivolumab monotherapy, please refer to the nivolumab SmPC.

In a dataset of cabozantinib 40 mg once daily in combination with nivolumab 240 mg every two weeks in RCC (n =320), with a minimum follow-up of 16 months, the most common serious adverse drug reactions (≥1% incidence) are diarrhoea, pneumonitis, pulmonary embolism, pneumonia, hyponatraemia, pyrexia, adrenal insufficiency, vomiting, dehydration.

The most frequent adverse reactions (≥25%) were diarrhoea, fatigue, palmar-plantar erythrodysaesthesia syndrome, stomatitis, musculoskeletal pain, hypertension, rash, hypothyroidism, decrease appetite, nausea, abdominal pain. The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Tabulated list of adverse reactions

Adverse reactions identified in the clinical study of cabozantinib in combination with nivolumab are listed in Table 3, 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 (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Adverse reactions with cabozantinib in combination with nivolumab

Infections and infestations	
Very Common	upper respiratory tract infection
Common	pneumonia
Blood and lymphatic system disorders	
Common	eosinophilia
Immune system disorders	
Common	hypersensitivity (including anaphylactic reaction)
Uncommon	infusion related hypersensitivity reaction
Endocrine disorders	
Very common	hypothyroidism, hyperthyroidism
Common	adrenal insufficiency
Uncommon	hypophysitis, thyroiditis
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	dehydration
Nervous system disorders	

Very common	dysgeusia, dizziness, headache
Common	peripheral neuropathy
Uncommon	encephalitis autoimmune, Guillain-Barré syndrome, myasthenic syndrome
Ear and labyrinth disorders	
Common	tinnitus
Eye disorders	
Common	dry eye, blurred vision
Uncommon	uveitis
Cardiac disorders	
Common	atrial fibrillation, tachycardia
Uncommon	myocarditis
Vascular disorders	
Very common	hypertension
Common	thrombosis[a]
Uncommon	embolism arterial
Respiratory, thoracic and mediastinal disorders	
Very common	dysphonia, dyspnoea, cough
Common	pneumonitis, pulmonary embolism, epistaxis, pleural effusion
Uncommon	pneumothorax
Gastrointestinal disorders	
Very common	diarrhoea, vomiting, nausea, constipation, stomatitis, abdominal pain, dyspepsia
Common	colitis, gastritis, oral pain, dry mouth, haemorrhoids
Uncommon	pancreatitis, small intestine perforation[b], glossodynia
Hepatobiliary disorders	
Common	hepatitis
Not known	vanishing bile duct syndrome[c]
Skin and subcutaneous tissue disorders	
Very common	palmar-plantar erythrodysaesthesia syndrome, rash[d], pruritus
Common	alopecia, dry skin, erythema, hair colour change
Uncommon	psoriasis, urticaria
Not known	cutaneous vasculitis
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain[e], arthralgia, muscle spasm,
Common	arthritis
Uncommon	myopathy, osteonecrosis of the jaw, fistula
Renal and urinary disorders	
Very common	proteinuria
Common	renal failure, acute kidney injury
Uncommon	nephritis
General disorders and administration site conditions	
Very common	fatigue, pyrexia, oedema
Common	pain, chest pain
Investigations[f]	

Very common	increased ALT, increased AST, hypophosphataemia, hypocalcaemia, hypomagnesaemia, hyponatraemia, hyperglycaemia, lymphopenia, increased alkaline phosphatase, increased lipase, increased amylase, thrombocytopenia, increased creatinine, anaemia, leucopenia, hyperkalaemia, neutropenia, hypercalcaemia, hypoglycaemia, hypokalaemia, increased total bilirubin, hypermagnesaemia, hypernatraemia, weight decreased
Common	blood cholesterol increased, hypertriglyceridaemia

Adverse reaction frequencies presented in Table 3 may not be fully attributable to cabozantinib alone but may contain contributions from the underlying disease or from nivolumab used in a combination.

[a] Thrombosis is a composite term which includes portal vein thrombosis, pulmonary vein thrombosis, pulmonary thrombosis, aortic thrombosis, arterial thrombosis, deep vein thrombosis, pelvic vein thrombosis, vena cava thrombosis, venous thrombosis, venous thrombosis limb

[b] Fatal cases have been reported

[c] With prior or concomitant immune checkpoint inhibitor exposure

[d] Rash is a composite term which includes dermatitis, dermatitis acneiform, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic and drug eruption

[e] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain

[f] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements with the exception of weight decreased, blood cholesterol increased and hypertriglyceridaemia

Description of selected adverse reactions

Data for the following reactions are based on patients who received CABOMETYX 60 mg orally once daily as monotherapy in the pivotal studies in RCC following prior VEGF-targeted therapy and in treatment-naïve RCC, in HCC following prior systemic therapy, in DTC in patient refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy, in progressive NET following prior systemic therapy or in patients who received CABOMETYX 40 mg orally once daily in combination with nivolumab in first-line advanced RCC (section 5.1).

Gastrointestinal (GI) perforation (see section 4.4)

In the RCC study (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.
In the HCC study (CELESTIAL), GI perforations were reported in 0.9% of cabozantinib-treated patients (4/467). All events were Grade 3 or 4. Median time to onset was 5.9 weeks.
In the DTC study (COSMIC-311), GI perforation grade 4 was reported in one patient (0.6%) of cabozantinib-treated patients and occurred after 14 weeks of treatment.
In the NET study (CABINET), GI perforations were reported in 1.3% of cabozantinib-treated patients (3/227). Events were Grade 3, 4 and 5. Median time to onset was 21.6 weeks.
In combination with nivolumab in advanced RCC in first-line treatment (CA2099ER) the incidence of GI perforations was 1.3% (4/320) treated patients. One event was grade 3, two events were grade 4 and one event was grade 5 (fatal).
Fatal perforations have occurred in the cabozantinib clinical program.

Hepatic encephalopathy (see section 4.4)

In the HCC study (CELESTIAL), hepatic encephalopathy (hepatic encephalopathy, encephalopathy, hyperammonaemic encephalopathy) was reported in 5.6% of cabozantinib-treated patients (26/467); Grade 3-4 events in 2.8%, and one (0.2%) Grade 5 event. Median time to onset was 5.9 weeks.
In the NET study (CABINET), hepatic encephalopathy was reported in 0.9% of cabozantinib-treated patients (2/227); There was one Grade 3 event (0.4%) for which median time to onset was 14.3 weeks.

No cases of hepatic encephalopathy were reported in the RCC studies (METEOR, CABOSUN and CA2099ER) and in the DTC study (COSMIC-311).

Diarrhoea (see section 4.4)
In the RCC study (METEOR), diarrhoea was reported in 74% of cabozantinib-treated RCC patients (245/331); Grade 3-4 events in 11%. Median time to onset was 4.9 weeks.
In the treatment-naïve RCC study (CABOSUN), diarrhoea was reported in 73% of cabozantinib-treated patients (57/78); Grade 3-4 events in 10%.
In the HCC study (CELESTIAL), diarrhoea was reported in 54% of cabozantinib-treated patients (251/467); Grade 3-4 events in 9.9%. Median time to onset of all events was 4.1 weeks. Diarrhoea led to dose modifications, interruptions and discontinuations in 84/467 (18%), 69/467 (15%) and 5/467 (1%) of subjects, respectively.
In the DTC study (COSMIC-311), diarrhoea was reported in 62% of cabozantinib treated patients (105/170); Grade 3-4 events in 7.6%. Diarrhoea led to dose reduction and interruption in 24/170 (14%) and 36/170 (21%) of subjects respectively.
In the NET study (CABINET), diarrhoea was reported in 63% of cabozantinib treated patients (144/227); Grade 3 events in 8.4%, no Grade 4 events. Median time to onset of Grade 3 events was 5.1 weeks.
In combination with nivolumab in advanced RCC in first-line treatment (CA2099ER), the incidence of diarrhoea was reported in 64.7% (207/320) of treated patients; Grade 3-4 events in 8.4% (27/320). Median time to onset of all events was 12.9 weeks. Dose delay or reduction occurred in 26.3% (84/320) and discontinuation in 2.2% (7/320) of patients with diarrhoea, respectively.

Fistulas (see section 4.4)
In the RCC study (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 were Grade 2. Median time to onset was 30.3 weeks.
In the treatment-naïve RCC study (CABOSUN), no cases of fistulas were reported.
In the HCC study (CELESTIAL), fistulas were reported in 1.5% (7/467) of the HCC patients. Median time to onset was 14 weeks.
In the DTC study (COSMIC-311), fistulas (two anal and one pharyngeal fistula) were reported in 1.8 % (3/170) of the cabozantinib treated patients.
In the NET study (CABINET), fistulas (two anal and one biliary fistula) were reported in 1.3 % (3/227) of the cabozantinib treated patients. Anal fistula events were Grade 1 and 3, biliary fistula was Grade 2. Median time to onset was 19.3 weeks.

In combination with nivolumab in advanced RCC in first-line treatment (CA2099ER) the incidence of fistula was reported in 0.9% (3/320) of treated patients and the severity was Grade 1.
Fatal fistulas have occurred in the cabozantinib clinical program.

Haemorrhage (see section 4.4)
In the RCC study (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.
In the HCC study (CELESTIAL), the incidence of severe haemorrhagic events (Grade ≥ 3) was 7.3% in cabozantinib-treated patients (34/467). Median time to onset was 9.1 weeks.
In the DTC study (COSMIC-311), the incidence of severe haemorrhagic events (grade ≥ 3) was 2.4% in cabozantinib-treated patients (4/170). Median time to onset was 11.5 weeks.
In the NET study (CABINET), the incidence of severe haemorrhagic events (grade ≥ 3) was 1.8% in cabozantinib-treated patients (4/227). Median time to onset was 14.1 weeks.
In combination with nivolumab in advanced RCC in first-line treatment (CA2099ER) the incidence of ≥ Grade 3 haemorrhage was in 1.9% (6/320) of treated patients.
Fatal haemorrhages have occurred in the cabozantinib clinical program.

Posterior reversible encephalopathy syndrome (PRES) (see section 4.4)
No case of PRES was reported in the METEOR, CABOSUN, CA2099ER or CELESTIAL studies, but PRES has been reported in one patient in the DTC study (COSMIC-311) and in one patient in the NET study (CABINET). PRES has been rarely reported in other clinical trials (in 2/4872 subjects; 0.04%).

Elevated liver enzymes when cabozantinib is combined with nivolumab in RCC
In a clinical study of previously untreated patients with RCC receiving cabozantinib in combination with nivolumab, a higher incidence of Grades 3 and 4 ALT increased (10.1%) and AST increased (8.2%) were observed relative to cabozantinib monotherapy in patients with advanced RCC (ALT increased of 3.6% and AST increased of 3.3% in METEOR study). The median time to onset of grade ≥ 2 increased ALT or AST was 10.1 weeks (range: 2 to 106.6 weeks; n=85). In patients with grade ≥ 2 increased ALT or AST, the elevations resolved to Grades 0-1in 91% with median time to resolution of 2.3 weeks (range: 0.4 to 108.1 weeks).
Among the 45 patients with Grade ≥2 increased ALT or AST who were rechallenged with either cabozantinib (n=10) or nivolumab (n=10) administered as a single agent or with both (n=25), recurrence of Grade ≥2 increased ALT or AST was observed in 4 patients receiving cabozantinib, in 3 patients receiving nivolumab and 8 patients receiving both cabozantinib and nivolumab.

