▼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 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.

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

4.2 DOSE AND METHOD OF ADMINISTRATION

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

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

Management of suspected adverse drug reactions may require temporary treatment interruption and/or dose reduction of CABOMETYX therapy (see Table 1 and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). When dose reduction is necessary, it is recommended to reduce to 40 mg daily, and then to 20 mg daily. Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities. Dose reductions are recommended for events that, if persistent, could become serious or intolerable.

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

Table 1: Recommended CABOMETYX dose modifications for adverse reactions

Adverse reaction and severity	**Treatment Modification**
Grade 1 and Grade 2 adverse reactions which are tolerable and easily managed	Dose adjustment is usually not required. 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.

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).

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 and 5.2). There is no clinical experience in patients with severe hepatic impairment (Child Pugh C) so, cabozantinib is not recommended for use in these patients (see section 5.2).

Patients with cardiac impairment

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

Paediatric population

The safety and efficacy of cabozantinib in children and adolescents aged <18 years have not yet been established. No data are available.

Method of administration

CABOMETYX is for oral use. The tablets should be swallowed whole and not crushed. Patients should be instructed to not eat anything for at least 2 hours before 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).

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.

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.

Hepatic effects
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).

Cabozantinib is eliminated mainly via the hepatic route. Closer monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment (see also sections 4.2 and 5.2). A higher relative proportion of patients with moderate hepatic impairment (Child-Pugh B) developed hepatic encephalopathy with cabozantinib treatment. 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). 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.

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.

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, 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
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. Cabozantinib treatment should be stopped until complete resolution of ONJ.

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

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.

Reversible posterior leukoencephalopathy syndrome
Reversible Posterior Leukoencephalopathy Syndrome (RPLS), also known as Posterior Reversible Encephalopathy Syndrome (PRES), has been observed with cabozantinib. This syndrome should be considered in any patient presenting with multiple symptoms, including

seizures, headache, visual disturbances, confusion or altered mental function. Cabozantinib treatment should be discontinued in patients with RPLS.

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

Biochemical laboratory test abnormalities
Cabozantinib has been associated with an increased incidence of electrolyte abnormalities (including hypo- and hyperkalaemia, hypomagnesaemia, hypocalcaemia, hyponatremia). 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 efficacy of cabozantinib in children and adolescents aged <18 years have not yet been established. No data are available.

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.

Summary of safety profile

The most common serious adverse drug reactions in the RCC population (≥1% incidence) are diarrhoea**,** hypertension, dehydration, hyponatraemia, nausea, decreased appetite, embolism, fatigue, hypomagnesaemia, 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, hypertension, fatigue, AST increased, ALT increased, nausea, decreased appetite, PPES, dysgeusia, platelet count decreased, stomatitis, anaemia, vomiting, weight decreased, dyspepsia, and constipation. Hypertension was observed more frequently in the treatment naïve RCC population (67%) compared to RCC patients following prior VEGF-targeted therapy (37%).

The most common serious adverse drug reactions in the HCC population (≥1% incidence) are hepatic encephalopathy, palmar-plantar erythrodysaesthesia syndrome, asthenia and diarrhoea. The most frequent adverse reactions of any grade (experienced by at least 25% of patients) in the HCC population included diarrhoea, palmar-plantar erythrodysaesthesia syndrome, fatigue, decreased appetite hypertension and nausea.

Tabulated list of adverse reactions

Adverse reactions are listed in Table 2 according to MedDRA System Organ Class and frequency categories. Frequencies are based on all grades and defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); not known (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 in patients treated with cabozantinib

MedDRA System Organ Class	Very Common	Common	Uncommon	Not Known
Infections and infestations		abscess		
Blood and lymphatic disorders	anaemia	thrombocytopenia, neutropenia	lymphopenia	
Endocrine disorders	hypothyroidism			
Metabolism and nutrition disorders	decreased appetite, hypomagnesaemia, hypokalaemia	dehydration, hypoalbuminaemia, hypophosphataemia, hyponatraemia, hypocalcaemia,		

