▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
CABOMETYX® cabozantinib (as (S)-malate) film-coated tablets

1 NAME OF THE MEDICINE

cabozantinib (S)-malate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CABOMETYX tablets contain cabozantinib*(S)*-malate equivalent to either 20 mg, 40 mg or 60 mg of cabozantinib as the active ingredient.

Each film-coated tablet contains either: 15.54 mg lactose (20 mg tablet), 31.07 mg lactose (40 mg tablet) or 46.61 mg lactose (60 mg tablet)

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

CABOMETYX 20 mg film-coated 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 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 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 the treatment of advanced renal cell carcinoma (RCC):

- in treatment-naïve adults with intermediate or poor risk
- in adults following prior treatment with vascular endothelial growth factor targeted therapy.

CABOMETYX in combination with nivolumab is indicated for the first-line treatment of advanced renal cell carcinoma.

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 and paediatric patients aged 12 years and older with locally advanced or metastatic differentiated thyroid carcinoma (DTC) that has progressed during or after prior VEGFR-targeted therapy and who are radioactive iodine (RAI) refractory or ineligible.

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

4.2 DOSE AND METHOD OF ADMINISTRATION

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

CABOMETYX as monotherapy
For RCC, HCC, DTC, and NET, the recommended dose of CABOMETYX in adults is 60 mg once daily.

For DTC only, the recommended dose of CABOMETYX in paediatric patients aged 12 years and older is based on body weight:

- ≥ 40 kg: 60 mg once daily,
- < 40 kg: 40 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 administered intravenously at either 240 mg every 2 weeks or 480 mg every 4 weeks. CABOMETYX 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 Australian Product Information for nivolumab for dosage and administration recommendations for nivolumab).

Treatment modification
Management of suspected adverse drug reactions may require temporary treatment interruption and/or dose reduction of CABOMETYX therapy (see Table 1 and Section 4.4 Special warnings and precautions for use).

When dose reduction is necessary in monotherapy, it is recommended to reduce to 40 mg daily, and then to 20 mg daily.

When dose reduction is necessary in paediatric patients aged 12 years and older and weighing less than 40 kg, it is recommended to reduce the dose to 20 mg of CABOMETYX once daily, and then to 20 mg every other day.

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 Australian Product Information for nivolumab 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 CABOMETYX.
Liver enzyme 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 resolve to Grades 0-1

Adverse reaction and severity	Treatment Modification
	Corticosteroid therapy may be considered. 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 Product Information.
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 PI).

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

Special populations

Elderly patients

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

Race

No dose adjustment is necessary based on ethnicity (see section 5.2 Pharmacokinetic properties).

Patients with renal impairment

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

Patients with hepatic impairment

In patients with mild 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 Special warnings and precautions for use and 5.2 Pharmacokinetic properties). 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 Pharmacokinetic properties).

Patients with cardiac impairment

There is limited data in patients with cardiac impairment. No specific dosing recommendations can be made.

Paediatric population

The safety and efficacy of cabozantinib in children and adolescents aged <18 years have not yet been established.

CABOMETYX should not be used in children with DTC aged less than 12 years old. The dosing regimen for paediatric patients with DTC is based on simulated pharmacokinetic data (see section 5.2 Pharmacokinetic properties).

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 and 1 hour after taking CABOMETYX.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (see Section 6.1 List of excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As most events that require dose modification or interruption occur early in the course of treatment, the physician should evaluate the patient closely during the first eight weeks of treatment to determine if this is necessary. Events that generally have early onset include hypocalcaemia, hypokalaemia, thrombocytopenia, hypertension, palmar-plantar erythrodysaesthesia syndrome (PPES), proteinuria, and gastrointestinal (GI) events (abdominal pain, mucosal inflammation, constipation, diarrhoea, vomiting).

Management of suspected adverse reactions may require temporary interruption or dose reduction of cabozantinib therapy (see Section 4.2 Dose and method of administration):

In renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy, dose reductions and dose interruptions due to an adverse event occurred in 59.8% and 70%, respectively, of cabozantinib-treated patients in the pivotal clinical trial (METEOR). The median daily dose of cabozantinib was 43 mg. Two dose reductions were required in 19.3% of patients. The median time to first dose reduction was 55 days, and to first dose interruption was 38 days.

In treatment-naïve renal cell carcinoma, dose reductions and dose interruptions occurred in 46% and 73%, respectively, of cabozantinib-treated patients in the clinical trial (CABOSUN). The median daily dose of cabozantinib was 50.3 mg in this study.

Safety and efficacy of cabozantinib has not been evaluated in patients with NYHA Class 3 or 4 Heart Failure and patients with endobronchial manifestations of RCC.

When cabozantinib is given in combination with nivolumab in first-line advanced renal cell carcinoma, dose interruption or reduction due to an AE of either cabozantinib or nivolumab

occurred in 83% of patients: 46% cabozantinib only, 3% nivolumab only, and 28% both drugs in the clinical trial (CA2099ER).

In hepatocellular carcinoma following prior systemic therapy, dose reductions and dose interruptions occurred in 62% and 84%, respectively, of cabozantinib-treated patients in the clinical trial (CELESTIAL). Two dose reductions were required in 33% of patients. The median time to first dose reduction was 38 days, and to first dose interruption was 28 days. Closer monitoring is advised in patients with mild or moderate hepatic impairment.

In differentiated thyroid carcinoma, dose reductions and dose interruptions occurred in 67% and 71% respectively of cabozantinib treated patients in the clinical trial (COSMIC-311). Two dose reductions were required in 33% of patients. The median time to first dose reduction was 57 days and to first dose interruption was 38.5 days.

In neuroendocrine tumours following prior therapy, dose reduction and dose interruption of cabozantinib due to an AE occurred in 62% and 74%, respectively, of cabozantinib-treated patients in the clinical trial (CABINET). Two dose reductions were required in 27% of patients. The median time to first dose reduction was 49 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 Dose and method of administration).

When cabozantinib is given in combination with nivolumab, higher frequencies of Grades 3 and 4 ALT and AST elevations have been reported in patients with advanced RCC (see section 4.8 Adverse effects (Undesirable effects)). 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 Dose and method of administration and refer to the Product Information 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 Dose and method of administration and 5.2 Pharmacokinetic properties). A higher relative proportion of patients with moderate hepatic impairment (Child-Pugh B) developed hepatic encephalopathy with cabozantinib treatment. CABOMETYX is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) as

cabozantinib has not been studied in this population and exposure might be increased in these patients.

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 gastrointestinal (GI) perforations and fistulas, sometimes fatal, have been observed with cabozantinib. Patients who have inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, peritonitis, diverticulitis, or appendicitis), have tumour infiltration in the GI tract, or have complications from prior GI surgery (particularly when associated with delayed or incomplete healing) should be carefully evaluated before initiating cabozantinib therapy and subsequently they should be monitored closely for symptoms of perforations and fistulas including abscesses and sepsis. Persistent or recurring diarrhoea while on treatment may be a risk factor for the development of anal fistula. Cabozantinib should be discontinued in patients who experience a GI perforation or a fistula that cannot be adequately managed.

Gastrointestinal (GI) disorders
Diarrhoea, nausea/vomiting, decreased appetite, and stomatitis/oral pain were some of the most commonly reported GI adverse reactions (see section 4.8 Adverse effects (Undesirable effects)). 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.

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. Cabozantinib should be used with caution in patients receiving systemic anticoagulation in the context of a considered benefit risk assessment.

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.

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), 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.

Osteonecrosis of the jaw
Events of osteonecrosis of the jaw (ONJ) have been observed with cabozantinib. Osteonecrosis of the jaw (ONJ) can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain or slow healing of the mouth or jaw after dental surgery. An oral examination should be performed prior to initiation of cabozantinib and periodically during cabozantinib treatment. Patients should be advised to maintain good oral hygiene practices. Cabozantinib treatment should be stopped at least 28 days prior to 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.

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 anti-hypertensive 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.

Diarrhoea
Diarrhoea has been observed with cabozantinib and can be severe. If diarrhoea cannot be managed with standard antidiarrhoeal treatment, interruption of treatment with cabozantinib should be considered. Cabozantinib should be restarted with a lower dose when diarrhoea has been resolved to grade 1.

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, hyponatremia). 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 Section 4.2 Dose and method of administration and Section 4.5 Interactions with other medicines and other forms of interactions).

P-glycoprotein substrates
Cabozantinib was an inhibitor (IC_{50} = 7.0 μM), but not a substrate, of P-glycoprotein (P-gp) transport activities *in vitro*. 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, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib (see Section 4.5 Interactions with other medicines and other forms of interactions).

MRP2 inhibitors
Administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations. Therefore, concomitant use of MRP2 inhibitors (e.g. cyclosporine, efavirenz, emtricitabine) should be approached with caution (see Section 4.5 Interactions with other medicines and other forms of interactions).

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

Use in hepatic impairment
Liver function should be monitored in patients with known intra-hepatic metastasis as clinically indicated.

Use in the elderly

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

Paediatric use

The safety and effectiveness of CABOMETYX for the treatment of differentiated thyroid cancer (DTC) in paediatric patients aged 12 years and older is based on simulated pharmacokinetic data derived from the adequate and well-controlled studies of CABOMETYX in adults. The additional population pharmacokinetic data demonstrated that cabozantinib exposure is within the same range between adults and paediatric patients aged 12 years and older at the recommended dosages.

Physeal widening has been observed in children with open growth plates when treated with cabozantinib. Therefore, physeal and longitudinal growth monitoring is recommended in children with open growth plates.

The safety and effectiveness of CABOMETYX in paediatric patients less than 12 years of age have not been established.

In juvenile rat studies, target organs for toxicity were generally similar to those seen in adult animals. Tooth abnormalities and whitening as well as effects on bones including reduced bone mineral content and density, physeal hypertrophy, and decreased cortical bone also occurred at all dose levels. Adverse effects on the developing reproductive systems were also noted. The findings in juvenile rats indicate a potential risk for children and adolescents.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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, H_2 receptor antagonists, and antacids) are co-administered with cabozantinib.

MRP2 inhibitors

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

Bile salt-sequestering agents

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

Effect of cabozantinib on other medicinal products

The effect of cabozantinib on the pharmacokinetics of contraceptive steroids has not been investigated. As unchanged contraceptive effect may not be guaranteed, an additional contraceptive method, such as a barrier method, is recommended.

Because of high plasma protein binding levels of cabozantinib (see Section 5.2 Pharmacokinetic properties) a plasma protein displacement interaction with warfarin may be possible. In case of such combination, INR values should be monitored.