Hypothyroidism
In the RCC study (METEOR), the incidence of hypothyroidism was 21% (68/331).
In the treatment-naïve RCC study (CABOSUN), the incidence of hypothyroidism was 23% (18/78) in cabozantinib-treated RCC patients.
In the HCC study (CELESTIAL), the incidence of hypothyroidism was 8.1% (38/467) in cabozantinib-treated patients and Grade 3 events in 0.4% (2/467).
In the DTC study (COSMIC-311), the incidence of hypothyroidism was 2.4% (4/170), all grade 1-2, none requiring modification of treatment.
In the NET study (CABINET), the incidence of hypothyroidism was 26% (59/227) in cabozantinib-treated patients, all grade 1-2.
In combination with nivolumab in advanced RCC in first-line treatment (CA2099ER) the incidence of hypothyroidism was 35.6% (114/320) of treated patients.

Paediatric population (see section 5.1)

In study ADVL1211, a limited dose-escalation study of cabozantinib in paediatric and adolescent patients with recurrent or refractory solid tumours including CNS tumours, the following events: aspartate aminotransferase (AST) increased (very common, 76.9%), alanine aminotransferase (ALT) increased (very common, 71.8%), lymphocyte count decreased (very common, 48.7%), neutrophil count decreased (very common, 35.9%), and lipase increased (very common, 33.3%) were observed at a higher frequency in all subjects across all dose groups included in the safety population (N=39), compared to adults. The increased rates for these Preferred Terms (PTs) concern any grade as well as grade 3/4 of these ADRs. The adverse events reported are in line qualitatively with the recognised safety profile for cabozantinib in adult populations. However, the small numbers of subjects preclude a conclusive assessment of trends and frequencies and further comparison with the recognised safety profile of cabozantinib.

In study ADVL1622 of cabozantinib in children and young adults with the following solid tumour strata: Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcomas (NRSTS), osteosarcoma, Wilms tumour and other rare solid tumours (nonstatistical cohort), the safety profile of cabozantinib treated children and young adults in all strata was comparable with that observed in adults treated with cabozantinib.

Physeal widening has been observed in children with open growth plates when treated 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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: L01EX07.

Mechanism of action
Cabozantinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodelling, 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 once daily) was observed in a controlled clinical trial 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, HCC or NET studies (at a dose of 60 mg).

Clinical efficacy and safety

Renal cell carcinoma
Randomized study in RCC patients who have received prior vascular endothelial growth factor (VEGF)-targeted therapy (METEOR)
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, multicentre 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 randomised (1:1) to receive cabozantinib (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 randomised. Secondary efficacy endpoints were objective response rate (ORR) and overall survival (OS). Tumour 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 cabozantinib 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 favourable (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 cabozantinib and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

A statistically significant improvement in PFS was demonstrated for cabozantinib compared to everolimus (Figure 1 and Table 4). 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 randomised to cabozantinib 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 cabozantinib 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 5.

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) (METEOR)

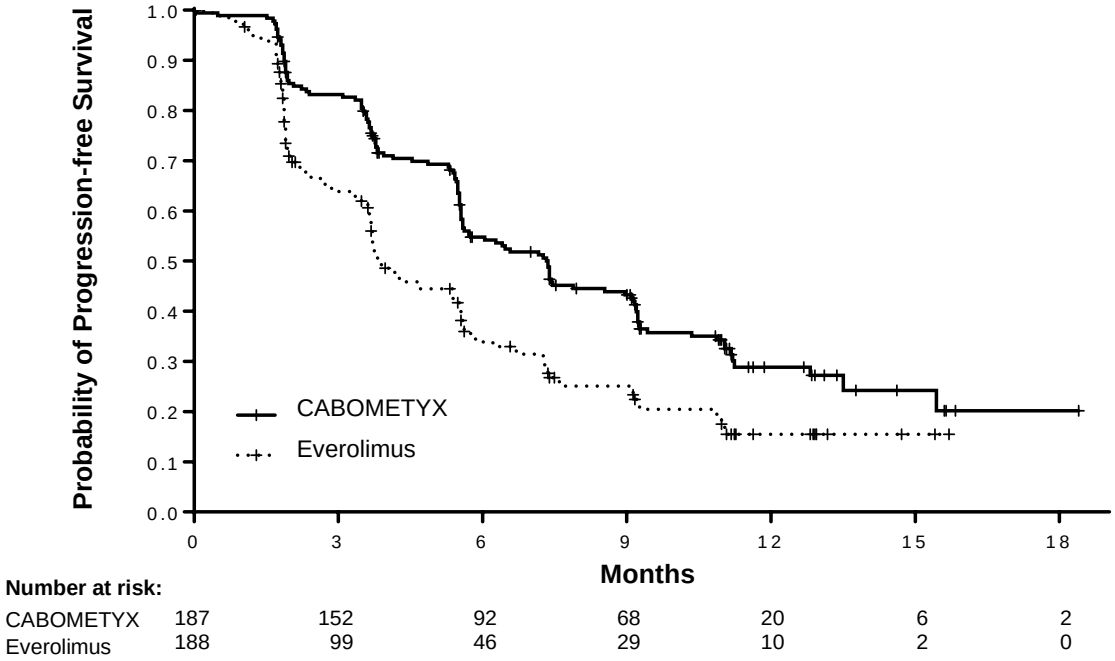


Table 4: Summary of PFS findings by independent radiology review committee in RCC subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy **(METEOR)**

	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 (METEOR)

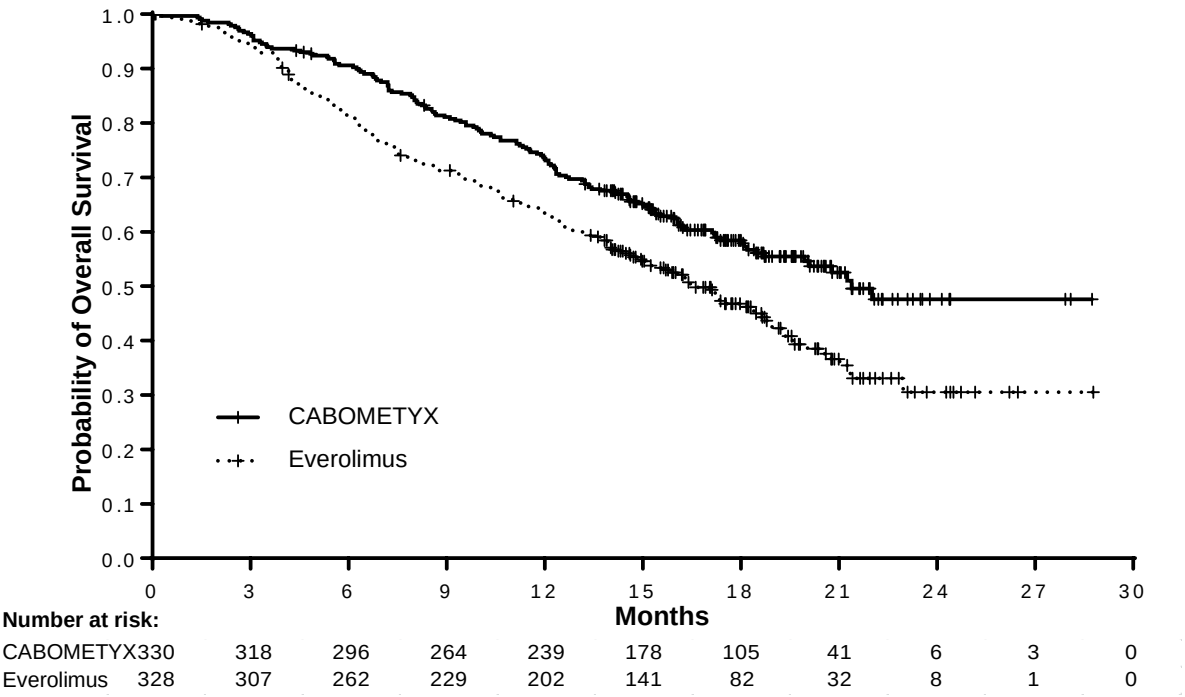


Table 5: Summary of ORR findings per independent radiology committee review (IRC) and investigator review, in RCC subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy

	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

Randomized study in treatment-naïve renal cell carcinoma patients (CABOSUN)

The safety and efficacy of CABOMETYX for the treatment of treatment-naïve renal cell carcinoma were evaluated in a randomised, open-label, multicentre study (CABOSUN). Patients (N=157) with previously untreated, locally advanced or metastatic RCC with a clear cell component were randomised (1:1) to receive cabozantinib (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). Tumour assessments were conducted every 12 weeks.

The baseline demographic and disease characteristics were similar between the cabozantinib 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.

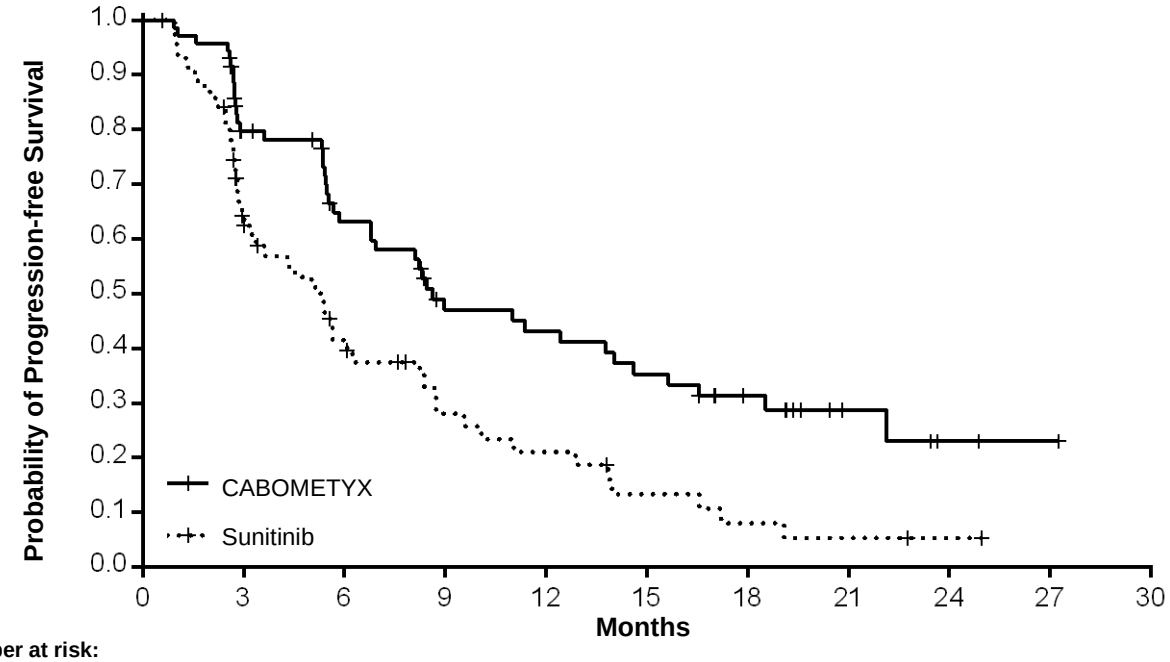
A statistically significant improvement in PFS as retrospectively assessed by a blinded Independent Radiology Committee (IRC) was demonstrated for cabozantinib compared to sunitinib (Figure 3 and Table 6). The results from the investigator determined analysis and IRC-determined analysis of PFS were consistent.

Patients with both positive and negative MET status showed a favourable effect with cabozantinib 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.

Cabozantinib treatment was associated with a trend for longer survival compared to sunitinib (Table 6). The study was not powered for the OS analysis and the data are immature.

Objective response rate (ORR) findings are summarized in Table 6.