		hyperkalaemia, hyperbilirubinemia, hyperglycaemia, hypoglycaemia		
Nervous system disorders	dysgeusia, headache, dizziness	peripheral sensory neuropathy	convulsion	cerebrovascular accident
Ear and labyrinth disorders		tinnitus		
Cardiac disorders				myocardial infarction
Vascular disorders	hypertension, haemorrhage	venous thrombosis, arterial thrombosis		
Respiratory, thoracic, and mediastinal disorders	dysphonia, dyspnoea, cough	pulmonary embolism		
Gastrointestinal disorders	diarrhoea, nausea, vomiting, stomatitis, constipation, abdominal pain, dyspepsia, upper abdominal pain	gastrointestinal perforation, fistula, gastro-oesophageal reflux disease, haemorrhoids, oral pain, dry mouth	pancreatitis, glossodynia	
Hepatobiliary disorders		hepatic encephalopathy	hepatitis cholestatic	
Skin and subcutaneous tissue disorders	palmar-plantar erythrodysaesthesia syndrome, rash	pruritis, alopecia, dry skin, dermatitis acneiform, hair colour change		
Musculoskeletal and connective tissue disorders	pain in extremity	muscle spasms, arthralgia	osteonecrosis of the jaw	
Renal and urinary disorders		proteinuria		
General disorders and administration site conditions fatigue	fatigue, mucosal inflammation, asthenia, peripheral oedema			

Investigations	weight decreased, serum ALT increased, AST increased	blood ALP increased, GGT increased, blood creatinine increased, amylase increased, lipase increased, blood cholesterol increased, white blood cells decreased	blood triglycerides increased	
Injury, poisoning and procedural complications			wound complications	

Description of selected adverse reactions

Data for the following reactions are based on patients who received CABOMETYX 60 mg once daily in the pivotal studies in RCC following prior VEGF-targeted therapy, in treatment-naïve RCC and in HCC following prior systemic therapy (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.

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.

No cases of hepatic encephalopathy were reported in the RCC studies (METEOR and CABOSUN)

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.

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.

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.

Fatal haemorrhages have occurred in the cabozantinib clinical program.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
No cases of RPLS were reported in the METEOR,CABOSUN or CELESTIAL studies, but RPLS has been reported rarely in other clinical studies (in 2/4872 subjects; 0.04%).

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 or HCC studies (at a dose of 60 mg).

Clinical trials

Renal Cell Carcinoma - following prior vascular endothelial growth factor (VEGF)-targeted therapy

The safety and efficacy of CABOMETYX for the treatment of renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy were evaluated in a 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 3). A planned interim analysis of OS was conducted at the time of the PFS analysis and did not reach the interim boundary for statistical significance (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 4).

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 5.

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)

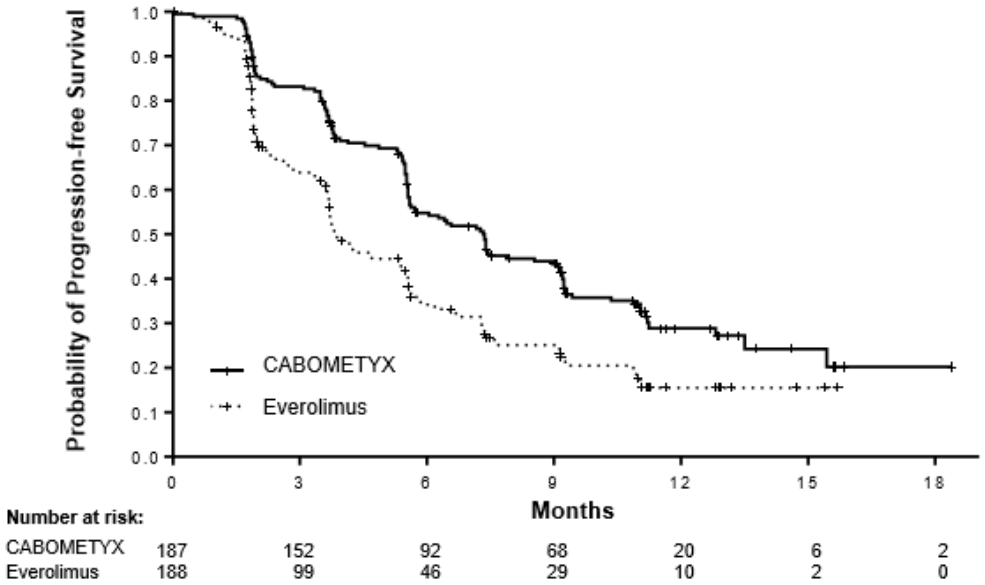


Table 3: Summary of PFS findings by independent radiology review committee in RCC subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy (METEOR)