P-glycoprotein substrates

Cabozantinib was an inhibitor (IC_{50} = 7.0 μM), but not a substrate, of P-gp transport activities *in vitro*. 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, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, saxagliptin, sitagliptin, tolvaptan) while receiving cabozantinib.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

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

Use in pregnancy (Category D)

There are no studies in pregnant women using cabozantinib. Studies in animals have shown embryofoetal lethality and teratogenic effects. 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.

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 Interactions with other medicines and other forms of interactions).

Cabozantinib crossed the placenta in rats and rabbits. In embryofetal development studies in pregnant rats, daily oral administration of cabozantinib throughout organogenesis caused increased embryofetal lethality at ≥0.03 mg/kg/day. Foetal findings included delayed ossification and skeletal variations at ≥0.01 mg/kg/day and foetal oedema, cleft palate/lip, dermal aplasia and kinked or rudimentary tail at 0.6 mg/kg/day.

In pregnant rabbits, daily oral administration of cabozantinib throughout organogenesis resulted in findings of visceral malformations and variations including reduced spleen size and missing lung lobe at 3 mg/kg/day. Exposures (AUC) at doses causing adverse embryofetal effects in rats and rabbits were well below the human AUC at the recommended dose.

Use in lactation

It is not known whether cabozantinib and/or its metabolites are excreted in human milk. Cabozantinib appeared to be excreted in the milk of rats as significant levels of cabozantinib were detected in the plasma of breast-fed pups. 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.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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

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 frequent adverse reactions of any grade (experienced by at least 25% of patients) in the HCC population included diarrhoea, decreased appetite, PPES, fatigue, nausea, hypertension and vomiting.

The most frequent serious adverse reactions in the DTC population with a median duration of treatment of 6.03 months (range 0.2 – 18.8) (≥1% incidence) are diarrhoea, pleural effusion, pneumonia, pulmonary embolism, hypertension, anaemia, deep vein thrombosis, hypocalcaemia, osteonecrosis of jaw, pain, palmar-plantar erythrodysaesthesia syndrome (PPES), vomiting and renal impairment.

The most frequent adverse reactions of any grade (experienced by at least 25% of patients) in the DTC population included diarrhoea, PPES, hypertension, fatigue, decreased appetite, nausea, alanine aminotransferase increased, aspartate aminotransferase increased and hypocalcaemia.

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

The most frequent adverse reactions of any grade (experienced by at least 25% of patients) in the NET population included fatigue, aspartate aminotransferase increased, alanine aminotransferase increased, diarrhoea, hypertension, stomatitis, palmar-plantar erythrodysaesthesia syndrome, platelet count decreased, nausea, dysgeusia, white blood cell count decreased, decreased appetite and neutrophil count decreased.

A higher incidence of hypertension, fatigue, stomatitis and dysgeusia was observed in the NET population in both the cabozantinib and placebo arms of the CABINET study, compared to the other cabozantinib monotherapy studies.

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

MedDRA System Organ Class	Very Common	Common	Uncommon	Not Known
Infections and infestations		abscess, pneumonia		
Blood and lymphatic disorders	anaemia, thrombocytopenia[a]	neutropenia[a], lymphopenia[a]		
Endocrine disorders	hypothyroidism			
Metabolism and nutrition disorders	decreased appetite, hypomagnesaemia[b], hypokalaemia[b], hypoalbuminaemia[b], hypocalcaemia[b]	dehydration, hypophosphataemia[b], hyponatraemia[b], hyperkalaemia[c], hyperbilirubinemia[c], hyperglycaemia[c], hypoglycaemia[b]		
Nervous system disorders	dysgeusia, headache, dizziness	peripheral neuropathy[d]	Convulsion, cerebro-vascular accident, posterior reversible encephalopathy syndrome	

MedDRA System Organ Class	Very Common	Common	Uncommon	Not Known
Ear and labyrinth disorders		tinnitus		
Cardiac disorders			acute myocardial infarction	
Vascular disorders	hypertension[g], haemorrhage[*]	venous thrombosis[f], hypotension	hypertensive crisis, arterial thrombosis, embolism arterial	aneurysms and artery dissections
Respiratory, thoracic, and mediastinal disorders	dysphonia, dyspnoea, cough	pulmonary embolism, rhinitis allergic		
Gastrointestinal disorders	diarrhoea[*], nausea, vomiting, stomatitis, constipation, abdominal pain[e], dyspepsia	gastrointestinal perforation[*], pancreatitis, fistula[*], gastro-oesophageal reflux disease, haemorrhoids, oral pain, dry mouth, dysphagia, flatulence	glossodynia	
Hepatobiliary disorders		hepatic encephalopathy[*]	hepatitis cholestatic	
Skin and subcutaneous tissue disorders	palmar-plantar erythrodysaesthesia syndrome, rash	pruritus, alopecia, dry skin, dermatitis acneiform, hair colour change, hyperkeratosis, erythema		cutaneous vasculitis
Musculoskeletal and connective tissue disorders	pain in extremity, arthralgia	muscle spasms	osteonecrosis of the jaw	
Renal and urinary disorders		proteinuria		
General disorders and administration site conditions	fatigue, mucosal inflammation, asthenia, peripheral oedema			
Investigations	weight decreased, serum ALT increased, AST	GGT increased, blood creatinine increased, amylase increased, lipase		

MedDRA System Organ Class	Very Common	Common	Uncommon	Not Known
	increased, blood ALP increased	increased, blood cholesterol increased[c], blood triglycerides increased[c], white blood cell count decreased		
Injury, poisoning and procedural complications			wound complications[h]	

*See section 4.8 Description of selected adverse reactions for further characterisation.
The following terms have been combined to derive appropriate frequency categorisation:
[a] Lowered haematology parameters: Lymphopenia and lymphocyte count decreased; Neutropenia and neutrophil count decreased; Thrombocytopenia and platelet count decreased.
[b] Lowered biochemistry parameters: Hypoalbuminaemia and blood albumin decreased; Hypocalcaemia and blood calcium decreased; Hypoglycaemia and blood glucose decreased; Hypokalaemia and blood potassium decreased; Hypomagnesaemia and blood magnesium decreased; Hyponatraemia and blood sodium decreased; Hypohosphataemia and blood phosphorus decreased.
[c] Elevated biochemistry parameters: Blood cholesterol increased and hypercholesterolaemia; Hyperbilirubinaemia and blood bilirubin increased; Hyperglycaemia and blood glucose increased; Hypothyroidism and blood thyroid stimulating hormone increased; Hyperkalaemia and blood potassium increased; Triglycerides increased and hypertriglyceridaemia.
[d.] including peripheral neuropathy, mainly sensory and polyneuropathy
[e] Abdominal pain, abdominal discomfort, abdominal pain upper and abdominal pain lower.
[f] All venous thrombosis including deep vein thrombosis
[g] Hypertension and blood pressure increased.
[h] Impaired healing, incision site complication and wound dehiscence.

Table 3 summarises the adverse reactions in patients with pNET and epNET in CABINET.

Table 3 Adverse reactions (≥15%) in patients with pNET or epNET who received cabozantinib in CABINET

	Pancreatic NET cohort				Extrapancreatic NET Cohort			
	CABOMETYX (N=63)		Placebo (N=31)		CABOMETYX (N=132)		Placebo (N=67)	
Adverse Reaction	All Grades[1]	Grade 3 or 4	All Grades[1]	Grade 3 or 4	All Grades[1]	Grade 3 or 4	All Grades[1]	Grade 3 or 4
	Percentage (%) of Patients							
General								
Fatigue[2]	79	14	61	6	73	14	58	9
Edema[3]	-	-	-	-	16	1.5	10	0
Vascular								
Hypertension[4]	67	25	55	16	64	27	37	6
Thromboembolic events[5]	19	11	3.2	0	-	-	-	-
Gastrointestinal								
Diarrhea[6]	63	6	23	0	65	11	42	4.5
Stomatitis[7]	49	6	10	0	40	3.8	10	0
Nausea	37	8	32	3.2	39	2.3	21	0

	Pancreatic NET cohort				Extrapancreatic NET Cohort			
	CABOMETYX (N=63)		Placebo (N=31)		CABOMETYX (N=132)		Placebo (N=67)	
Adverse Reaction	**All Grades[1]**	**Grade 3 or 4**	**All Grades[1]**	**Grade 3 or 4**	**All Grades[1]**	**Grade 3 or 4**	**All Grades[1]**	**Grade 3 or 4**
	Percentage (%) of Patients							
Abdominal pain[8]	25	3.2	16	6	29	9	43	8
Vomiting	25	6	16	0	17	2.3	10	1.5
Dyspepsia[9]	16	0	6	0	-	-	-	-
Skin and Subcutaneous Tissue								
Rash[10]	57	11	23	0	50	3.0	10	0
Musculoskeletal and Connective Tissue Disorders								
Musculoskeletal pain[11]	41	1.6	19	0	36	8	33	1.5
Nervous System								
Dysgeusia[12]	30	0	6	0	35	0	1.5	0
Dizziness[13]	25	0	3.2	0	17	0	6	0
Endocrine disorders								
Hypothyroidism[14]	25	0	3.2	0	34	0	4.5	0
Metabolism and Nutrition								
Decreased appetite	25	3.2	19	0	33	1.5	15	1.5
Investigations								
Weight decreased	19	3.2	10	0	27	4.5	8	0
Respiratory, Thoracic, and Mediastinal								
Dyspnea[15]	16	0	3.2	0	-	-	-	-
Cough[16]	-	-	-	-	17	0	10	0

[1] NCI CTCAE Version 5.0

[2] Includes fatigue, asthenia

[3] Includes edema, edema peripheral, generalized edema, localized edema, periorbital edema, face edema, eye edema

[4] Includes hypertension, blood pressure increased, blood pressure systolic increased, systolic hypertension

[5] Includes thromboembolic event, pulmonary embolism, embolism, deep vein thrombosis, vena cava thrombosis, embolism venous, embolism arterial

[6] Includes diarrhea, colitis

[7] Includes stomatitis, aphthous ulcer, mucosal inflammation, cheilitis, glossitis

[8] Includes abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain, abdominal discomfort, hepatic pain

[9] Includes dyspepsia, gastroesophageal reflux disease

[10] Includes rash, palmar-plantar erythrodysesthesia syndrome, dermatitis acneiform, skin exfoliation, erythema multiforme, rash macular, rash maculo-papular, rash pustular, dermatitis, dermatitis bullous, dermatitis contact, erythema, dermatitis psoriasiform

[11] Includes musculoskeletal pain, non-cardiac chest pain, back pain, arthralgia, pain in extremity, myalgia, bone pain, arthritis, neck pain, musculoskeletal chest pain, musculoskeletal stiffness, chest discomfort

[12] Includes dysgeusia, taste disorder, ageusia, anosmia

[13] Includes dizziness, vertigo

[14] Includes hypothyroidism, blood thyroid stimulating hormone increased

[15] Includes dyspnea, dyspnea exertional

[16] Includes cough, upper-airway cough syndrome, productive cough

Table 4 summarises the laboratory abnormalities in patients with pNET and epNET in CABINET.