Figure 3: Kaplan Meier curve for progression-free survival by IRC in treatment-naïve 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 6: 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 favour of cabozantinib

Randomised phase 3 study of cabozantinib in combination with nivolumab vs. sunitinib (CA2099ER)
The safety and efficacy of cabozantinib 40 mg orally daily in combination with nivolumab 240 mg intravenously every 2 weeks for the first-line treatment of advanced/metastatic RCC was evaluated in a phase 3, randomised, open label study (CA2099ER). The study included patients (18 years or older) with advanced or metastatic RCC with a clear cell component, Karnofsky Performance Status (KPS) ≥ 70%, and measurable disease as per RECIST v1.1 were included regardless of their PD-L1 status or IMDC risk group. The study excluded patients with autoimmune disease or other medical conditions requiring systemic immunosuppression, patients who had prior treatment with an anti-PD-1, anti PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, poorly controlled hypertension despite antihypertensive therapy, active brain metastases and uncontrolled adrenal insufficiency. Patients were stratified by IMDC prognostic score, PD-L1 tumour expression, and region.

A total of 651 patients were randomised to receive either cabozantinib 40 mg once daily orally in combination with nivolumab 240 mg (n=323) administered intravenously every 2 weeks or sunitinib (n = 328) 50 mg daily, administered orally for 4 weeks followed by 2 weeks off. Treatment continued until disease progression or unacceptable toxicity with nivolumab administration up to 24 months. Treatment beyond initial Investigator-assessed RECIST version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug, as determined by investigator. First tumour assessment post-baseline was performed at 12 weeks (± 7 days) following randomisation. Subsequent tumour assessments occurred at every 6 weeks (± 7 days) until Week 60, then every 12 weeks (± 14 days) until radiographic progression, confirmed by the Blinded

Independent Central review (BICR). The primary efficacy outcome measure was PFS as determined by a BICR. Additional efficacy measures included OS and ORR as key secondary endpoints.

Baseline characteristics were generally balanced between the two groups. The median age was 61 years (range: 28-90) with 38.4% ≥ 65 years of age and 9.5% ≥ 75 years of age. The majority of patients were male (73.9%) and white (81.9%). Eight percent of patients were Asian, 23.2% and 76.5% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. Patient distribution by IMDC risk categories was 22.6% favourable, 57.6% intermediate, and 19.7% poor. For tumour PD-L1 expression, 72.5% of patients had PD-L1 expression < 1% or indeterminate and 24.9% of patients had PD-L1 expression ≥ 1%. 11.5% of patients had tumours with sarcomatoid features. The median duration of treatment was 14.26 months (range: 0.2-27.3 months) in cabozantinib with nivolumab-treated patients and was 9.23 months (range: 0.8-27.6 months) in sunitinib-treated patients.

The study demonstrated a statistically significant benefit in PFS, OS, and ORR for patients randomised to cabozantinib in combination with nivolumab as compared to sunitinib.
Efficacy results from the primary analysis (minimum follow-up 10.6 months; median follow-up 18.1 months) are shown in Table 7.

Table 7: Efficacy results (CA2099ER)

	cabozantinib + nivolumab (n = 323)	**sunitinib (n = 328)**
PFS per BICR		
Events	144 (44.6%)	191 (58.2%)
Hazard ratio[a]	0.51	
95% CI	(0.41, 0.64)	
p-value[b, c]	< 0.0001	
Median (95% CI)[d]	16.59 (12.45, 24.94)	8.31 (6.97, 9.69)
OS		
Events	67 (20.7%)	99 (30.2%)
Hazard ratio[a]	0.60	
98.89% CI	(0.40, 0.89)	
p-value[b,c,e]	0.0010	
Median (95% CI)	N.E.	N.E. (22.6, N.E.)
Rate (95% CI)		
At 6 months	93.1 (89.7, 95.4)	86.2 (81.9,89.5)
ORR per BICR (CR + PR)	180 (55.7%)	89 (27.1%)
(95% CI)[f]	(50.1, 61.2)	(22.4, 32.3)
Difference in ORR (95% CI)[g]	28.6 (21.7, 35.6)	
p-value[h]	< 0.0001	
Complete response (CR)	26 (8.0%)	15 (4.6%)
Partial response (PR)	154 (47.7%)	74 (22.6%)
Stable disease (SD)	104 (32.2%)	138 (42.1%)
Median duration of response[d]		
Months (range)	20.17 (17.31, N.E.)	11.47 (8.31, 18.43)
Median time to response		
Months (range)	2.83 (1.0-19.4)	4.17 (1.7-12.3)

[a] Stratified Cox proportional hazards model. Hazard ratio is cabozantinib and nivolumab over sunitinib.
[b] 2-sided p-values from stratified regular log-rank test.
[c] Log-rank test stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumour expression (≥1% versus <1% or indeterminate) and region (US/Canada/W Europe/N Europe, ROW) as entered in the IRT.
[d] Based on Kaplan-Meier estimates.
[e] Boundary for statistical significance p-value <0.0111.
[f] CI based on the Clopper and Pearson method.

[g] Strata adjusted difference in objective response rate (cabozantinib + nivolumab - Sunitinib) based on DerSimonian and Laird

[h] 2-sided p-value from CMH test.

NE = non-estimable

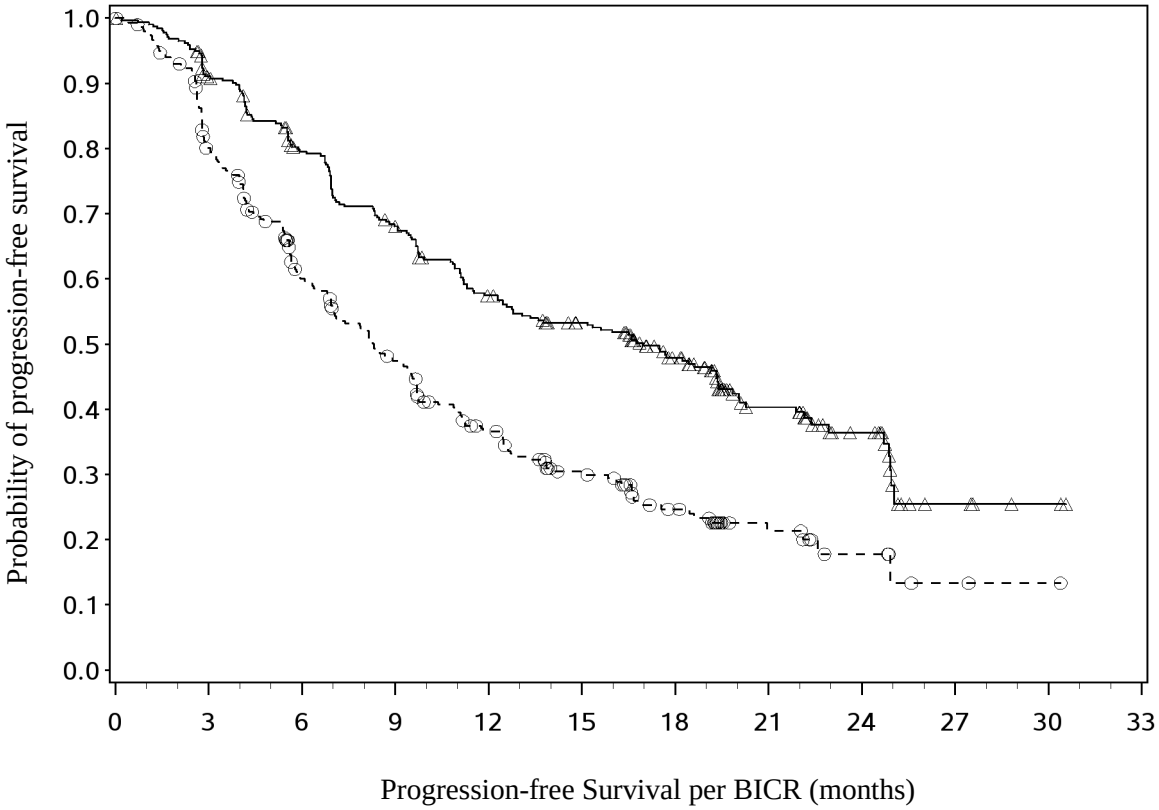
The primary analysis of PFS included censoring for new anti-cancer treatment (Table 7). Results for PFS with and without censoring for new anti-cancer treatment were consistent.

PFS benefit was observed in the cabozantinib in combination with nivolumab arm vs. sunitinib regardless of tumour PD L1 expression. Median PFS for tumour PD L1 expression ≥ 1% was 13.08 for cabozantinib in combination with nivolumab, and was 4.67 months in the sunitinib arm (HR = 0.45; 95% CI: 0.29, 0.68). For tumour PD L1 expression < 1%, the median PFS was 19.84 months for the cabozantinib in combination with nivolumab, and 9.26 months in the sunitinib arm (HR = 0.50; 95% CI: 0.38, 0.65).

PFS benefit was observed in the cabozantinib in combination with nivolumab arm vs. sunitinib regardless of the (IMDC) risk category. Median PFS for the favourable risk group was not reached for cabozantinib in combination with nivolumab, and was 12.81 months in the sunitinib arm (HR = 0.60; 95% CI: 0.37, 0.98). Median PFS for the intermediate risk group was 17.71 months for cabozantinib in combination with nivolumab and was 8.38 months in the sunitinib arm (HR = 0.54; 95% CI: 0.41, 0.73). Median PFS for the poor risk group was 12.29 months for cabozantinib in combination with nivolumab and was 4.21 months in the sunitinib arm (HR = 0.36; 95% CI: 0.23, 0.58).

An updated PFS and OS analysis were performed when all patients had a minimum follow-up of 16 months and a median follow-up of 23.5 months (see figures 4 and 5). The PFS hazard ratio was 0.52 (95% CI: 0.43; 0.64). The OS hazard ratio was 0.66 (95% CI: 0.50; 0.87). Updated efficacy data (PFS and OS) in subgroups for the IMDC risk categories and PD-L1 expression levels confirmed the original results. With the updated analysis, median PFS is reached for the favourable risk group.