	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)

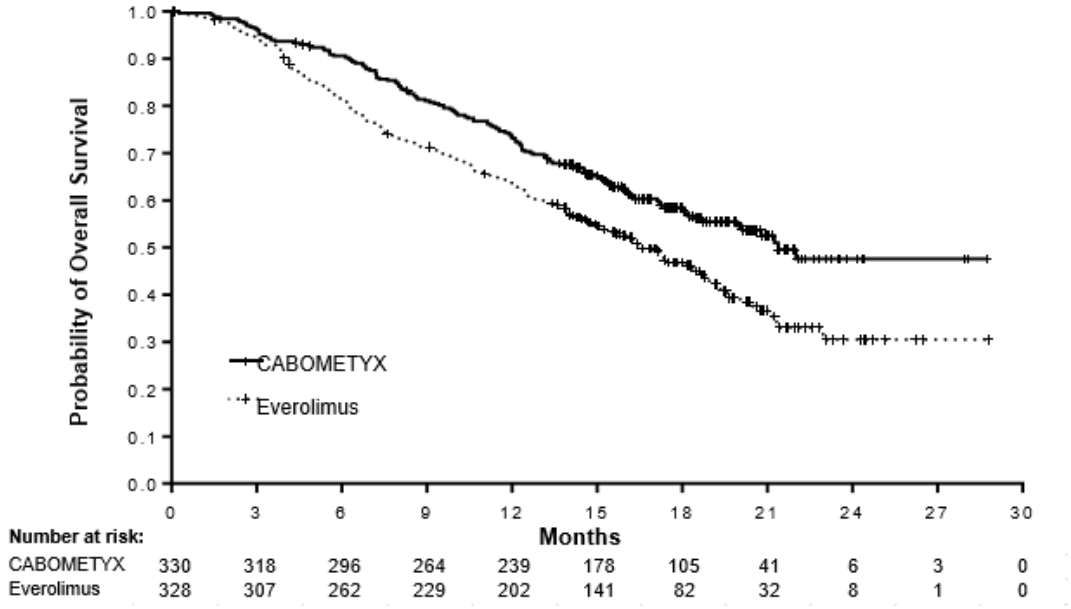


Table 4: Summary of OS findings in RCC subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy (METEOR)

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

Renal Cell Carcinoma - in treatment-naïve patients

The safety and efficacy of CABOMETYX for the treatment of treatment-naïve renal cell carcinoma were evaluated in a randomized, open-label, multicenter study (CABOSUN). Patients (N=157) with previously untreated, locally advanced or metastatic RCC with a clear cell component were randomized (1:1) to receive CABOMETYX (N=79) or sunitinib (N=78). Patients had to have intermediate or poor risk disease as defined by the International Metastatic RCC Database Consortium (IMDC) risk group categories. Patients were stratified by IMDC risk group and presence of bone metastases (yes/no). Approximately 75% of patients had a nephrectomy prior to onset of treatment.

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

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

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

A statistically significant improvement in PFS as retrospectively assessed by a blinded Independent Radiology Committee (IRC) was demonstrated for CABOMETYX compared to