Table 4 Select laboratory abnormalities (≥10%) reported as adverse reactions in patients with pNET or epNET who received cabozantinib in CABINET

	Pancreatic NET cohort				Extrapancreatic NET Cohort			
	CABOMETYX (N=63)		Placebo (N=31)		CABOMETYX (N=132)		Placebo (N=67)	
Laboratory Abnormality	All Grades[1] (%)	Grade 3 or 4 (%)	All Grades[1] (%)	Grade 3 or 4 (%)	All Grades[1] (%)	Grade 3 or 4 (%)	All Grades[1] (%)	Grade 3 or 4 (%)
Chemistry								
Increased AST	76	1.6	48	0	70	3.8	21	1.5
Increased ALT	75	1.6	39	3.2	63	0.8	18	1.5
Hyperglycemia[2]	37	3.2	48	3.2	30	0.8	39	1.5
Hypophosphatemia[3]	25	0	6	0	19	0.8	4.5	0
Increased ALP[4]	22	3.2	23	0	29	4.5	30	6
Hypocalcemia[5]	17	0	3.2	0	20	0	4.5	0
Hyponatremia[6]	16	1.6	16	0	16	2.3	7	1.5
Blood bilirubin increased[7]	14	4.8	6	3.2	20	3	10	6
Hyperkalemia[8]	14	1.6	10	0	-	-	-	-
Hypoalbuminemia[9]	14	0	10	0	20	0.8	9	0
Hypoglycemia[10]	11	0	6	0	-	-	-	-
Hypomagnesemia[11]	11	0	6	0	20	0.8	4.5	0
Hypokalemia[12]	10	1.6	3.2	0	20	2.3	10	1.5
Hematology								
Platelet count decreased[13]	37	0	19	0	55	1.5	13	1.5
Neutrophil count decreased[14]	27	1.6	6	0	36	3	6	0
Hemoglobin decreased[15]	25	1.6	32	0	30	2.3	19	0
Lymphocyte count decreased[16]	22	8	16	0	28	9	18	1.5
White blood cell count decreased[17]	19	1.6	3.2	0	37	3	4.5	0

[1] NCI CTCAE Version 5.0

[2] Includes hyperglycemia, blood glucose increased

[3] Includes hypophosphatemia, blood phosphorus decreased

[4] Includes blood alkaline phosphatase, blood alkaline phosphatase increased

[5] Includes hypocalcemia, blood calcium decreased, adjusted calcium decreased

[6] Includes hyponatremia, blood sodium decreased

[7] Includes blood bilirubin increased, hyperbilirubinemia

[8] Includes hyperkalemia, blood potassium increased

[9] Includes hypoalbuminemia, blood albumin decreased

[10] Includes hypoglycemia, blood glucose decreased

[11] Includes hypomagnesemia, blood magnesium decreased

[12] Includes hypokalemia, blood potassium decreased

[13] Includes platelet count decreased, thrombocytopenia

[14] Includes neutrophil count decreased, neutropenia

[15] Includes hemoglobin decreased, anemia

[16] Includes lymphocyte count decreased, lymphopenia

[17] Includes white blood cell count decreased, leukopenia

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 Product Information for nivolumab prior to initiation of treatment. For additional information on the safety profile of nivolumab monotherapy, please refer to the nivolumab Product Information.

In the 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 reactions (≥ 1%) were: diarrhoea, pneumonitis, pulmonary embolism, pneumonia, hyponatremia, pyrexia, adrenal insufficiency, vomiting and dehydration.

The most frequent adverse reactions (≥25%) were diarrhoea, fatigue, palmar-plantar erythrodysaesthesia syndrome, stomatitis, musculoskeletal pain, hypertension, rash, hypothyroidism, decreased appetite, nausea and 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 5, 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 5: Adverse drug reactions (ADRs) with cabozantinib in combination with nivolumab

MedDRA System Organ Class	Very Common	Common	Uncommon	Not known
Infections and infestations	upper respiratory tract infection[a]	pneumonia[b]		
Blood and lymphatic disorders		eosinophilia		
Immune system disorders		hypersensitivity (including anaphylactic reaction)	infusion related hypersensitivity reaction	
Endocrine disorders	hypothyroidism[c], hyperthyroidism,	adrenal insufficiency	hypophysitis, thyroiditis[d]	
Metabolism and nutrition disorders	decreased appetite	dehydration		
Nervous system disorders	Dysgeusia, dizziness[e], headache	peripheral neuropathy[f]	encephalitis autoimmune, Guillain-Barré syndrome, myasthenic syndrome	
Ear and labyrinth disorders		tinnitus		
Eye disorders		dry eye[g], blurred vision	uveitis	

MedDRA System Organ Class	Very Common	Common	Uncommon	Not known
Cardiac disorders		atrial fibrillation, tachycardia[h]	myocarditis	
Vascular disorders	hypertension[i]	thrombosis[j]	embolism arterial	
Respiratory, thoracic, and mediastinal disorders	Dysphonia, dyspnoea, cough[l]	pneumonitis[k], pulmonary embolism, epistaxis, pleural effusion		
Gastrointestinal disorders	diarrhoea, vomiting, nausea, constipation, stomatitis[m], abdominal pain[n], dyspepsia[o]	colitis, gastritis, oral pain, dry mouth, haemorrhoids	pancreatitis[p], small intestine perforation, glossodynia,	
Hepatobiliary disorders		hepatitis[q]		vanishing bile duct syndrome[r]
Skin and subcutaneous tissue disorders	palmar-plantar erythrodysaesthesia syndrome, rash[s], pruritus	alopecia, dry skin, erythema, hair colour change	psoriasis, urticaria	cutaneous vasculitis
Musculoskeletal and connective tissue disorders	musculoskeletal pain[t], arthralgia, muscle spasm	arthritis[u]	myopathy, osteonecrosis of the jaw, fistula	
Renal and urinary disorders	proteinuria	renal failure, acute kidney injury	nephritis	
General disorders and administration site conditions fatigue	fatigue[v], pyrexia, oedema[w]	pain, chest pain[x]		
Investigations[y]	increased ALT, increased AST, hypophosphataemia, hypocalcaemia, hypomagnesaemia, hyponatraemia, hyperglycaemia, lymphopaenia, increased	blood cholesterol increased, hypertriglyceridaemia		

MedDRA System Organ Class	Very Common	Common	Uncommon	Not known
	alkaline phosphatase, increased lipase, increased amylase, thrombocytopaenia, increased creatinine, anaemia, leucopoenia, hyperkalaemia, neutropaenia, hypercalcaemia, hypoglycaemia, hypokalaemia, increased total bilirubin, hypermagnesaemia, hypernatraemia, weight decreased			

Adverse reactions from clinical studies are presented using frequencies for investigator drug-related adverse events

[a] Upper respiratory tract infection is a composite term which includes nasopharyngitis, pharyngitis, rhinitis

[b] Pneumonia includes pneumonia necrotising

[c] Hypothyroidism includes primary hyperthyroidism

[d] Thyroiditis includes thyroiditis acute

[e] Dizziness includes dizziness postural, vertigo

[f] Peripheral neuropathy is a composite term which includes dysaesthesia, hypoaesthesia, hyperaesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy

[g] Dry eye includes xerophthalmia

[h] Tachycardia includes sinus tachycardia

[i] Hypertension includes blood pressure increased, blood pressure systolic increased

[j] 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

[k] Pneumonitis includes interstitial lung disease

[l] Cough includes productive cough

[m] Stomatitis is a composite term which includes mucosal inflammation, aphthous ulcer, mouth ulceration

[n] Abdominal pain includes abdominal discomfort, abdominal pain lower, abdominal pain upper

[o] Dyspepsia includes gastroesophageal reflux

[p] Pancreatitis includes pancreatitis acute

[q] Hepatitis includes autoimmune hepatitis

[r] With prior or concomitant immune checkpoint inhibitor exposure

[s] 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

[t] 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

[u] Arthritis includes autoimmune arthritis

[v] Fatigue includes asthenia

[w] Oedema includes generalised oedema, peripheral oedema, peripheral swelling

[x] Chest pain includes chest discomfort, non-cardiac chest pain

[y] 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 once daily as monotherapy in the pivotal studies in RCC following prior VEGF-targeted therapy, in treatment-naïve RCC, in HCC following prior systemic therapy, in DTC in patient refractory or not candidate to radioactive iodine (RAI) who have progressed during or after prior systemic therapy, in previously treated, locally advanced/unresectable or metastatic, well-differentiated pNET or epNET, or in patients who received CABOMETYX 40 mg once daily in combination with nivolumab in first-line advanced RCC (see Section 5.1 Pharmacodynamic properties – Clinical trials).

Gastrointestinal (GI) perforation

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

In the treatment-naïve RCC study (CABOSUN), GI perforations were reported in 2.6% (2/78) of cabozantinib-treated patients. Events were Grade 4 and 5.

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 combination with nivolumab in advanced RCC in first-line treatment (CA2099ER) the incidence of GI perforations was 1.3% (4/320) treated patients.

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 151 days.

Fatal perforations have occurred in the cabozantinib clinical program.

Hepatic encephalopathy

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%). Median time to onset was 14.3 weeks.

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

Diarrhoea
In the study in RCC following prior VEGF-targeted therapy (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 63.4% 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 63.8% (204/320) of treated patients; Grade 3-4 events in 6.9% (22/320). Median time to onset of all events was 12.6 weeks. Dose delay or reduction occurred in 24.4% (78/320) and discontinuation in 0.6% (2/320) of patients with diarrhoea, respectively.

Fistulas
In the study in RCC following prior VEGF-targeted therapy (METEOR), fistulas were reported in 1.2% (4/331) of cabozantinib-treated patients and included anal fistulas in 0.6% (2/331) cabozantinib-treated patients. One event was Grade 3; the remainder 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) 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. Median time to onset was 135 days.

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

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

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 80.5 days.

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 98.5 days.

In combination with nivolumab in advanced RCC in first-line treatment (CA2099ER) the incidence of ≥ Grade 3 haemorrhage was in 1.6% (5/320) of treated patients.