Figure 4: Kaplan Meier curves of PFS (CA2099ER)



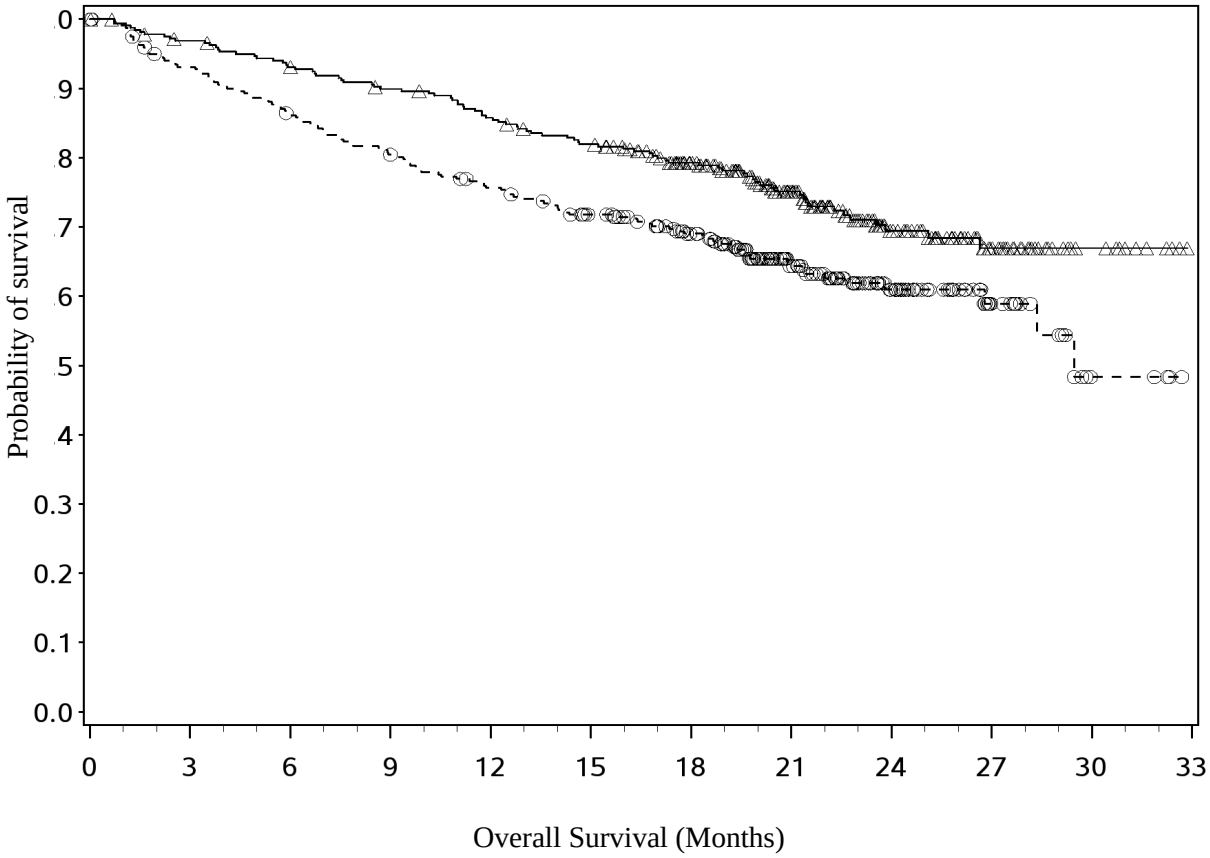
Number of subjects at risk

Cabozantinib + nivolumab											
323	280	236	201	166	145	102	56	26	5	2	0
Sunitinib											
328	230	160	122	87	61	37	17	7	2	1	0

Cabozantinib + nivolumab (events: 175/323), median and 95.0% CI: 16.95 (12.58, 19.38)

Sunitinib (events: 206/328), median and 95.0% CI:8.31 (6.93, 9.69)

Figure 5 : Kaplan Meier curves of OS (CA2099ER)



Number of subjects at risk

Cabozantinib + nivolumab											
323	308	295	283	269	255	220	147	84	40	10	0
Sunitinib											
328	295	272	254	236	217	189	118	62	22	4	0

Cabozantinib + nivolumab (events: 86/323), median and 95% CI: NE

Sunitinib (events: 116/328), median and 95% CI:29.47 (28.35, NE)

Hepatocellular carcinoma

Controlled study in patients who have received sorafenib (CELESTIAL)

The safety and efficacy of CABOMETYX were evaluated in a randomised, double-blind, placebo--controlled phase 3 study (CELESTIAL). Patients (N=707) with HCC not amenable to curative treatment and who had previously received sorafenib for advanced disease were randomized (2:1) to receive cabozantinib (N=470) or placebo (N=237). Patients could have received one other prior systemic therapy for advanced disease in addition to sorafenib. Randomisation was stratified by aetiology 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 efficacy endpoint was overall survival (OS). Secondary efficacy endpoints were progression-free survival (PFS) and objective response rate (ORR), as assessed by the investigator using Response Evaluation Criteria in Solid Tumours (RECIST) 1.1. Tumour assessments were conducted every 8 weeks. Subjects continued blinded study treatment after radiological disease progression whilst they experienced clinical benefit or until the need for subsequent systemic or liver-directed local anticancer therapy. Crossover from placebo to cabozantinib was not allowed during the blinded treatment phase.

The baseline demographic and disease characteristics were similar between the cabozantinib and placebo arms and are shown below for all 707 randomised patients.
The majority of patients (82%) were male: the median age was 64 years. The majority of patients (56%) were Caucasian and 34% of patients were Asian. Fifty three percent (53%) of patients had ECOG performance status (PS) 0 and 47% had ECOG PS 1. Almost all patients (99%) were Child Pugh A and 1% were Child Pugh B. Aetiology for HCC included 38% hepatitis B virus (HBV), 21% hepatitis C virus (HCV), 40% other (neither HBV nor HCV). Seventy-eight percent (78%) had macroscopic vascular invasion and/or extra-hepatic tumour spread, 41% had alfa-fetoprotein (AFP) levels ≥400µg/L, 44% had been treated by loco-regional transarterial embolisation or chemoinfusion procedures, 37% had radiotherapy prior to cabozantinib treatment. Median duration of sorafenib treatment was 5.32 months. Seventy-two percent (72%) of patients had received 1 and 28% had received 2 prior systemic therapy regimens for advanced disease.
A statistically significant improvement in OS was demonstrated for cabozantinib compared to placebo (Table 8 and Figure 6).

PFS and ORR findings are summarised in Table 8.

Table 8: 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 aetiology 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 6: Kaplan-Meier curve of overall survival (CELESTIAL)

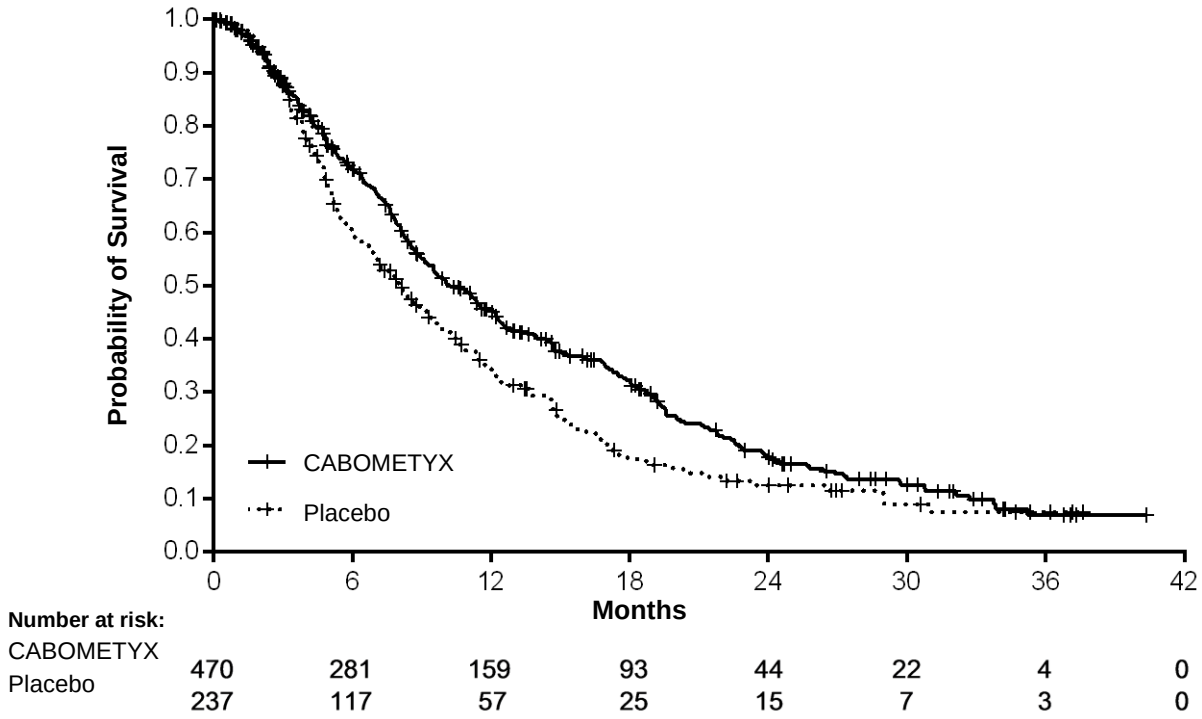
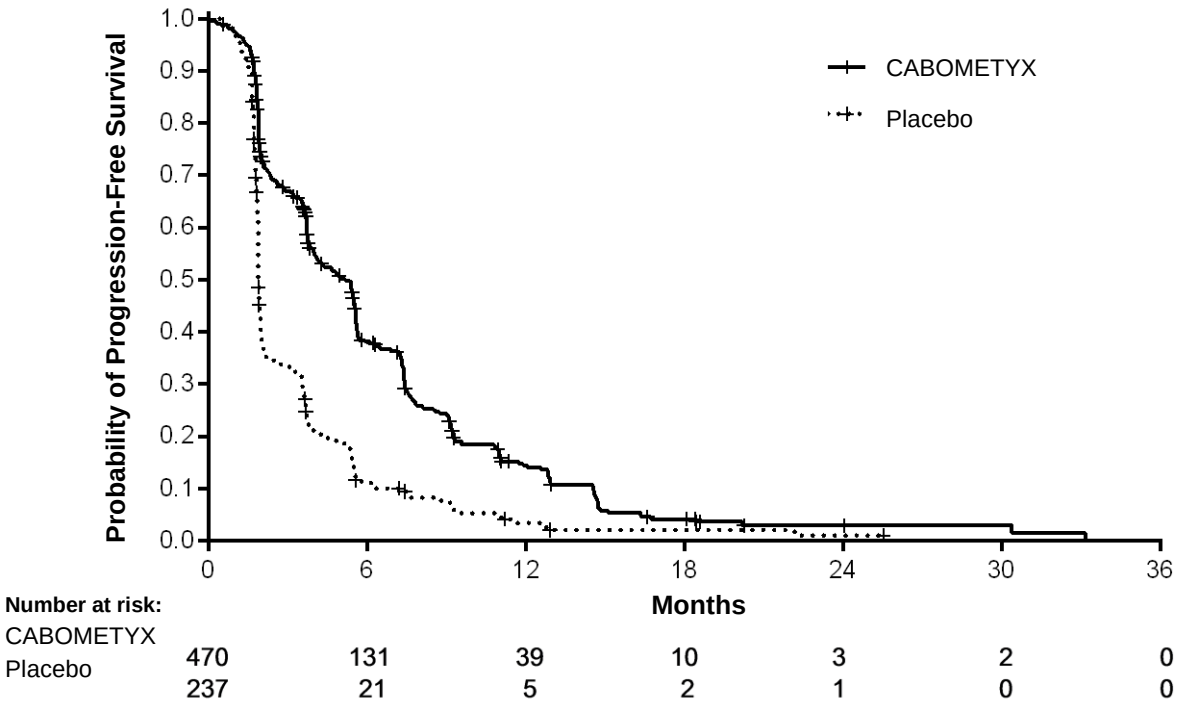


Figure 7: Kaplan Meier curve for progression-free survival (CELESTIAL)



The incidence of systemic non-radiation and local liver-directed systemic non-protocol anticancer therapy (NPACT) was 26% in the cabozantinib arm and 33% in the placebo arm. Subjects receiving these therapies had to discontinue study treatment. An exploratory OS analysis censoring for the use

of NPACT supported the primary analysis: the HR, adjusted for stratification factors (per IxRS), was 0.66 (95% CI: 0.52, 0.84; stratified logrank p-value = 0.0005). The Kaplan- Meier estimates for median duration of OS were 11.1 months in the cabozantinib arm versus 6.9 months in the placebo arm, an estimated 4.2-month difference in the medians.

Non-disease specific quality of life (QoL) was assessed using the EuroQoL EQ-5D-5L. A negative effect of cabozantinib versus placebo on the EQ-5D utility index score was observed during the first weeks of treatment. Only limited QoL data are available after this period.