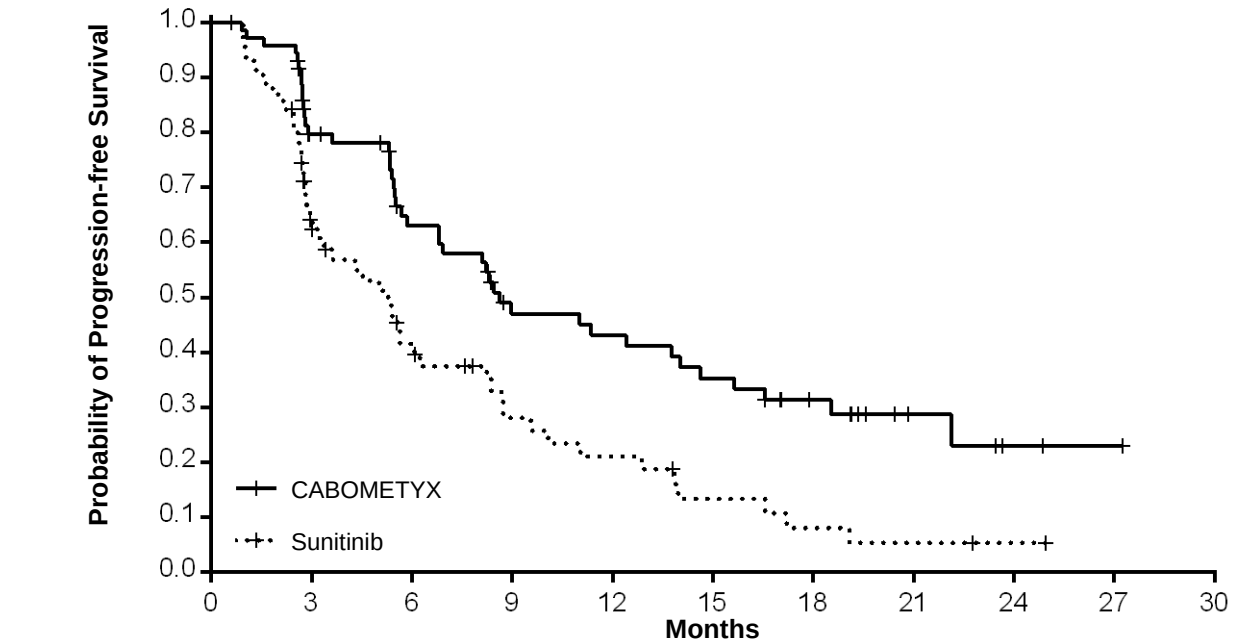
sunitinib (Figure 3 and Table 6). The results from the Investigator determined analysis and IRC-determined analysis of PFS were consistent.

Patients with both positive and negative MET status showed a favourable effect with 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 6). The study was not powered for the OS analysis and the data are immature.

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

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



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

Table 6: Efficacy results in treatment-naïve RCC (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

Hepatocellular Carcinoma

The safety and efficacy of CABOMETYX were evaluated in a randomized, 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 7 and Figure 4).

PFS and ORR findings are summarized in Table 7.

Table 7: Efficacy results in HCC (ITT population, CELESTIAL)

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

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

Figure 4: Kaplan-Meier curve of overall survival (CELESTIAL)