Fatal haemorrhages have occurred in the cabozantinib clinical program.

Posterior reversible encephalopathy syndrome (PRES)
No cases of PRES were reported in the METEOR, CABOSUN or 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 studies (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 (9.8%) and AST increased (7.9%) were observed. In patients with grade ≥ 2 increased ALT or AST (n=83): median time to onset was 2.3 months (range: 2.0 to 88.3 weeks), 28% received corticosteroids for median duration of 1.7 weeks (range: 0.9 to 52.3 weeks), and resolution to Grades 0-1 occurred in 89% with median time to resolution of 2.1 weeks (range: 0.4 to 83.6 weeks).

Among the 44 patients who were rechallenged with either nivolumab (n=11) or cabozantinib (n=9) monotherapy or with both (n=24), Grade ≥2 increased ALT or AST was observed in 2 patients receiving nivolumab, 2 patients receiving cabozantinib, and 7 patients receiving both nivolumab and cabozantinib. There were no Grade 5 hepatic events.

Hypothyroidism
In the study in RCC following prior VEGF-targeted therapy (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.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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.

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 study in medullary thyroid cancer patients. This effect was not associated with a change in cardiac wave form morphology or new rhythms. No cabozantinib-treated subjects in this study had a confirmed QTcF >500 ms, nor did any cabozantinib-treated subjects in the RCC, HCC, or NET studies (at a dose of 60 mg).

Clinical trials

Renal Cell Carcinoma (RCC)

Controlled 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 randomised, 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 CABOMETYX (N=330) or everolimus (N=328). Patients could have received other prior therapies, including cytokines, and antibodies targeting VEGF, the programmed death 1 (PD-1) receptor, or its ligands. Patients with treated brain metastases were allowed. Progression-free survival (PFS) was assessed by a blinded independent radiology review committee, and the primary analysis was conducted among the first 375 subjects 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 CABOMETYX and everolimus arms. The majority of the patients were male (75%), with a median age of 62 years. Seventy-one percent (71%) received only one prior VEGFR TKI; 41% of patients received sunitinib as their only prior VEGFR TKI. According to the Memorial Sloan Kettering Cancer Centre 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 CABOMETYX and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

A statistically significant improvement in PFS was demonstrated for CABOMETYX compared to everolimus (Figure 1 and Table 6). A planned interim analysis of OS was

conducted at the time of the PFS analysis and did not reach the interim boundary for statistical significance (HR=0.68 [0.51, 0.90], p=0.006). In a subsequent unplanned interim analysis of OS, a statistically significant improvement was demonstrated for patients randomised to CABOMETYX as compared with everolimus (median of 21.4 months vs. 16.5 months; HR=0.66 [0.53, 0.83], p=0.0003; Figure 2 and Table 7).

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

Objective response rate findings are summarised in Table 8**.**

Figure 1: Kaplan Meier curve for PFS by independent radiology review committee, in RCC subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy (Primary PFS analysis population - first 375 subjects randomised) (METEOR)

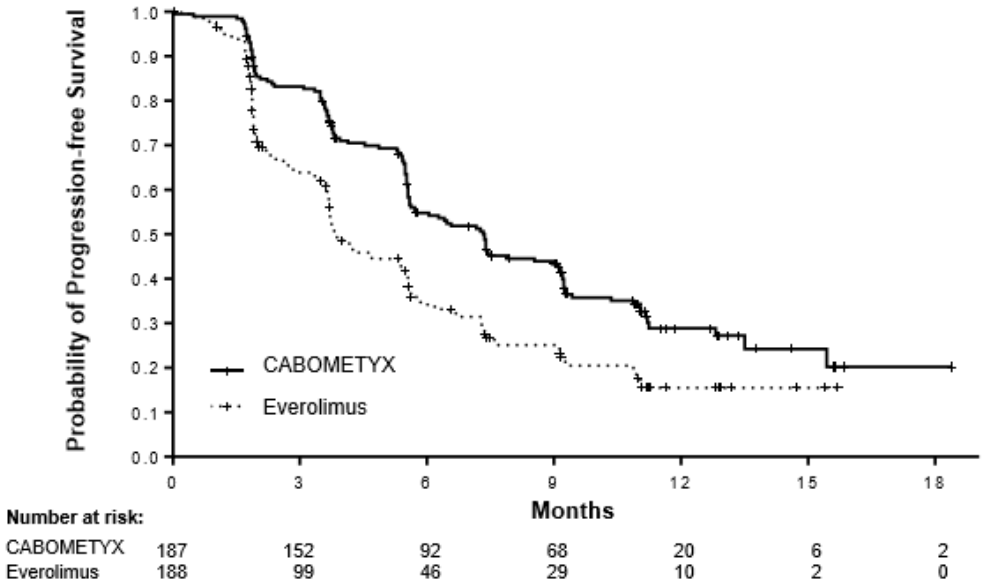


Table 6: Summary of PFS findings by independent radiology review committee in RCC subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy (METEOR)

	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)

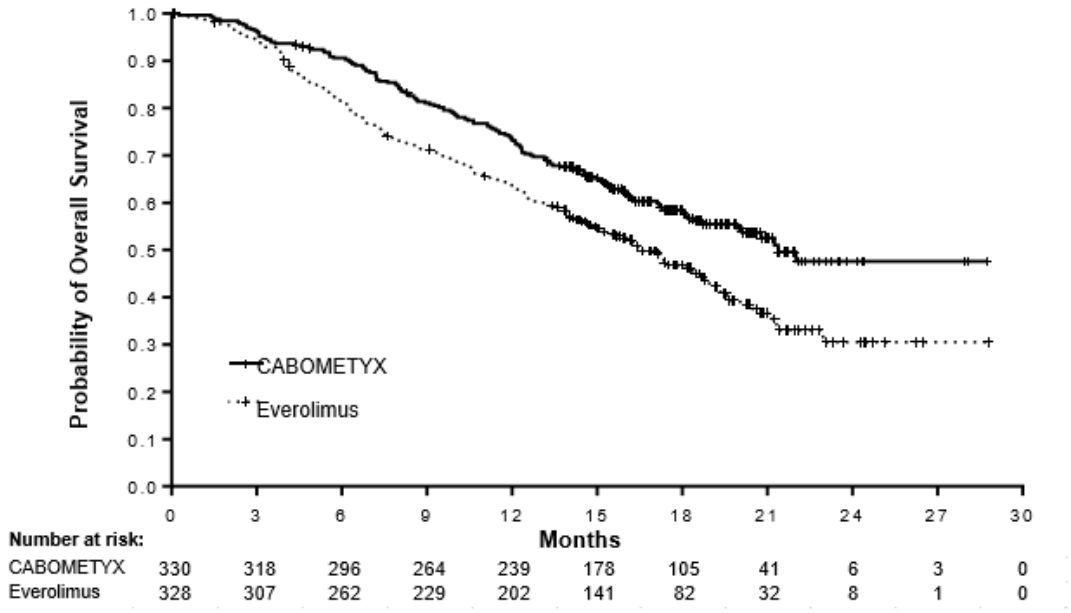


Table 7: Summary of OS findings in RCC subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy (METEOR)

	CABOMETYX	**Everolimus**
	N = 330	N = 328
Death n (%)	140 (42)	180 (55)
Median OS (95%CI), months	21.4 (18.7, NE)	16.5 (14.7, 18.8)
HR (95% CI), p-value[1]	0.66 (0.53, 0.83), p=0.0003	

[1] Stratified log-rank test

Table 8: 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 (METEOR)

	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

Controlled study in treatment-naïve RCC 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 CABOMETYX (N=79) or sunitinib (N=78). Patients had to have intermediate or poor risk disease as defined by the International Metastatic RCC Database Consortium (IMDC) risk group categories. Patients were stratified by IMDC risk group and presence of bone metastases (yes/no). Approximately 75% of patients had a nephrectomy prior to onset of treatment.

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

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

The baseline demographic and disease characteristics were similar between the CABOMETYX and sunitinib arms. The majority of the patients were male (78%) with a median age of 62 years. Patient distribution by IMDC risk groups was 81% intermediate (1-2 risk factors) and 19% poor (≥3 risk factors). Most patients (87%) had ECOG performance status of 0 or 1; 13% had an ECOG performance status of 2. Thirty-six percent (36%) of patients had bone metastases.

A statistically significant improvement in PFS as retrospectively assessed by a blinded Independent Radiology Committee (IRC) was demonstrated for CABOMETYX compared to sunitinib (Figure 3 and Table 9). The results from the Investigator determined analysis and IRC-determined analysis of PFS were consistent.

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

CABOMETYX treatment was associated with a trend for longer survival compared to sunitinib (Table 9). The study was not powered for the OS analysis and the data are immature.

Objective response rate (ORR) findings are summarized in Table 9.

Figure 3: Kaplan Meier curve for progression-free survival by IRC in treatment-naïve RCC subjects (CABOSUN)

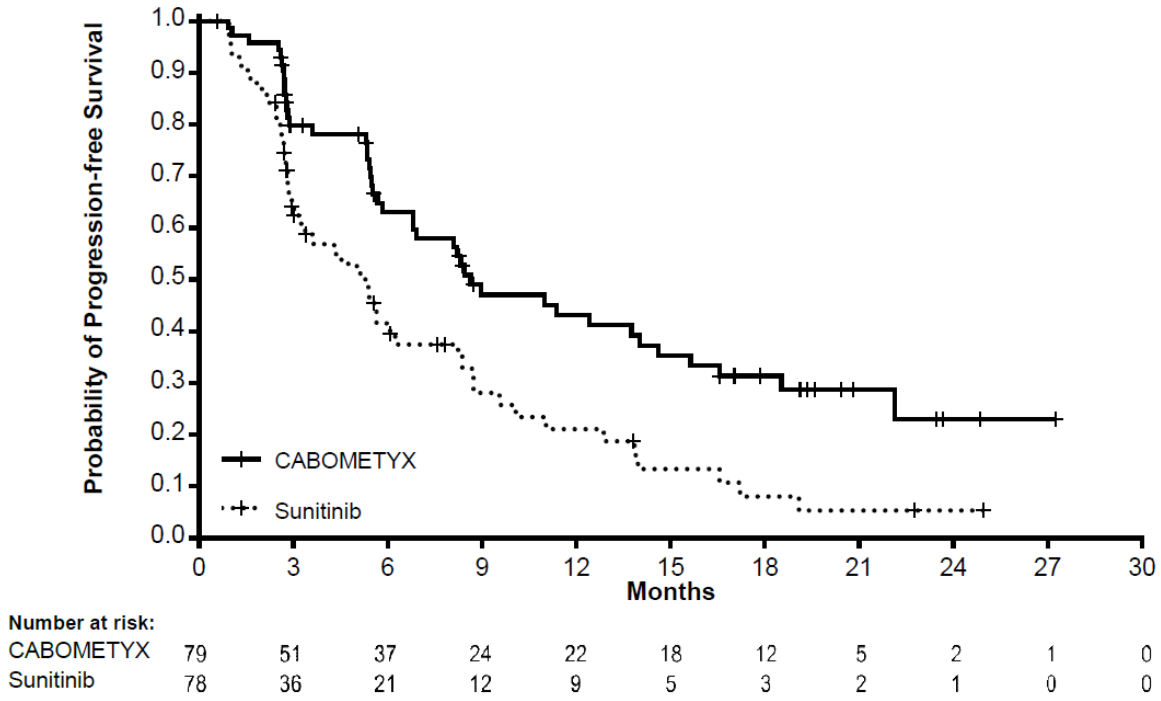


Table 9: Efficacy results in treatment-naïve RCC (ITT population, CABOSUN)