Differentiated thyroid carcinoma (DTC)
Placebo -Controlled study in adult patients who have received prior systemic therapy and are refractory or not eligible to radioactive iodine (COSMIC-311)
The safety and efficacy of CABOMETYX were evaluated in COSMIC-311, a randomised (2:1), double-blind, placebo-controlled, multicentre trial in adult patients with locally advanced or metastatic disease with differentiated thyroid cancer that had progressed following up to two prior VEGFR-targeting therapy (including, but not limited to, lenvatinib or sorafenib) and were radioactive iodine-refractory or not eligible. Patients with measurable disease and documented radiographic progression per RECIST 1.1 per the Investigator, during or following treatment with VEGFR-targeting TKI, were randomised (N=258) to receive cabozantinib 60 mg orally once daily (N=170) or placebo (N=88).

Randomisation was stratified by prior receipt of lenvatinib (yes vs. no) and age (≤ 65 years vs. > 65 years). Eligible patients randomised to placebo were allowed to cross-over to cabozantinib upon confirmation of progressive disease by blinded independent radiology review committee (BIRC). Subjects continued blinded study treatment as long as they experienced clinical benefit or until there was unacceptable toxicity. The primary efficacy outcome measures were progression-free survival (PFS) in the ITT population, and objective response rate (ORR) in the first 100 randomised patients, as assessed by BIRC per RECIST 1.1. Tumour assessments were conducted every 8 weeks after randomisation during the first 12 months on study, then every 12 weeks thereafter. Overall survival (OS) was an additional endpoint.

The primary analysis of PFS included 187 randomised patients, 125 to cabozantinib and 62 to placebo. Baseline demographics and disease characteristics were generally balanced for both treatment groups. The median age was 66 years (range 32 to 85 years), 51% being ≥ 65 years of age, 13% being ≥ 75 years of age. The majority of patients were white (70%), 18% of patients were Asian and 55% were female. Histologically, 55% had a confirmed diagnosis of papillary thyroid carcinoma, 48% had follicular thyroid carcinoma including 17% patients with Hürthle cell thyroid cancer. Metastases were present in 95% of the patients: lungs in 68%, lymph nodes in 67%, bone in 29%, pleura in 18% and liver in 15%. Five patients had not received prior RAI due to ineligibility, 63% had received prior lenvatinib, 60% had received prior sorafenib and 23% had received both sorafenib and lenvatinib. Baseline ECOG performance status was 0 (48%) or 1 (52%).
The median duration of treatment was 4.4 months in the cabozantinib arm and 2.3 months in the placebo arm.

The results of the primary analysis (with a cut-off date of 19 August 2020 and median follow up 6.2 months for the PFS), and the updated analysis (with a cut-off date of 08 February 2021 and median follow-up 10.1 months for the PFS) are presented in Table 9. The trial did not demonstrate a statistically significant improvement in ORR for patients randomised to cabozantinib (n=67) compared with placebo (n=33): 15% vs. 0%. The trial demonstrated a statistically significant improvement in PFS (median follow up 6.2 months) for patients randomised to cabozantinib (n=125) compared with placebo (n=62).
An updated analysis of PFS and OS (median follow up 10.1 months) was performed including 258 randomised patients, 170 to cabozantinib and 88 to placebo.
The overall survival analysis was confounded as placebo-treated subjects with confirmed disease progression had the option to cross over to cabozantinib.

Table 9: Efficacy Results from COSMIC-311

	Primary Analysis[1] (ITT)		Updated Analysis[2] (Full ITT)	
	CABOMETYX (n=125)	**Placebo (n=62)**	**CABOMETYX (n=170)**	**Placebo (n=88)**
Progression-Free Survival*				
Number of Events, (%)	31 (25)	43 (69)	62 (36)	69 (78)
Progressive Disease	25 (20)	41 (66)	50 (29)	65 (74)
Death	6 (4.8)	2 (3.2)	12 (7.1)	4 (4.5)
Median PFS in Months (96% CI)	NE (5.7, NE)	1.9 (1.8, 3.6)	11.0 (7.4, 13.8)	1.9 (1.9, 3.7)
Hazard Ratio (96% CI)[3]	0.22 (0.13, 0.36)		0.22 (0.15, 0.32)	
p-value[4]	< 0.0001			
Overall Survival				
Events, n (%)	17 (14)	14 (23)	37 (22)	21 (24)
Hazard Ratio[3] (95% CI)	0.54 (0.27, 1.11)		0.76 (0.45, 1.31)	
	Primary Analysis[1]			
Objective response rate (ORR)[5]				
	CABOMETYX (n=67)		**Placebo (n=33)**	
Overall response, (%)	10 (15)		0 (0)	
Complete response	0		0	
Partial response	10 (15)		0	
Stable disease	46 (69)		14 (42)	
Progressive disease	4 (6)		18 (55)	

* The primary analysis of PFS included censoring for new anti-cancer treatment. Results for PFS with and without censoring for new anti-cancer treatment were consistent.

CI, confidence interval; NE, not evaluable

[1] The cut-off date of the primary analysis is 19 August 2020.

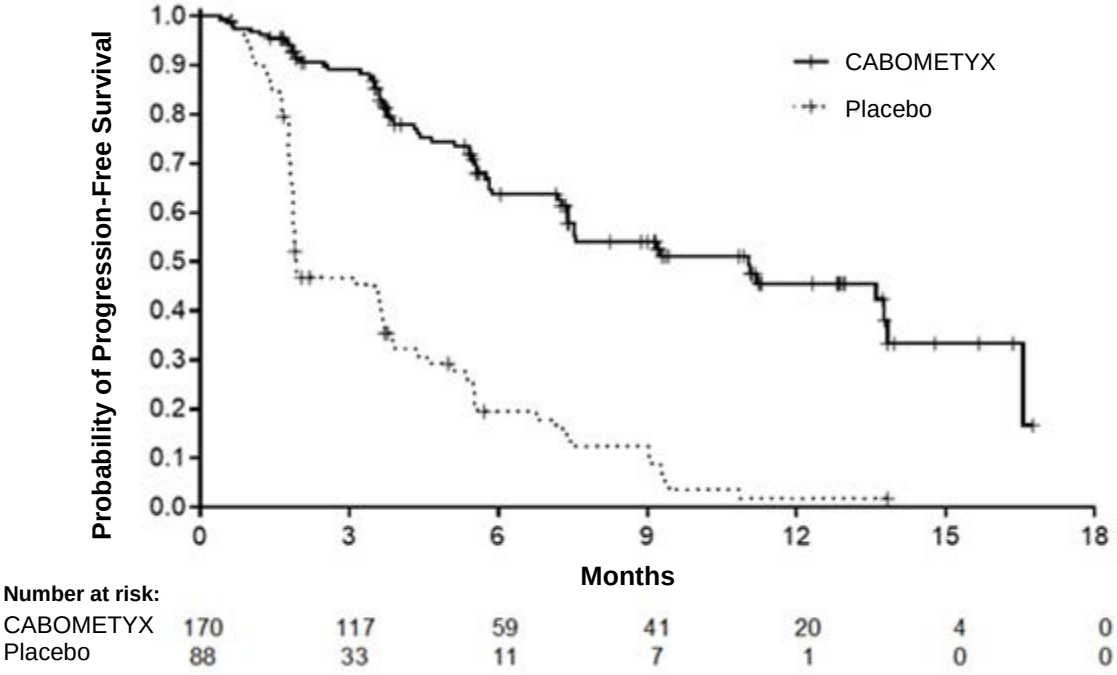
[2] The cut-off date of the secondary analysis is 08 February 2021.

[3] Estimated using the Cox proportional-hazard model.

[4] Log-rank test stratified by receipt of prior lenvatinib (yes vs. no) and age (≤ 65 years vs. > 65 years) as stratification factors (per IXRS data).

[5] Based on the first 100 patients included in the study with a median follow-up of 8.9 months, n=67 in CABOMETYX group and n=33 in placebo group. The improvement in ORR was not statistically significant.

Figure 8: Kaplan-Meier Curve of Progression-Free Survival in COSMIC-311 (updated analysis [cut-off date: 08 February 2021], N=258)



Neuroendocrine Tumours (NETs)

Placebo -controlled study in adult patients with locally advanced or metastatic epNET and pNET that have progressed after prior therapy (CABINET)

The safety and efficacy of CABOMETYX were evaluated in CABINET, a multicentre, randomised (2:1), double-blinded placebo-controlled phase 3 study in adult patients with locally advanced or metastatic well-differentiated pNET (cabozantinib: N = 64; placebo: N= 31) and epNET (cabozantinib: N = 134; placebo: N= 69) that have progressed after prior approved treatment.

Patients with epNET and pNET were allocated into two separate cohorts which were randomised and analysed independently.

Patients continued blinded study treatment until disease progression, unacceptable toxicity or withdrawal of consent. Eligible patients randomised to placebo were allowed to cross-over to open-label cabozantinib upon confirmation of progressive disease by real-time central review. The primary efficacy outcome measure was progression-free survival (PFS) in the ITT population as assessed by a blinded independent review committee (BIRC) using Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 with stratification factors at randomisation as follow:

- epNET: Concurrent somatostatin analogues (SSA) and primary tumour site (midgut GI/ unknown vs. non midgut GI/Lung/other)
- pNET: Concurrent SSA and prior sunitinib

Tumour assessments were conducted every 12 weeks following the start of study treatment until disease progression. Overall survival (OS) was a secondary endpoint.

epNET cohort:

The majority of patients 51.7%, were female. Median age was 66 years. The majority of patients, 83.7%, were White. Additionally, 39.9% of patients had an ECOG performance status of 0, while 59.1% had a performance status of 1. Site of origin of primary tumours was most commonly the small bowel with 32.5%, followed by the lungs with 19.2%, other sites with 17.2%, and unknown sites with

11.8%. Most patients had a non-functioning tumour, accounting for 53.7% of cases, while 32.5% had a functioning tumour. For 13.8% of patients, the functional status was unknown. The most common tumour grade was grade 2, observed in 66% of patients, and grade 1 in 25.6% of patients. The majority of patients, 69%, used SSA concomitantly, and 92.6% had prior SSA use. 45.3% of patients had only one prior treatment other than SSA. Most tumours were well-differentiated, representing 93.6% of cases, while 6.4% were not specified. The most common metastatic sites were the liver, affected in 89.7% of cases, lymph nodes in 70% of cases, bones in 49.3% of cases, other sites in 35% of cases, and lungs in 21.2% of cases.