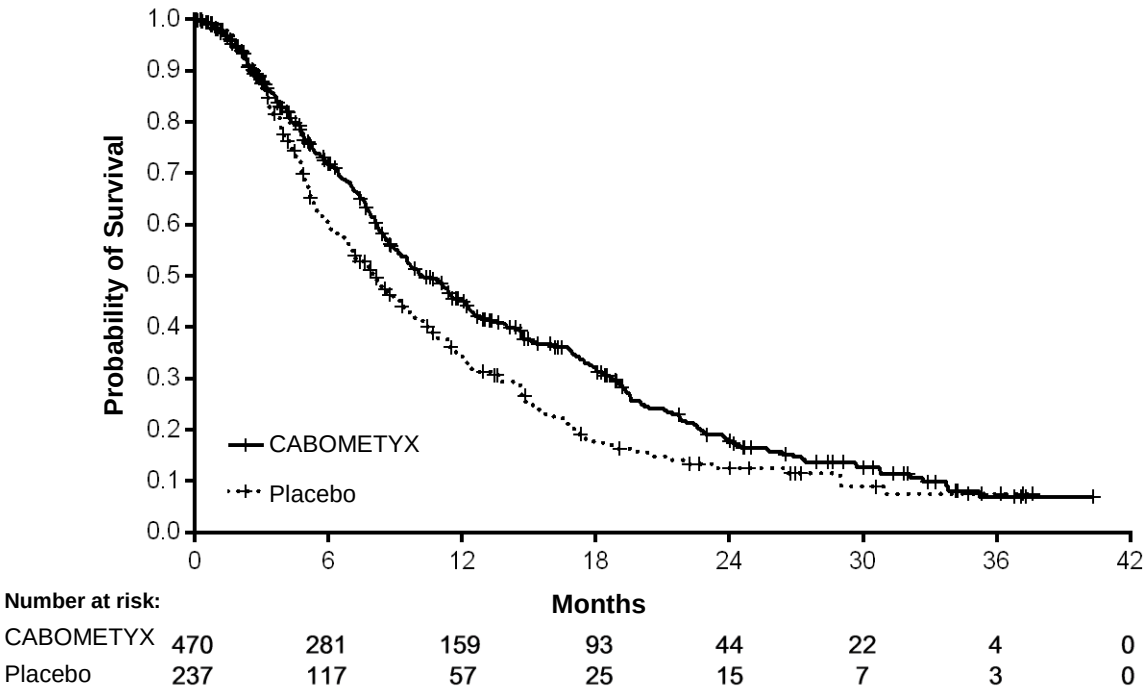
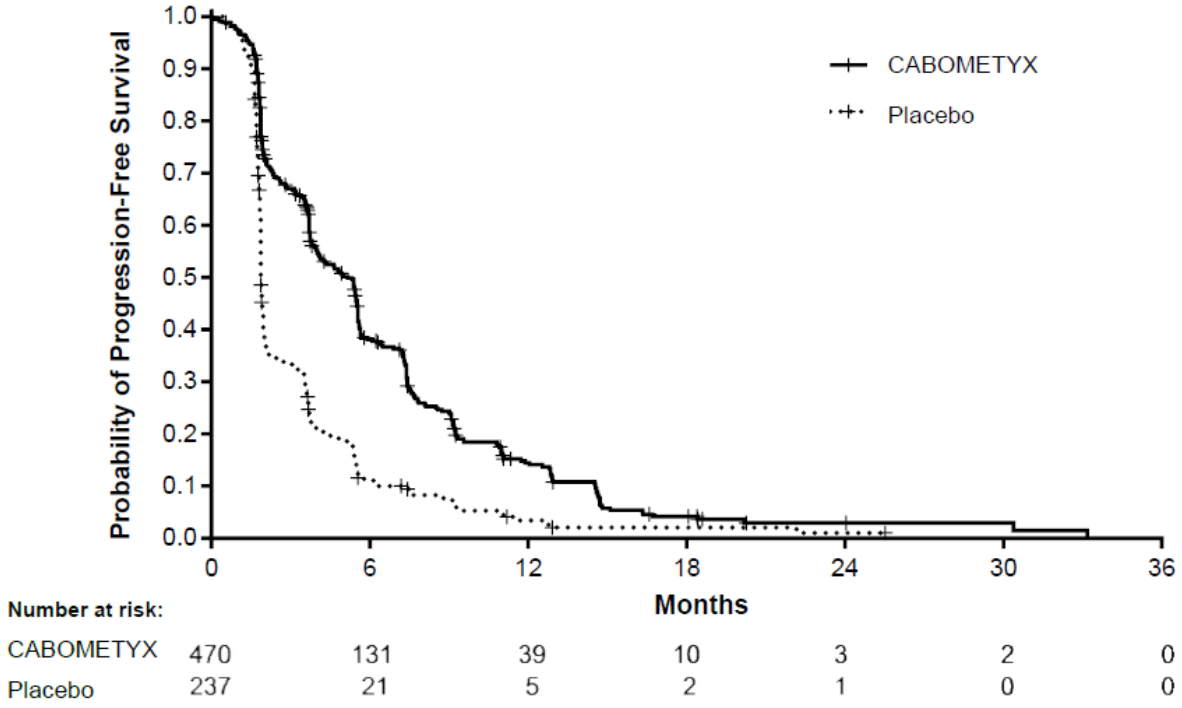


Figure 5: Kaplan Meier curve for progression-free survival (CELESTIAL)



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.

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 (ie, 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.

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.

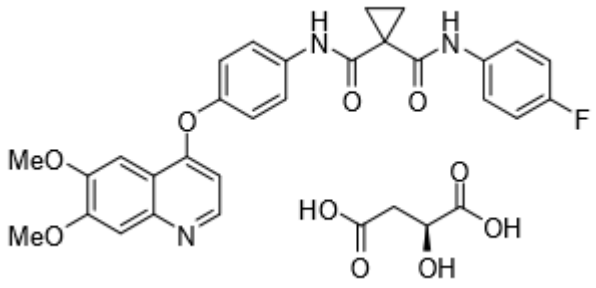
6.7 PHYSICOCHEMICAL PROPERTIES

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 2, Building 4
Brandon Office Park
540 Springvale Road
Glen Waverley Victoria 3150

Telephone: 1800 317 033

9 DATE OF FIRST APPROVAL

19 January 2018

10 DATE OF REVISION

28 May 2019

Summary table of changes

Section changed	Summary of new information
4.1, 4.2, 4.4, 4.8, 5.1, 5.2	Updates to add new indication including updated ADR table and clinical trial information.