	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 [a,b]	0.48 (0.32, 0.73)	
Two-sided log-rank p-value: stratified [a]	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 [a]	p=0.0042	
Overall Survival		
Median OS in months (95% CI)	30.3 (14.6, NE)	21.0 (16.3, 27.0)
HR (95% CI); stratified [b,c]	0.74 (0.47, 1.14)	
Objective Response Rate n (%) by IRC		
Complete responses	0	0
Partial responses	16 (20)	7 (9)
ORR (partial responses only)	16 (20)	7 (9)
Stable disease	43 (54)	30 (38)
Progressive Disease	14 (18)	23 (29)
Objective Response Rate n (%) by Investigator		
Complete responses	1 (1)	0
Partial responses	25 (32)	9 (12)
ORR (partial responses only)	26 (33)	9 (12)
Stable disease	34 (43)	29 (37)
Progressive Disease	14 (18)	19 (24)

[a] in accord with EU censoring

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

[c] Estimated using the Cox proportional hazard model adjusted for stratification factors per IxRS. Hazard ratio < 1 indicates progression-free survival in favor of cabozantinib

Controlled study of cabozantinib in combination with nivolumab in previously untreated RCC patients (CA2099ER)

The safety and efficacy of cabozantinib 40 mg in combination with nivolumab 240 mg 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) $\geq$ 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).

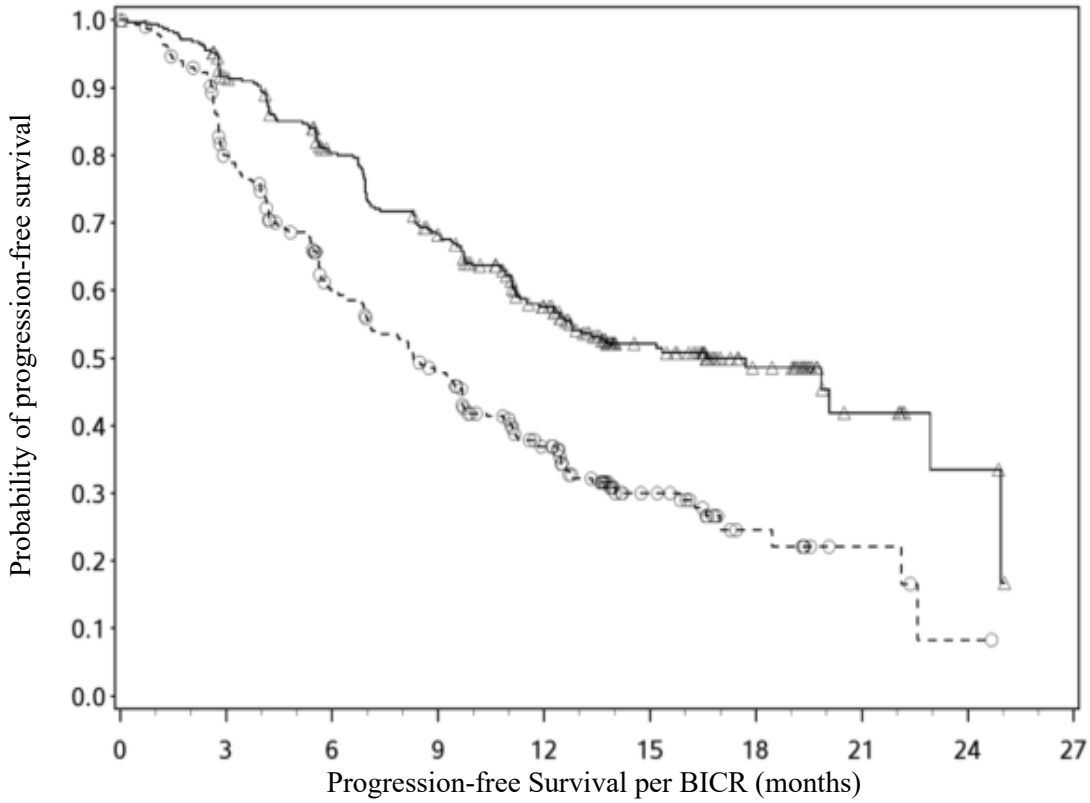
Baseline characteristics were generally balanced between the two groups. The median age was 61 years (range: 28-90) with 38.4% ≥ 65 years of age and 9.5% ≥ 75 years of age. The majority of patients were male (73.9%) and white (81.9%), and 23.2% and 76.5% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. 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. Patient distribution by IMDC risk categories was 22.6% favourable, 57.6% intermediate, and 19.7% poor.

The primary efficacy outcome measure was PFS as determined by a BICR. Additional efficacy measures included OS and ORR as key secondary endpoints for hierarchical statistical testing.

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.

The Kaplan Meier curves for PFS and OS (with a minimum follow up of 10.6 months) in all risk patients are shown in Figure 4 and Figure 5.

Figure 4: Kaplan Meier curves of PFS (CA2099ER)



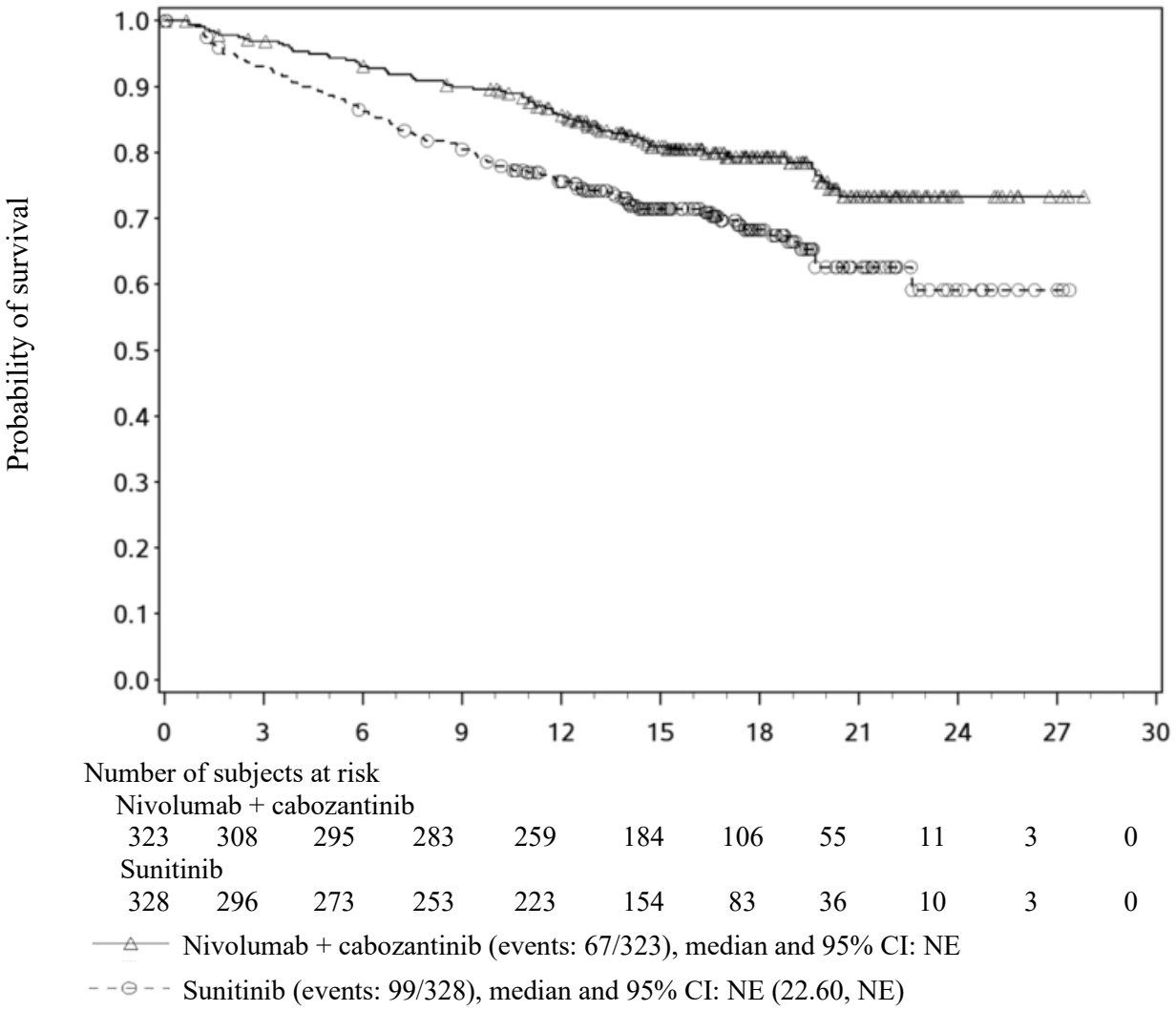
Number of subjects at risk

323	279	234	196	144	77	35	11	4	0
328	228	159	122	79	31	10	4	1	0

Nivolumab + cabozantinib (events: 142/323), median and 95.0% CI: 16.59 (12.45, 24.94)

Sunitinib (events: 191/328), median and 95.0% CI:8.31 (6.97, 9.69)

Figure 5: Kaplan Meier curves of OS (CA2099ER)



Efficacy results from the primary analysis (minimum follow-up 10.6 months) are shown in Table 10.