Table 10: Efficacy Results in epNET Cohorts from CABINET Study

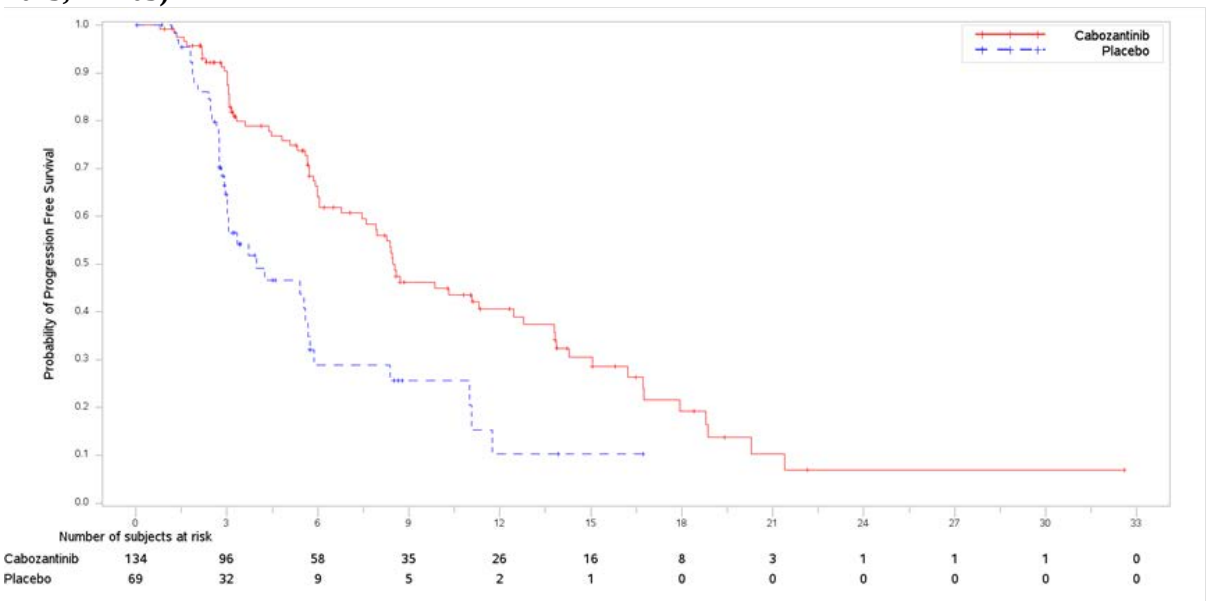
Endpoint	Cabozantinib (N=134)	Placebo (N=69)
Progression-Free Survival		
Number of events, n (%)	71 (53)	40 (58)
Documented progression, n (%)	53 (40)	35 (51)
Death, n (%)	18 (13)	5 (7.2)
Median PFS in Months[1] (95% CI)	8.5 (7.5, 12.5)	4.0 (3.0, 5.7)
Hazard Ratio[2] (95% CI)	0.38 (0.25, 0.58)	

Median follow up was 23 months for both arms. Per BIRC assessments of progression and response with a cutoff date of 24 August 2023

[1] Based on Kaplan-Meier estimates

[2] Estimated using the Cox proportional hazard model. The CABINET study was stopped for efficacy at the time of an interim analysis that was planned for futility only. Type I error was not formally controlled and p-values are not presented. The presented 95% confidence interval is descriptive and does not imply statistical significance was reached.

Figure 9: epNET: Kaplan-Meier Curves of Progression-Free Survival (cut-off date: 24 August 2023, N=203)



An updated exploratory OS analysis (DCO: Sept 2024) with 126 OS events was performed, showing: median OS was 21.95 months in the cabozantinib arm and 22.47 months in the placebo arm, with a hazard ratio (HR) of 1.04 (95% CI: 0.71, 1.52). By the time of analysis 28 (41%) patients crossed over from placebo to cabozantinib.

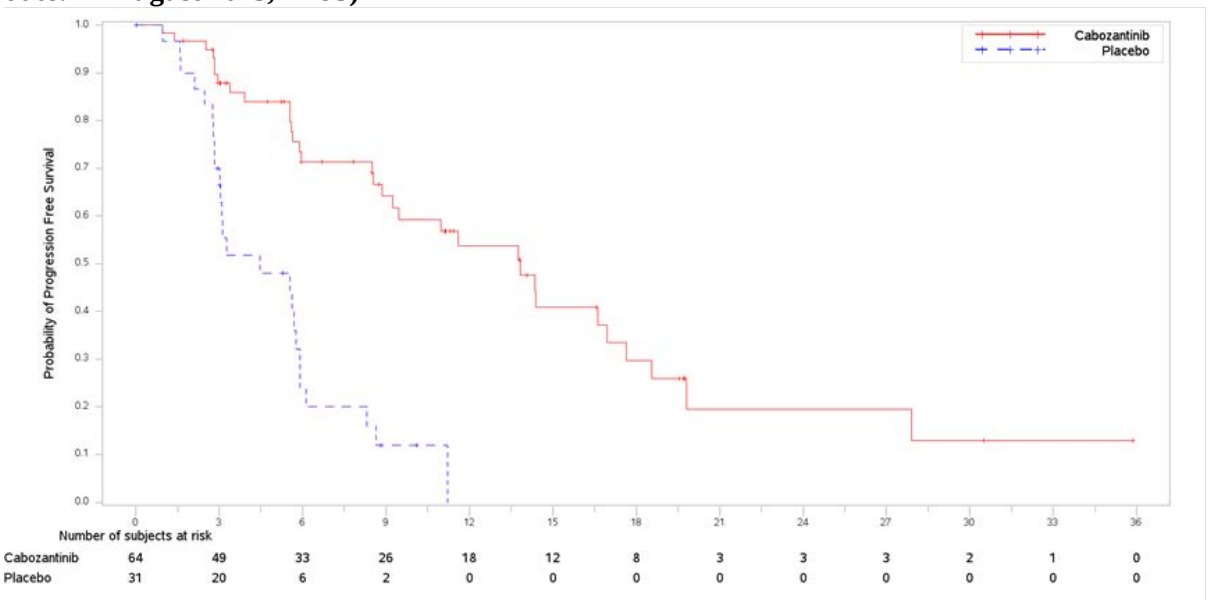
pNET cohort:
The majority of patients, 57.9%, were male. Median age was 59.5 years in cabozantinib arm, and 64 years in placebo arm. The majority of patients, 83.2%, were White. Additionally, 52.6% of patients had an ECOG performance status of 0, while 46.3%% had a performance status of 1.
Most patients had a non-functioning tumour, accounting for 73.7% of cases, while 16.8% had a functioning tumour. For 9.5% of patients, the functional status was unknown. The most common tumour grade was grade 2, observed in 61.1% of patients; grade 1 was observed in 22.1%, grade 3 in 11.6% of patients, and it was unknown in 5.3% of patients. The majority of patients, 54.7%, used SSA concomitantly, and 97.9% had prior SSA use. 28.4% of patients had only one prior treatment other than SSA. Most tumours were well-differentiated, representing 97.9% of cases, while 2.1% were not specified. The most common metastatic sites were the liver, affected in 96.8% of cases, lymph nodes in 48.4% of cases, bone in 27.4% of cases, other sites in 13.7% of cases.

Table 11: Efficacy Results in pNET Cohorts from CABINET Study

	Cabozantinib (N=64)	**Placebo (N=31)**
Progression-Free Survival		
Number of events, n (%)	32 (50)	25 (81)
Documented Progression, n (%)	25 (39)	21 (68)
Death, n (%)	7 (11)	4 (13)
Median PFS in Months[1] (95% CI)	13.8 (8.9, 17.0)	4.5 (3.0, 5.8)
Hazard Ratio[2] (95% CI)	0.23 (0.12, 0.42)	

Median follow up was 23 months (cabozantinib) and 25 months (placebo). Per BIRC assessments of progression and response with a cutoff date of 24 August 2023
[1] Based on Kaplan-Meier estimates
[2] Estimated using the Cox proportional hazard model. The CABINET study was stopped for efficacy at the time of an interim analysis that was planned for futility only. Type I error was not formally controlled and p-values are not presented. The presented 95% confidence interval is descriptive and does not imply statistical significance was reached.

Figure 10: pNET: Kaplan-Meier Curve of Progression-Free Survival in CABINET (cut-off date: 24 August 2023, N=95)



An updated exploratory OS analysis (DCO: Sept 2024) with 46 OS events was performed showing: median Kaplan-Meier estimate of OS was 40.08 months in the cabozantinib arm and 31.11 months in the placebo arm, with an HR of 1.11 (0.59, 2.09). By the time of analysis 14 (45%) patients crossed over from placebo to cabozantinib.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of some studies with CABOMETYX in one or more subsets of the paediatric population in treatment of solid malignant tumours (see section 4.2 for information on paediatric use).

ADVL 1211

A phase 1 study (ADVL1211) of cabozantinib in paediatric patients with solid tumours has been conducted by the Children Oncology Group (COG). Eligible patients were ≥2 years and ≤18 years. This study enrolled patients at 3 dose levels: 30 mg/m2, 40 mg/m2, and 55 mg/m2 once daily on a continuous dosing schedule (weekly dosing by BSA and rounded to the nearest 20 mg). Cabozantinib was dosed based on body surface area (BSA) according to a dosing nomogram

The objective was to define dose limiting toxicities (DLTs), to determine the recommended phase 2 dose (RP2D), to obtain preliminary pharmacokinetics data in children and to explore efficacy in solid tumours. Forty-one patients were enrolled, of whom 36 were fully evaluable. Patients had a variety of solid tumours: MTC (n=5), osteosarcoma (n=2), EWS (n=4), rhabdomyosarcoma (RMS) (n=2), other soft tissue sarcoma (STS) (n=4), Wilms tumour (WT) (n=2), hepatoblastoma (n=2), HCC (n=2), RCC (n=3), central nervous system (CNS) tumours (n=9), and others (n=6).

Of the 36 subjects in the evaluable population, four subjects (11.1%) had best overall response of PR and eight subjects (22.2%) had SD (lasting at least 6 cycles). Of the 12 subjects with PR or SD greater than or equal to 6 cycles 10 subjects were in the cabozantinib 40 mg/m2 or 55 mg/m2 groups (seven and three, respectively).

Based on central review, partial responses were seen in 2/5 patients with MTC, one patient with Wilms tumour, and one patient with clear cell sarcoma.

ADVL1622

ADVL1622 assessed the activity of cabozantinib in selected paediatric solid tumours. This multicentre, open label two-stage phase 2 trial included the following solid tumour strata: non-osteosarcoma strata (including Ewing sarcoma, rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) and Wilms tumour), osteosarcoma stratum and rare solid tumours strata (including medullary thyroid carcinoma (MTC), renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), hepatoblastoma, adrenocortical carcinoma and other solid tumours). Cabozantinib was administered orally once daily on a continuous dosing schedule of 28-day cycles at a dose of 40 mg/m2/day (cumulative weekly dose of 280 mg/m2 using a dosing nomogram). Subjects were ≥2 and ≤30 years of age at the time of study entry for all strata except upper age limit of ≤18 years of age for MTC, RCC and HCC.

For non-osteosarcoma and rare tumours strata the primary endpoint was the objective response rate (ORR). For the osteosarcoma stratum, a two-stage design that incorporated dual endpoints of objective response (CR + PR) based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria and treatment success as defined by SD for ≥4 months was utilised. The PK of cabozantinib in paediatric and adolescent subjects was assessed (please refer to section 5.2)

Efficacy Results Summary

At the data cutoff date (30 June 2021), 108/109 subjects had received at least one dose of cabozantinib. Each statistical cohort in the non-osteosarcoma strata included 13 subjects. No responses were observed

in these statistical cohorts. The osteosarcoma stratum included in total 29 subjects including 17 children (aged 9 to 17 years) and 12 adults (aged 18 to 22 years).

In the osteosarcoma stratum, all subjects had received prior systemic therapy A PR was observed in one adult and one child. The Disease Control Rate (DCR) was 34.5% (95% CI: 17.9, 54.3).

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 compared to the capsule formulation was observed. A less than 10% difference in the AUC was observed between cabozantinib tablet and capsule 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 of the central compartment (Vc/F) was estimated to be 212 L.

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 neutralising antibody to CYP3A4 inhibited formation of metabolite XL184 N-oxide by >80% in a NADPH-catalysed human liver microsomal (HLM) incubation; in contrast, neutralising antibodies to CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation. A neutralising 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 1883 patients and 140 healthy volunteers following oral administration of a range of doses from 20 to 140 mg, the plasma terminal half-life of cabozantinib is approximately 110 hours. Mean clearance (CL/F) at steady-state was estimated to be 2.48 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
In a renal impairment study conducted with a single 60 mg dose of cabozantinib, the ratios of geometric LS mean for total plasma cabozantinib, C_{max} and AUC_{0-inf} were 19% and 30% higher, for subjects with mild renal impairment (90% CI for C_{max} 91.60% to 155.51%; AUC_{0-inf} 98.79% to 171.26%) and 2% and 6-7% higher (90% CI for C_{max} 78.64% to 133.52%; AUC_{0-inf} 79.61% to 140.11%), for subjects with moderate renal impairment compared to subjects with normal renal function. The geometric LS means for unbound plasma cabozantinib AUC_{0-inf} was 0.2% higher for subjects with mild renal impairment (90% CI 55.9% to 180%) and 17% higher (90% CI 65.1% to 209.7%) for subjects with moderate renal impairment compared to subjects with normal renal function. Subjects with severe renal impairment have not been studied.

Hepatic impairment
Based on an integrated population pharmacokinetic analysis of cabozantinib in healthy subjects and cancer patients (including HCC), no clinically significant difference in the mean cabozantinib plasma exposure was observed amongst subjects with normal liver function (n=1425) and mild hepatic impairment (n=558). There is limited data in patients with moderate hepatic impairment (n=15) as per NCI-ODWG (National Cancer Institute – Organ Dysfunction working Group) criteria. The pharmacokinetics of cabozantinib was not evaluated in patients with severe hepatic impairment.

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

Paediatrics
Data obtained from simulation performed with the population pharmacokinetic model developed in healthy subjects as well as adult patients with different type of malignancies show that in adolescent patients aged 12 years and older, a dose of 40 mg of cabozantinib once daily for patients < 40 kg, or a dose of 60 mg once daily in patients ≥ 40 kg results in a similar plasma exposure attained in adults treated with 60 mg of cabozantinib once daily (see section 4.2).

In the two clinical studies conducted by the COG in paediatric patients with solid tumours (ADVL1211 and ADVL1622), cabozantinib was dosed based on body surface area (BSA) according to a dosing nomogram, using available 20 mg and 60 mg tablets intended for adults. Among the 55 patients, median age was 13 years (range: 4 to 18 years). A population PK analysis was built using PK data collected in both studies. The PK of cabozantinib was adequately described by a two-compartment model with first-order elimination and first-order absorption processes. There was no evidence that age, sex, race ethnicity and tumour type affected cabozantinib PK in children and adolescent patients. Only BSA was found to be a significant predictor of cabozantinib PK. No dose dependency was seen in the developed model across the three tested dose levels (30, 40 and 55 mg/m²). The exposures in children and adolescent subjects following an administration of a BSA-based dose of 40mg/m² are similar to exposures in adults with a fixed dose of 60mg QD.

5.3 Preclinical safety data

Adverse reactions not observed in clinical trials, 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 paediatric 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 paediatric population) showed similar treatment-related findings, with additional findings in male reproductive system (degeneration and/or atrophy of seminiferous tubules in testes, reduced luminal sperm in epididymis), and 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
Anhydrous lactose
Hydroxypropyl cellulose
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

Film-coating
Hypromellose 2910
Titanium dioxide (E171)
Triacetin
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottle with a polypropylene child-resistant closure, three silica gel desiccant canisters and polyester coil. 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. MARKETING AUTHORISATION HOLDER

Ipsen Pharma
70 rue Balard
75015 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

Cabometyx 20 mg film-coated tablets
EU/1/16/1136/002

Cabometyx 40 mg film-coated tablets
EU/1/16/1136/004

Cabometyx 60 mg film-coated tablets
EU/1/16/1136/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 September 2016
Date of latest renewal: 21 April 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Patheon France
40 Boulevard de Champaret
38300 Bourgoin-Jallieu
France

Tjoapack Netherlands B.V.
Nieuwe Donk 9
4879 AC Etten-Leur
The Netherlands

Rottendorf Pharma GmbH
Ostenfelderstrasse 51 – 61
D-59320 Ennigerloh
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1.NAME OF THE MEDICINAL PRODUCT

CABOMETYX 20 mg film-coated tablets
cabozantinib

2.STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains cabozantinib (*S*)-malate equivalent to 20 mg of cabozantinib.

3.LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4.PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
30 film-coated tablets

5.METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7.OTHER SPECIAL WARNING(S), IF NECESSARY

8.EXPIRY DATE

EXP

9.SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma
70 rue Balard
75015 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1136/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CABOMETYX 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1.NAME OF THE MEDICINAL PRODUCT

CABOMETYX 40 mg film-coated tablets
cabozantinib

2.STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains cabozantinib (*S*)-malate equivalent to 40 mg of cabozantinib.

3.LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4.PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
30 film-coated tablets

5.METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7.OTHER SPECIAL WARNING(S), IF NECESSARY

8.EXPIRY DATE

EXP

9.SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma
70 rue Balard
75015 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1136/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CABOMETYX 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1.NAME OF THE MEDICINAL PRODUCT

CABOMETYX 60 mg film-coated tablets
cabozantinib

2.STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains cabozantinib (*S*)-malate equivalent to 60 mg of cabozantinib.

3.LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4.PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
30 film-coated tablets

5.METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7.OTHER SPECIAL WARNING(S), IF NECESSARY

8.EXPIRY DATE

EXP

9.SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma
70 rue Balard
75015 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1136/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CABOMETYX 60 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1.NAME OF THE MEDICINAL PRODUCT

CABOMETYX 20 mg film-coated tablets
cabozantinib

2.STATEMENT OF ACTIVE SUBSTANCE(S)

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

3.LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4.PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5.METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7.OTHER SPECIAL WARNING(S), IF NECESSARY

8.EXPIRY DATE

EXP

9.SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11.NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma
70 rue Balard
75015 Paris
France

12.MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1136/002

13.BATCH NUMBER

Lot

14.GENERAL CLASSIFICATION FOR SUPPLY

15.INSTRUCTIONS ON USE

16.INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1.NAME OF THE MEDICINAL PRODUCT

CABOMETYX 40 mg film-coated tablets
cabozantinib

2.STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains cabozantinib (*S*)-malate equivalent to 40 mg cabozantinib.

3.LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4.PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5.METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7.OTHER SPECIAL WARNING(S), IF NECESSARY

8.EXPIRY DATE

EXP

9.SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11.NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma
70 rue Balard
75015 Paris
France

12.MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1136/004

13.BATCH NUMBER

Lot

14.GENERAL CLASSIFICATION FOR SUPPLY

15.INSTRUCTIONS ON USE

16.INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1.NAME OF THE MEDICINAL PRODUCT

CABOMETYX 60 mg film-coated tablets
cabozantinib

2.STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains cabozantinib (*S*)-malate equivalent to 60 mg cabozantinib.

3.LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4.PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5.METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7.OTHER SPECIAL WARNING(S), IF NECESSARY

8.EXPIRY DATE

EXP

9.SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11.NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma
70 rue Balard
75015 Paris
France

12.MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1136/006

13.BATCH NUMBER

Lot

14.GENERAL CLASSIFICATION FOR SUPPLY

15.INSTRUCTIONS ON USE

16.INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

CABOMETYX 20 mg film-coated tablets
CABOMETYX 40 mg film-coated tablets
CABOMETYX 60 mg film-coated tablets
cabozantinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What CABOMETYX is and what it is used for

What CABOMETYX is

CABOMETYX is a cancer medicine that contains the active substance cabozantinib.
It is used in adults to treat:
- advanced kidney cancer called advanced renal cell carcinoma
- liver cancer when a specific anticancer medicine (sorafenib) is no longer stopping the disease from progressing.
- Advanced neuroendocrine tumours – tumours that originate from the pancreas, stomach, bowels, lung or other organs. It is given when patients with these tumours no longer respond to a previous treatment option.

CABOMETYX is also used to treat locally advanced or metastatic differentiated thyroid cancer, a type of cancer in the thyroid gland, in adults when radioactive iodine and anticancer medicine treatments are no longer stopping the disease from progressing.

CABOMETYX may be given in combination with nivolumab for advanced kidney cancer. It is important that you also read the package leaflet of nivolumab. If you have any questions about these medicines, please ask your doctor.

How CABOMETYX works

CABOMETYX blocks the action of proteins called receptor tyrosine kinases (RTKs), which are involved in the growth of cells and the development of new blood vessels that supply them. These proteins can be present in high amounts in cancer cells, and by blocking their action this medicine can

slow down the rate at which the tumour grows and help to cut off the blood supply that the cancer needs.

2. What you need to know before you take CABOMETYX

Do not take CABOMETYX

- if you are allergic to cabozantinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking CABOMETYX if you:

- have high blood pressure
- have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall
- have diarrhoea
- have a recent history of significant bleeding
- have had surgery within the last month (or if surgical procedures are planned), including dental surgery
- have inflammatory bowel disease (for example, Crohn's disease or ulcerative colitis, diverticulitis, or appendicitis)
- have a recent history of blood clot in the leg, stroke, or heart attack
- have thyroid problems. Tell your doctor if you get tired more easily, generally feel colder than other people, or your voice deepens whilst taking this medicine.
- have liver or kidney disease.

Tell your doctor if any of these affect you.

You may need treatment for them, or your doctor may decide to change your dose of CABOMETYX or stop treatment altogether. See also section 4 "*Possible side effects*".
You should also tell your dentist that you are taking this medicine. It is important for you to practice good mouth care during treatment.

Children and adolescents

CABOMETYX is not recommended for children or adolescents. The effects of this medicine in people younger than 18 years old are not known.

Other medicines and CABOMETYX

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is because CABOMETYX can affect the way some other medicines work. Also, some medicines can affect the way CABOMETYX works. This could mean that your doctor needs to change the dose(s) that you take. You should tell your doctor about every medicine, but in particular if taking:

- 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 to treat angina pectoris (chest pain owing to inadequate supply to the heart) such as ranolazine
- Medicines used to treat epilepsy or fits such as phenytoin, carbamazepine, and phenobarbital

- Herbal preparations containing St. John's Wort *(Hypericum perforatum)*, sometimes used for treating depression or depression-related conditions such as anxiety
- Medicines used to thin the blood, such as warfarin and dabigatran etexilate
- Medicines to treat high blood pressure or other heart conditions, such as aliskiren, ambrisentan, digoxin, talinolol, 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 prevent transplant rejection (ciclosporin) and ciclosporin-based regimens in rheumatoid arthritis and psoriasis

CABOMETYX with food

Avoid consuming grapefruit-containing products for as long as you are using this medicine, as they may increase the levels of CABOMETYX in your blood.

Pregnancy, breast-feeding and fertility

Avoid becoming pregnant while being treated with CABOMETYX. If you or your partner could become pregnant, use adequate contraception during treatment and for at least 4 months after treatment has finished. Talk to your doctor about which methods of contraception are appropriate while you are taking this medicine (see also under Other medicines and CABOMETYX, above).

Tell your doctor if you or your partner become pregnant or plan to become pregnant while you are being treated with this medicine.

Talk to your doctor BEFORE taking this medicine if you or your partner are considering or planning to have a baby after your treatment has finished. There is a possibility your fertility could be affected by treatment with this medicine.

Women taking this medicine should not breast-feed during treatment and for at least 4 months after treatment has finished, as cabozantinib and/or its metabolites may be excreted in breast milk and be harmful to your child.

If you take this medicine whilst using oral contraceptives, the oral contraceptives may be ineffective. You should also use a barrier contraceptive (e.g. condom or diaphragm) whilst taking this medicine and for at least 4 months after treatment has finished.