Table 10: Efficacy results of cabozantinib in combination with nivolumab in previously untreated RCC (CA2099ER)

	nivolumab + cabozantinib (n = 323)	**sunitinib (n = 328)**
Progression-free survival		
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)
Overall survival		
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)
At 9 months	89.9 (86.0, 92.8)	80.5 (75.7, 84.4)
Confirmed objective response (BICR)[f]	180 (55.7%)	89 (27.1%)
(95% CI)	(50.1, 61.2)	(22.4, 32.3)
Difference in ORR (95% CI)[f]	28.6 (21.7, 35.6)	
p-value[g]	< 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 nivolumab and cabozantinib over sunitinib.

[b] Based on Kaplan-Meier estimates.

[c] Log-rank test stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumor expression (≥1% versus <1% or indeterminate) and region (US/Canada/W Europe/N Europe, ROW) as entered in the IRT.

[d] 2-sided p-values from stratified regular log-rank test.

[e] Boundary for statistical significance p-value <0.0111.

[f] CI based on the Clopper and Pearson method.

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

NE = non-estimable

PFS, OS, ORR benefit was observed in the cabozantinib in combination with nivolumab arm vs. sunitinib regardless of tumour PD L1 expression.

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).

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 randomised (2:1) to receive CABOMETYX (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 CABOMETYX and placebo arms and are shown below for all 707 randomised patients:

Male: 82%
Median age: 64 years.
Caucasian: 56%, Asian: 34%
ECOG performance status (PS) 0: 53% or ECOG PS 1: 47%.
Child Pugh A: 99%, Child Pugh B: 1 %

Aetiology for HCC included 38% hepatitis B virus (HBV), 21% hepatitis C virus (HCV), 40% other (neither HBV nor HCV).
Presence of macroscopic vascular invasion and/ or extra-hepatic tumour spread:78%.
Alfa-fetoprotein (AFP) levels ≥400 µg/L: 41%.
Loco-regional transarterial embolisation or chemoinfusion procedures: 44%
Radiotherapy prior to cabozantinib treatment: 37%
Median duration of sorafenib treatment: 5.32 months

Seventy-two percent (72%) of patients had received one and 28% had received 2 prior systemic therapy regimens for advanced disease.

A statistically significant improvement in OS was demonstrated for CABOMETYX compared to placebo (Table 11 and Figure 6).

PFS and ORR findings are summarized in Table 11.

Table 11: Efficacy results in HCC (ITT population, CELESTIAL)

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

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

Figure 6: Kaplan-Meier curve of overall survival (CELESTIAL)

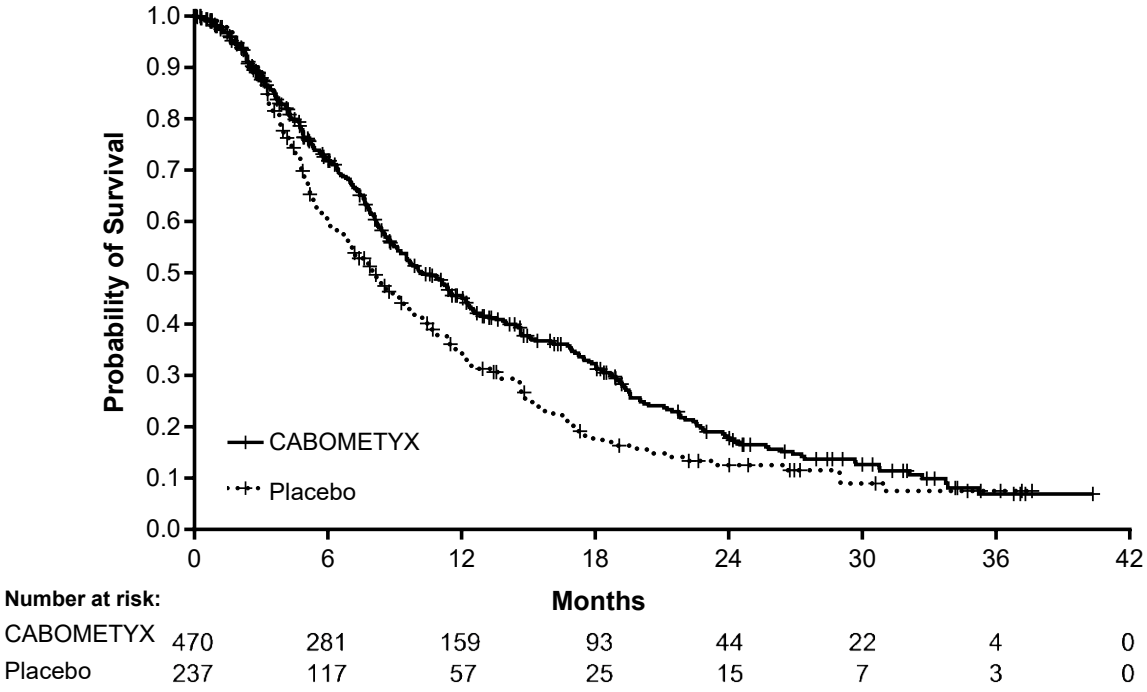
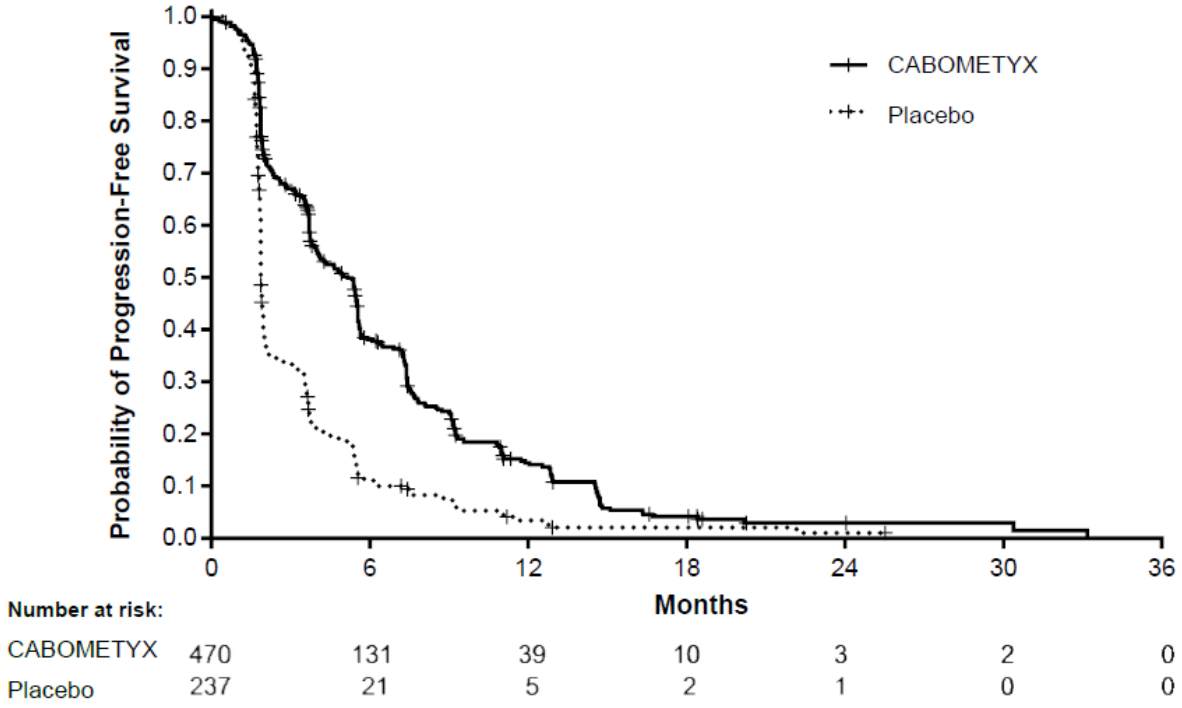


Figure 7: Kaplan Meier curve for progression-free survival (CELESTIAL)



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 CABOMETYX 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)

Controlled study in patients who have received prior systemic therapy and refractory to radioactive iodine (COSMIC-311)

The safety and efficacy of CABOMETYX was evaluated in COSMIC-311, a randomised (2:1), double-blind, placebo-controlled, multicentre trial in patients with radioiodine refractory differentiated thyroid cancer who have progressed after VEGFR-targeting therapy. Patients were randomised (N=258) to receive CABOMETYX 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 CABOMETYX 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 (median follow up 6.2 months) included 187 randomised patients, 125 to CABOMETYX 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 trial demonstrated a statistically significant improvement in PFS (median follow up 6.2 months) for patients randomised to CABOMETYX compared with placebo. Efficacy results are summarised in

Table 12. The trial did not demonstrate a statistically significant improvement in ORR for patients randomised to CABOMETYX (n=67) compared with placebo (n=33) (15% vs. 0%, p=0.0281). An updated analysis of PFS and OS was performed with median follow up of 10.1 months.

Table 12: Efficacy Results from COSMIC-311

	Primary Analysis		**Updated Analysis[1]**	
	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)
Median PFS in months (95% CI)	NR (5.7, NE)	1.9 (1.8, 3.6)	11.0 (7.4, 13.8)	1.9 (1.9, 3.7)
Hazard Ratio (95% CI)[2]	0.22 (0.14, 0.35)		0.22 (0.15, 0.31)	
p-value[3]	< 0.0001			
Overall Response Rate (95% CI)				
Overall Response, % (95% CI) [4, 5]	15% (7%, 26%)	0% (0.0%, 11%)	18% (10%, 29%)	0% (0.0%, 11%)
p-value[6]	0.0281			

CI, confidence interval; NR, not reached; NE, not evaluable

1 No formal statistical testing was conducted at the time of the updated analysis

2 Estimated using the Cox proportional-hazard model

3 Log-rank test stratified by receipt of prior lenvatinib (yes vs no) and age (≤ 65 years vs > 65 years)

4 All responses were partial responses

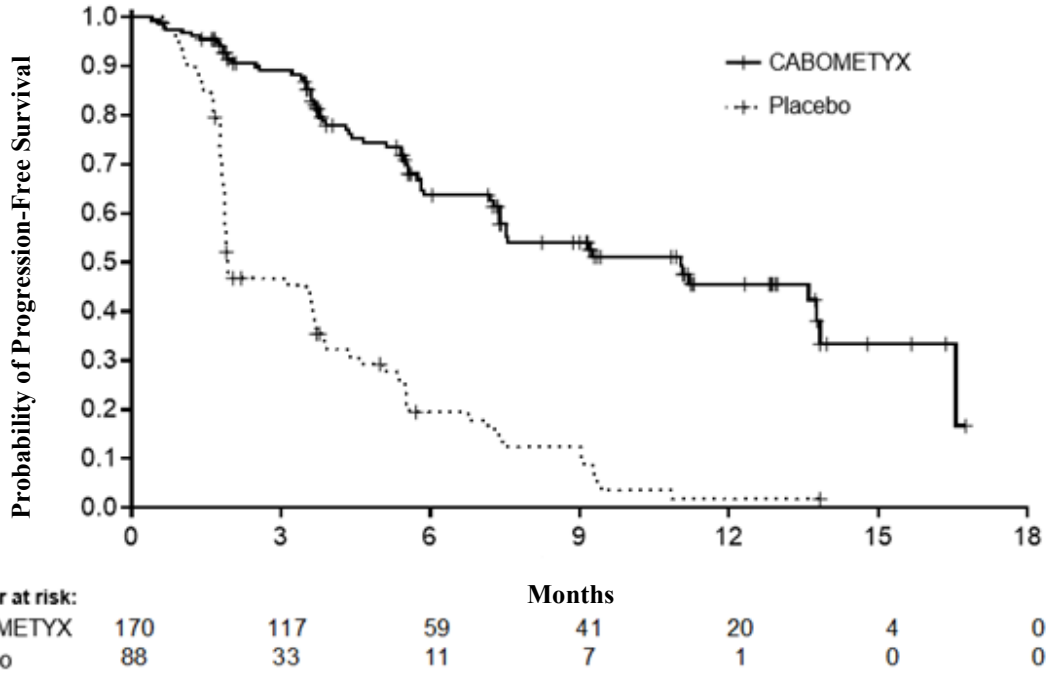
5 The analysis population overall response rate was the first 100 randomised patients (67 in the CABOMETYX arm, and 33 in the placebo arm)

6 Fisher's exact test compared to an alpha boundary of 0.01

Exploratory analyses of PFS in the ITT population have also shown consistent results in favour of CABOMETYX compared to placebo across different subgroups according to prior lenvatinib, prior sorafenib, number of prior VEGFR, age (≤ 65 years or > 65 years), histology type (papillary or follicular).

No clinically significant differences in patient-reported outcomes were observed between patients given CABOMETXY and patients given placebo.

Figure 8: Kaplan-Meier Curve of Progression-Free Survival in COSMIC-311 (Updated Analysis, N=258)



Neuroendocrine Tumours (NET)

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

The safety and efficacy of CABOMETYX were evaluated in CABINET, a multicenter, randomized (2:1), double-blinded placebo-controlled phase 3 study in adult patients with locally advanced/unresectable or metastatic well-differentiated pNET (Cabozantinib: N = 64; placebo: N = 31) and epNET (Cabozantinib: N = 134; placebo: N = 69) that have progressed on at least one prior systemic therapy not including a somatostatin analogue.

Eligible patients were required to have been previously treated with at least one prior therapy (pNET: everolimus, sunitinib, or lutetium Lu 177 dotatate; epNET: everolimus or lutetium Lu 177 dotatate), other than somatostatin analogues. Patients with active brain metastases or cranial epidural disease, and those who had prior treatment with cabozantinib were excluded. The study also excluded patients with clinically significant gastrointestinal (GI) bleeding, GI abnormalities, and tumour with invasion into the GI tract that may increase the risk for GI bleeding or perforation, and patients with tumour invading or encasing major blood vessels.

Patients with pNET and epNET were allocated into two separate cohorts which were randomized and analyzed independently.

Subjects 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 blinded independent radiology review committee (BIRC) using Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 with stratification factors at randomization as follow:

- epNET: Concurrent Somatostatin Analogs (SSA) and primary tumour site (midgut GI 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. Survival status was determined at scheduled visits and every 6 months after the post-treatment follow-up visit until death or 8 years after registration in the study.

As recommended by the Data and Safety Monitoring Board, the CABINET study was unblinded prior to the final prespecified efficacy analysis and all patients remaining on the placebo arm were permitted to crossover to treatment with cabozantinib. At the time of unblinding, the trial demonstrated a statistically significant improvement in PFS assessed by BIRC for cabozantinib compared to placebo.

epNET cohort:

Baseline demographics and disease characteristics were similar between treatment arms and are shown below.

In both treatment arms, the median age was 66.0 years, with 38% (cabozantinib) and 48% (placebo) of patients respectively being ≥65 years old. Most subjects were female (74 [55%] cabozantinib, 31 [45%] placebo) and White (115 [86%] cabozantinib, 55 [80%] placebo). Most patients in this cohort had a histologic type of carcinoid tumour (63% cabozantinib, 78% placebo). Primary site of origin was: midgut/unknown primary site in 47% (cabozantinib) and 41% (placebo); non-midgut GI/lung/other known primary site not listed in 50% (cabozantinib) and 55% (placebo). Approximately half of the patients had non-functional tumour: 56% (cabozantinib), 49% (placebo). The percentage of patients with tumour grade 1/2/3 was: 28%/64%/6% (cabozantinib), and 22%/70%/7.2% (placebo). The status of the primary tumour was primarily either resected with no residual tumour (34% cabozantinib, 45% placebo), resected with residual tumour (19% in both treatment arms) or unresected (30% cabozantinib, 28% placebo). The median time from initial diagnosis of the primary tumour to randomization was 64.7 months in the cabozantinib arm and 75.9 months in the placebo arm. ECOG performance status was: 0/1/2 in 37%, 63% and 0.7% (cabozantinib) and 46%, 52% and 1.4% (placebo). All patients had metastatic disease.

All patients in both treatment arms received prior non-radiation systemic anticancer therapy, and most patients (93%) in both treatment arms had received a prior SSA. The median number of prior systemic anticancer regimens excluding SSA was 2 in both treatment arms (ranging from 1 to 5 in the cabozantinib arm and 1 to 6 in the placebo arm);

74% (cabozantinib) and 78% (placebo) of patients respectively received ≤2 prior systemic anticancer treatment regimens. Excluding SSAs, the most frequently reported prior therapies were everolimus (72% cabozantinib, 64% placebo) and Lu-177 dotatate (60% cabozantinib, 59% placebo). In terms of stratification factors, 54% (cabozantinib) and 62% (placebo) had concurrent SSA use.

Median follow up was 23 months for both arms. Per BIRC assessments of progression and response with a cutoff date of 24 August 2023, PFS events occurred for 71 patients (53%) in the cabozantinib arm and 40 patients (58%) in the placebo arm. The Kaplan-Meier estimate of median PFS was 8.5 months (95% CI: 7.5, 12.5) in the cabozantinib arm compared with 4.0 months (95% CI: 3.0, 5.7) in the placebo arm. These results showed a statistically significant treatment effect, demonstrating a 62% reduction in the risk of disease progression or death in the cabozantinib arm compared with the placebo arm, with a stratified HR of 0.38 (95% CI: 0.25, 0.58; stratified 2-sided $p < 0.0001$).

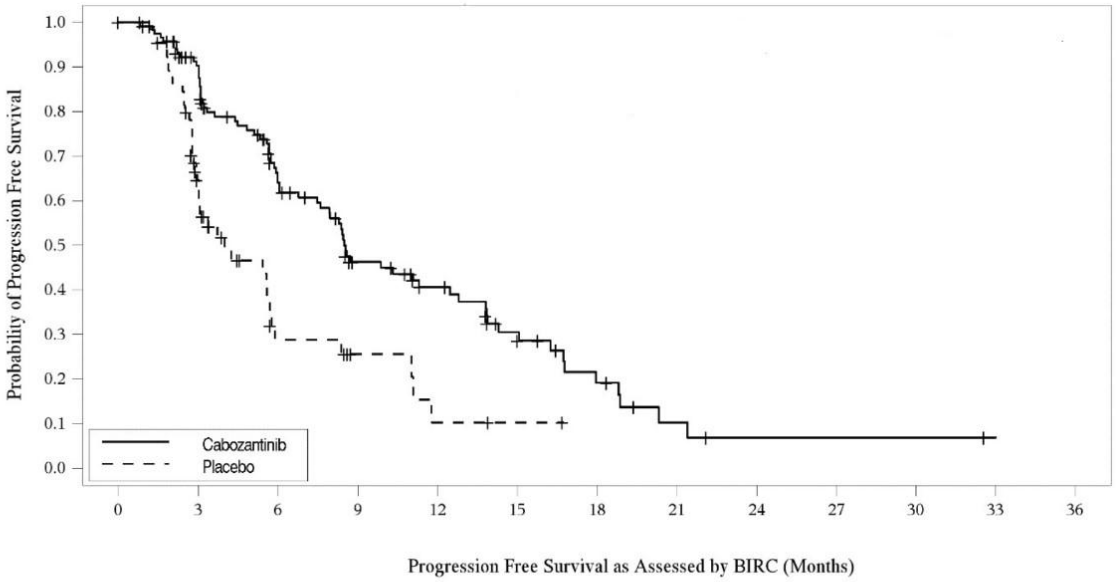
Table 13 Efficacy Results in epNET Cohorts from CABINET Study

	CABOMETYX (N=134)	**Placebo (N=69)**
Progression-Free Survival (PFS) [1]		
Number of Events (n/%)	71 (53)	40 (58)
Median PFS in months (95% CI)	8.5 (7.5, 12.5)	4.0 (3.0, 5.7)
Hazard Ratio (95% CI)	0.38 (0.25, 0.58)	
p-value	< 0.0001	
Objective Response Rate (ORR) [1]		
ORR[1] %	5.2	0
(95% CI), %	2.1, 10.5	0, 5.2
p-value	0.0524	
Duration of Response (DOR) [1]		
Median DOR (95% CI) (months)	8.26 (4.47, NE)	NE

CI, confidence interval; NE, not evaluable

[1] As per criteria by BIRC (Blinded Independent Review Committee)

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



Number of subjects at risk

Cabozantinib	134	96	58	35	26	16	8	3	1	1	1	0	0
Placebo	69	32	9	5	2	1	0	0	0	0	0	0	0

An updated OS analysis was conducted when 123 deaths were observed. OS data were not mature with 83 (63%) deaths in cabozantinib arm and 40 (60%) deaths in placebo arm (OS HR=1.05 [95% CI: 0.71, 1.54]). Thirty-seven percent of placebo arm patients crossed over to open label cabozantinib, which may impact the OS endpoint.

pNET cohort:

Baseline demographics and disease characteristics were similar between treatment arms and are shown below.