Driving and using machines

Use caution when driving or using machines. Keep in mind that treatment with CABOMETYX may make you feel tired or weak and can affect your ability to drive or use machines.

CABOMETYX contains lactose
This medicine contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

CABOMETYX contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

3. How to take CABOMETYX

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

You should continue to take this medicine until your doctor decides to stop your treatment. If you get serious side effects, your doctor may decide to change your dose or stop treatment earlier than originally planned. Your doctor will tell you if you need your dose adjusted.

CABOMETYX should be taken once a day. The usual dose is 60 mg, however your doctor will decide on the right dose for you.
When this medicine is given in combination with nivolumab for the treatment of advanced kidney cancer, the recommended dose of CABOMETYX is 40 mg once a day.

You should not take CABOMETYX with food. You should not eat anything for at least 2 hours before and for 1 hour after taking the medicine. Swallow the tablet with a full glass of water. Do not crush the tablets.

If you take more CABOMETYX than you should

If you have taken more of this medicine than you have been instructed to, talk to a doctor or go to the hospital with the tablets and this leaflet straight away.

If you forget to take CABOMETYX

- If there are still 12 hours or more before your next dose is due, then take the missed dose as soon as you remember. Take the next dose at the normal time.
- If your next dose is due in less than 12 hours, then do not take the dose that you have missed. Take your next dose at the normal time.

If you stop using CABOMETYX
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with this medicine unless you have discussed this with your doctor.

When this medicine is given in combination with nivolumab, you will first be given nivolumab followed by CABOMETYX.

Please refer to the package leaflet of nivolumab in order to understand the use of this medicine. If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you get side effects, your doctor may tell you to take CABOMETYX at a lower dose. Your doctor may also prescribe other medicines to help control your side effects.

Tell your doctor straight away if you notice any of the following side effects – you may need urgent medical treatment:

- Symptoms including pain in the abdomen, nausea (feeling sick), vomiting, constipation, or fever. These may be signs of a gastrointestinal perforation, a hole that develops in your stomach or intestine that could be life-threatening. Gastrointestinal perforation is common (it may affect up to 1 in 10 people).

- Severe or uncontrollable bleeding with symptoms such as: vomiting blood, black stools, bloody urine, headache, coughing up blood. It is common (it may affect up to 1 in 10 people)
- Feeling drowsy, confused or loss of consciousness. This may be due to liver problems which are common (they may affect up to 1 in 10 people).
- Swelling, or shortness of breath. These are very common (they may affect more than 1 in 10 people).
- A wound that does not heal. It is uncommon (it may affect 1 in 100 people)
- Fits, headaches, confusion, or finding it difficult to concentrate. These may be signs of a condition called posterior reversible encephalopathy syndrome (PRES). PRES is uncommon (it may affect 1 in 100 people).
- 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. These could be signs of bone damage in the jaw (osteonecrosis). It is uncommon (it may affect 1 in 100 people).

Other side effects with CABOMETYX alone include:

Very common side effects (may affect more than 1 in 10 people)

- Anaemia (low levels of red blood cells which carry oxygen), low levels of platelets (cells which help the blood to clot)
- Reduced thyroid activity; symptoms can include tiredness, weight gain, constipation, feeling cold and dry skin
- Decreased appetite, altered sense of taste
- Decreased amount of magnesium, potassium or calcium in the blood
- Decreased amount of protein albumin in blood (which carries substances such as hormones, medicines, and enzymes throughout your body)
- Headache, dizziness
- High blood pressure (hypertension)
- Bleeding
- Difficulty in speaking, hoarseness (dysphonia), cough and shortness of breath
- Stomach upset, including diarrhoea, nausea, vomiting, constipation, indigestion and abdominal pain
- Redness, swelling or pain in the mouth or throat (stomatitis)
- Skin rash sometimes with blisters, itching, pain of the hands or soles of the feet, rash
- Pain in the arms, hands, legs or feet, pain in joints
- Feeling tired or weak, inflammation of the oral and gastrointestinal mucosa, swelling in your legs and arms
- Weight loss
- Abnormal liver function tests (increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase)

Common side effects (may affect up to 1 in 10 people)

- Abscess (collection of pus, with swelling and inflammation)
- Dehydration
- Decreased amount of phosphate and sodium in the blood
- Increased amount of potassium in the blood
- Increased amount of the waste product bilirubin in the blood (which may result in jaundice/yellow skin or eyes)
- High (hyperglycaemia) or low (hypoglycaemia) sugar levels in the blood
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs)
- Ringing in ears (tinnitus)
- Blood clots in the veins, low blood pressure (hypotension)

- Blood clots in the lungs, inflammation of the lining of the nose (allergic rhinitis)
- Inflammation of the pancreas, a painful tear or abnormal connection of the tissues in your body (fistula), gastro-oesophageal reflux disease (bringing up stomach acid), haemorrhoids (piles), dry mouth and pain in the mouth, difficulty in swallowing, flatulence
- Severe itching of skin, alopecia (hair loss and thinning), dry skin, acne, hair colour change, thickening of the skin outer layer, redness of the skin
- Muscle spasms
- Protein in urine (seen in tests)
- Abnormal liver function tests (increased amounts of the liver enzyme gamma-glutamyl transferase in your blood)
- Abnormal kidney function tests (increased amounts of creatinine in your blood)
- Increased level of the enzyme that breaks down fats (lipase) and of the enzyme that breaks down starch (amylase)
- Increase in cholesterol or triglyceride levels in the blood
- Low levels of white blood cells (which are important in fighting infection)
- Lung infection (pneumonia)

Uncommon side effects (may affect 1 in 100 people)

- Fits, stroke
- Severe high blood pressure
- Blood clots in the arteries
- Decrease in bile flow from the liver
- A burning or painful sensation in the tongue (glossodynia)
- Heart attack
- Clot/embolus that travelled through your arteries and become stuck
- Collapsed lung with air trapped in the space between the lung and chest, often causing shortness of breath (pneumothorax)

Not known (proportion of people affected not known)

- An enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections)
- Inflammation of the blood vessels in the skin (cutaneous vasculitis)

The following side effects have been reported **with CABOMETYX in combination with nivolumab:**

Very common side effects (may affect more than 1 in 10 people)

- Infections of the upper respiratory tract
- Reduced thyroid activity; symptoms can include tiredness, weight gain, constipation, feeling cold and dry skin
- Increased thyroid activity; symptoms can include rapid heart rate, sweating and weight loss
- Decreased appetite, altered sense of taste
- Headache, dizziness
- High blood pressure (hypertension)
- Difficulty in speaking, hoarseness (dysphonia), cough and shortness of breath
- Stomach upset, including diarrhoea, nausea, vomiting, indigestion, abdominal pain and constipation
- Redness, swelling or pain in the mouth or throat (stomatitis)
- Skin rash sometimes with blisters, itching, pain of the hands or soles of the feet, rash or severe itching of skin
- Pain in joints (arthralgia), muscle spasm, muscle weakness and aching muscles
- Protein in the urine (seen in test)

- Feeling tired or weak, fever and oedema (swelling)
- Abnormal liver function tests (increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase in your blood, higher blood levels of the waste product bilirubin)
- Abnormal kidney function tests (increased amounts of creatinine in your blood)
- High (hyperglycaemia) or low (hypoglycaemia) sugar levels in the blood
- Anaemia (low levels of red blood cells which carry oxygen), low levels of white blood cells (which are important in fighting infection), low levels of platelets (cells which help the blood to clot)
- An increased level of the enzyme that breaks down fats (lipase) and of the enzyme that breaks down starch (amylase)
- Decreased amount of phosphate
- Increased or decreased amount of potassium
- Decreased or increased blood levels of calcium, magnesium, or sodium
- Decrease in body weight

Common side effects (may affect up to 1 in 10 people)

- Serious lung infection (pneumonia)
- Increase in some white blood cells called eosinophils
- Allergic reaction (including anaphylactic reaction)
- Decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys)
- Dehydration
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs)
- Ringing in ears (tinnitus)
- Dry eyes and blurred vision
- Changes in the rhythm or rate of the heartbeat, fast heart rate
- Blood clots in the blood vessels
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), blood clots in the lung, fluid around the lungs
- Nose bleeding
- Inflammation of the colon (colitis), dry mouth, pain in the mouth, inflammation of the stomach (gastritis) and haemorrhoids (piles)
- Inflammation of the liver (hepatitis)
- Dry skin and redness of the skin
- Alopecia (hair loss and thinning), hair colour change
- Inflammation of the joints (arthritis)
- Kidney failure (including abrupt loss of kidney function)
- Pain, chest pain
- Increase in triglyceride levels in the blood
- Increase in cholesterol levels in the blood

Uncommon side effects (may affect 1 in 100 people)

- Allergic reactions related to the infusion of the medicine nivolumab
- Inflammation of the pituitary gland situated at the base of the brain (hypophysitis), swelling of the thyroid gland (thyroiditis)
- A temporary inflammation of the nerves that causes pain, weakness and paralysis in the extremities (Guillain Barré syndrome); muscle weakness and tiredness without atrophy (myasthenic syndrome)
- Inflammation of the brain
- Inflammation of the eye (which causes pain and redness)

- Inflammation of the heart muscle
- Clot/embolus that travelled through your arteries and become stuck
- Inflammation of the pancreas (pancreatitis), intestinal perforation, burning or painful sensation in the tongue (glossodynia)
- Skin disease with thickened patches of red skin, often with silvery scales (psoriasis)
- Hives (itchy rash)
- Muscle tenderness of weakness, not caused by exercise (myopathy), bone damage in the jaw, painful tear or abnormal connection of the tissues in your body (fistula)
- Inflammation of the kidney
- Collapsed lung with air trapped in the space between the lung and chest, often causing shortness of breath (pneumothorax)

Not known (proportion of people affected not known)

- Inflammation of the blood vessels in the skin (cutaneous vasculitis)
- Progressive destruction and loss of intrahepatic bile ducts and jaundice

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store CABOMETYX

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6.Contents of the pack and other information

What CABOMETYX contains

The active substance is cabozantinib (*S*)-malate.

CABOMETYX 20 mg film-coated tablets: Each tablet contains cabozantinib (*S*)-malate equivalent to 20 mg of cabozantinib.
CABOMETYX 40 mg film-coated tablets: Each tablet contains cabozantinib (*S*)-malate equivalent to 40 mg of cabozantinib.
CABOMETYX 60 mg film-coated tablets: Each tablet contains cabozantinib (*S*)-malate equivalent to 60 mg of cabozantinib.

The other ingredients are:

- **Tablet contents:** microcrystalline cellulose, lactose anhydrous, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide anhydrous, magnesium stearate. (see section 2 for lactose content)
- **Film coating:** hypromellose, titanium dioxide (E171), triacetin, iron oxide yellow (E172)

What CABOMETYX looks like and contents of the pack

CABOMETYX 20 mg film-coated tablets are yellow, round with no score, and identified with “XL” on one side and “20” on the other side.
CABOMETYX 40 mg film-coated tablets are yellow, triangle shaped with no score, and identified with “XL” on one side and “40” on the other side.
CABOMETYX 60 mg film-coated tablets are yellow, oval shaped with no score, and identified with “XL” on one side and “60” on the other side.

CABOMETYX is available in packs containing one plastic bottle with 30 film-coated tablets. The bottle contains three silica gel desiccant canisters and a polyester coil to prevent damage to the film-coated tablets. Keep the canisters and the polyester coil in the bottle and do not swallow the desiccant canisters.

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.