The median age was 59.5 years (range: 29-79 years) in the cabozantinib arm and 64.0 years (range: 39-79 years) in the placebo arm, with 38% (cabozantinib) and 48% (placebo) being ≥ 65 years of age. Most patients were male (58% in each treatment arm) and White (84% cabozantinib, 81% placebo). The majority of patients had non-functional tumour: 75% (cabozantinib), 71% (placebo). The percentage of patients with tumour grade 1/2/3 was: 22%/61%/13% (cabozantinib) and 23%/61%/9.7% (placebo). The status of the primary tumour was primarily either unresected (41% cabozantinib, 52% placebo) or resected with no residual tumour (33% cabozantinib, 32% placebo). The median time from initial diagnosis of the primary tumour to randomization was 85.7 months in the cabozantinib arm and 86.1 months in the placebo arm. Most patients (98% cabozantinib, 94% placebo) had metastatic disease, and the most common metastatic sites were liver (98% cabozantinib, 94% placebo) and nodal (45% cabozantinib, 55% placebo). Most patients in both treatment arms (98% cabozantinib, 97% placebo) had received prior SSA. The median number of prior

systemic anticancer regimens excluding SSA was 3.0 (range: 1-8) in the cabozantinib arm and 2.0 (range: 1-7) in the placebo arm; 49% (cabozantinib) and 61% (placebo) of patients respectively had ≤2 prior systemic anticancer regimens. The most frequently reported prior therapies, excluding SSAs, were everolimus (80% cabozantinib, 81% placebo), temozolomide with or without capecitabine (67% cabozantinib, 52% placebo), and Lu-177 dotatate (59% cabozantinib, 58% placebo). Prior cytotoxic chemotherapy was received by 69% of patients in the cabozantinib arm, and 58% of patients in the placebo arm. ECOG performance status was: 0/1/2 in 55%, 44% and 1.6 % respectively (cabozantinib) and 48%, 52% and 0% (placebo). In terms of stratification factors, 56% (cabozantinib) and 55% (placebo) had concurrent SSA use; 28% (cabozantinib) and 23% (placebo) had prior sunitinib therapy.

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, PFS events had occurred for 32 patients (50%) in the cabozantinib arm and 25 patients (81%) in the placebo arm. The Kaplan-Meier median PFS was 13.8 months (95% CI: 8.9, 17.0) in the cabozantinib arm compared with 4.5 months (95% CI: 3.0, 5.8) in the placebo arm.

These results showed a statistically significant treatment effect, demonstrating a 77% reduction in the risk of disease progression or death in the cabozantinib arm compared with the placebo arm, with a stratified HR of 0.23 (95% CI: 0.12, 0.42; stratified 2-sided $p < 0.0001$).

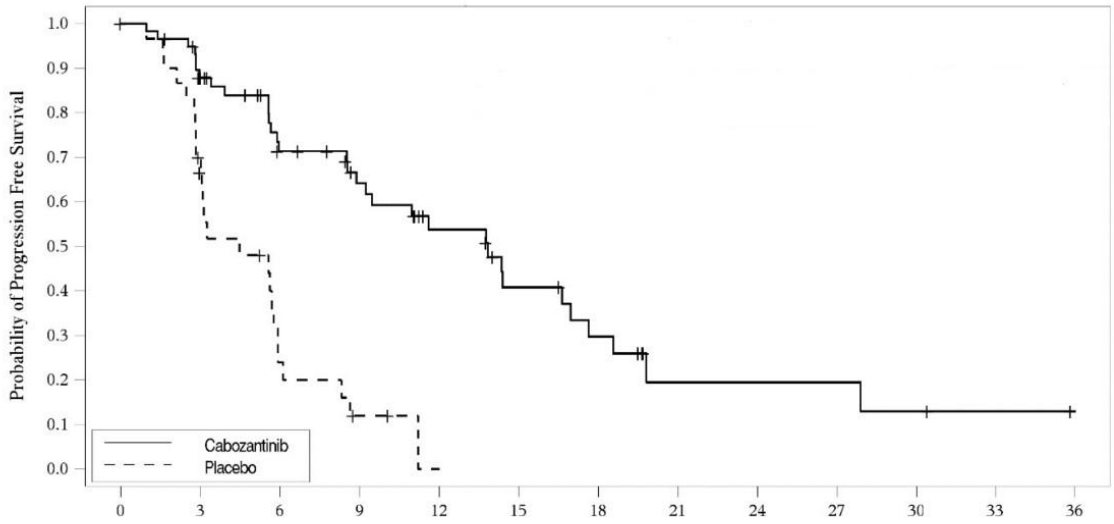
Table 14 Efficacy Results in pNET Cohorts from CABINET Study

	CABOMETYX (N=64)	**Placebo (N=31)**
Progression-Free Survival (PFS) [1]		
Number of events (n/%)	32 (50)	25 (81)
Median PFS in months (95% CI)	13.8 (8.9, 17.0)	4.5 (3.0, 5.8)
Hazard Ratio (95% CI)	0.23 (0.12, 0.42)	
p-value	< 0.0001	
Objective Response Rate (ORR) [1]		
ORR,%	19	0
(95% CI), %	10.1, 30.5	0, 11.2
p-value	0.0115	
Duration of Response (DOR) [1]		
Median DOR (95% CI) (months)	11.2 (5.8, NE)	NE

CI, confidence interval; NE, not evaluable

[1] As per criteria by BIRC (Blinded Independent Review Committee)

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



Number of subjects at risk

Cabozantinib	64	49	33	26	18	12	8	3	3	3	2	1	0
Placebo	31	20	6	2	0	0	0	0	0	0	0	0	0

An updated OS analysis was conducted when 49 deaths were observed. OS data were not mature with 32 (48%) deaths in cabozantinib arm and 17 (52%) deaths in placebo arm (OS HR=1.01 [95% CI: 0.55, 1.83]). Fifty-two percent of placebo arm patients crossed over to open label cabozantinib, which may impact the OS endpoint.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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

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

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

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

Distribution

Cabozantinib is highly protein bound in vitro in human plasma (≥ 99.7%). Based on the population pharmacokinetic (PK) model, the volume of distribution of the central compartment (Vc/F) was estimated to be 212 L. Protein binding was not altered in subjects with mild or moderately impaired renal or hepatic function.

Metabolism

Cabozantinib was metabolised *in vivo*. Four metabolites were present in plasma at exposures (AUC) greater than 10% of parent: cabozantinib-N-oxide, cabozantinib amide cleavage product, cabozantinib monohydroxy sulfate, and 6-desmethyl amide cleavage product sulfate. Two non-conjugated metabolites (cabozantinib -N-oxide and cabozantinib 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, neutralizing antibodies to CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation. A neutralizing antibody to CYP2C9 showed a minimal effect on cabozantinib metabolite formation (i.e., a <20% reduction).

Excretion

In a population PK analysis of cabozantinib using data collected from 1883 patients and 140 healthy volunteers following oral administration 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 2.8 L/hr. Within a 48-day collection period after a single dose of 14C-cabozantinib in healthy volunteers, approximately 81% of the total administered radioactivity was recovered with 54% in faeces and 27% in urine.

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 plasma cabozantinib, C_{max} and $AUC_{0\text{-}inf}$ were 19% and 30% higher, for subjects with mild renal impairment (90% CI for C_{max} 91.60% to 155.51%; $AUC_{0\text{-}inf}$ 98.79% to 171.26%) and 2% and 6-7% higher (90% CI for C_{max} 78.64% to 133.52%; $AUC_{0\text{-}inf}$ 79.61% to 140.11%), for subjects with moderate renal impairment compared to

subjects with normal renal function. 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

The dosing regimen for paediatric patients with DTC is based on simulation performed with the population pharmacokinetic analysis done in adult patients with DTC, by considering weight allometric scaling.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Cabozantinib has shown no mutagenic or clastogenic potential in a standard battery of genotoxicity assays (bacterial reverse mutation assay, chromosomal aberration assay using human lymphocytes and a mouse micronucleus test).

Carcinogenicity

The carcinogenic potential of cabozantinib has been evaluated in two species: rasH2 transgenic mice and Sprague-Dawley rats. Cabozantinib was not carcinogenic in the 26-week carcinogenicity study in rasH2 transgenic mice at doses ≤15 mg/kg/day, resulting in exposures approximately 4 times the human AUC at the recommended clinical dose of 60 mg/day. 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 of the adrenal medulla in both sexes at doses ≥0.1 mg/kg/day, resulting in 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet content
Microcrystalline cellulose
Lactose
Hyprolose
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

Film-coating
Hypromellose
Titanium dioxide
Triacetin
Iron oxide yellow

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25˚C

6.5 NATURE AND CONTENTS OF CONTAINER

CABOMETYX 20 mg film-coated tablets are available as a pack size of 30 film-coated tablets in a HDPE bottle with a polypropylene child-resistant closure and three silica gel desiccant canisters.

CABOMETYX 40 mg film-coated tablets are available as a pack size of 30 film-coated tablets in a HDPE bottle with a polypropylene child-resistant closure and three silica gel desiccant canisters.

CABOMETYX 60 mg film-coated tablets are available as a pack size of 30 film-coated tablets in a HDPE bottle with a polypropylene child-resistant closure and three silica gel desiccant canisters.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

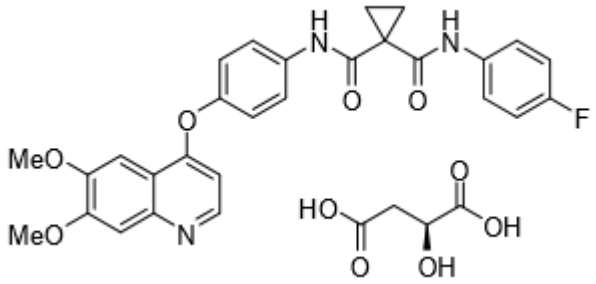
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

CABOMETYX contains the (S)-malate salt of cabozantinib, a kinase inhibitor. Cabozantinib (S)-malate is described chemically as N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate.

Cabozantinib (S)-malate is a white to off-white, non-hygroscopic, crystalline substance. It is practically insoluble above pH of 4 and in water.

The molecular formula is $C_{28}H_{24}FN_3O_5 \cdot C_4H_6O_5$ and the molecular weight is 635.6 Daltons as malate salt.



CAS number

CAS Number: 1140909-48-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Ipsen Pty Ltd
Level 5
627 Chapel Street
South Yarra Victoria 3141

Telephone: 1800 317 033

9 DATE OF FIRST APPROVAL

19 January 2018

10 DATE OF REVISION

18 July 2025

Summary table of changes

Section changed	Summary of new information
4.1	Addition of new indication for Neuroendocrine Tumours
4.4	Addition of precaution for treatment of Neuroendocrine Tumours
4.8	Addition of safety data for Neuroendocrine Tumours
5.1	Clinical trials – Addition of text from CABINET study of Neuroendocrine Tumours