**PROFESSIONAL INFORMATION**

**SCHEDULING STATUS**

**S4**

## 1 NAME OF THE MEDICINE

**CABOMETYX 20 mg** film-coated tablets

**CABOMETYX 40 mg** film-coated tablets

**CABOMETYX 60 mg** film-coated tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CABOMETYX 20 mg film-coated tablets:

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

Contains sugar: lactose 15,54 mg per film-coated tablet.

CABOMETYX 40 mg film-coated tablets:

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

Contains sugar: lactose 31,07 mg per film-coated tablet.

CABOMETYX 60 mg film-coated tablets:

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

Contains sugar: lactose 46,61 mg per film-coated tablet.

For full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Film-coated tablet.

CABOMETYX 20 mg film-coated tablets:

The tablets are yellow round with no score and debossed with “XL” on one side and “20” on

the other side of the tablet.

CABOMETYX 40 mg film-coated tablets:

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

CABOMETYX 60 mg film-coated tablets:

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

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

***Renal Cell Carcinoma (RCC)***

CABOMETYX is indicated for the treatment of advanced renal cell carcinoma (RCC):

- in treatment-naïve adults with intermediate or poor risk (see section 5.1)
- in adults following prior vascular endothelial growth factor (VEGF)- 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.

***Differentiated thyroid carcinoma (DTC)***

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

### 4.2 Posology and method of administration

Therapy with CABOMETYX should be initiated by a medical practitioner experienced in the

administration of anticancer medicines.

**Posology**

For RCC, HCC and DTC, 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 (see Table 1). When dose reduction is necessary, it is recommended to reduce to 40 mg daily, and then to 20 mg daily. Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities. Dose reductions are recommended for events that, if persistent, could become serious or intolerable.

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

**Table 1: Recommended CABOMETYX dose modifications for adverse reactions**

| **Adverse reaction and severity** | **Treatment modification** |
|---|---|
| Grade 1 and Grade 2 adverse reactions which are tolerable and easily managed | Dose adjustment is usually not required.<br>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.<br>Add supportive care as indicated.<br>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.<br>Add supportive care as indicated. |

| | |
|---|---|
| | Re-initiate at a reduced dose. |
| Grade 4 adverse reactions (except clinically nonrelevant laboratory abnormalities) | Interrupt treatment.<br>Institute appropriate medical care.<br>If adverse reaction resolves to Grade ≤1, re-initiate at a reduced dose.<br>If adverse reaction does not resolve, permanently discontinue the treatment. |

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

***Concomitant medicines***

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

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

**Special populations**

***Elderly patients***

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

***Race***

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

***Renal impairment***

CABOMETYX should be used with caution in patients with mild or moderate renal impairment. CABOMETYX is not recommended for use in patients with severe renal impairment as safety

and efficacy have not been established in this population.

***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 CABOMETYX is not recommended for use in these patients (see section 5.2).

***Cardiac impairment***

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

***Paediatric population***

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

**Method of administration**

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

## 4.3 Contraindications

Hypersensitivity to cabozantinib or to any of the excipients (see section 6.1).

## 4.4 Special warnings and precautions for use

As most adverse reactions occur early in the course of treatment, the medical practitioner should evaluate the patient closely during the first eight weeks of treatment to determine if

dose modifications are warranted. Adverse reactions that generally have early onset include hypocalcaemia, hypokalaemia, thrombocytopenia, hypertension, palmar-plantar erythrodysesthesia 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 CABOMETYX therapy (see section 4.2):
In renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy, dose reductions and dose interruptions due to an AE occurred in 59,8 % and 70 %, respectively, of cabozantinib-treated patients in the pivotal clinical trial (METEOR). Two dose reductions were required in 19,3 % of patients. The median time to first dose reduction was 55 days, and to first dose interruption was 38 days.

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

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.

***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).

Cases of vanishing bile duct syndrome have been reported. All cases have occurred in patients who have received immune checkpoint inhibitors, either before or concurrently with cabozantinib treatment.

Cabozantinib is eliminated mainly via the hepatic route. Closer monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment (see also sections 4.2 and 5.2). A higher relative proportion of patients with moderate hepatic impairment (Child-Pugh B) developed hepatic encephalopathy with cabozantinib treatment. Cabozantinib is not recommended for use in patients with severe hepatic impairment (Child-Pugh C).

***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 events (see section 4.8). Prompt medical management, including supportive care with antiemetics, antidiarrheals, 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 medicines. 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) and in the DTC study (COSMIC-311), thrombocytopenia and decreased platelets were reported. Platelet levels should be monitored during cabozantinib

treatment and the dose modified according to the severity of the thrombocytopenia (see Table 1).

***Wound complications***

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

***Hypertension***

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

***Osteonecrosis***

Events of osteonecrosis of the jaw (ONJ) have been observed with cabozantinib. An oral examination should be performed prior to initiation of cabozantinib and periodically during cabozantinib therapy. Patients should be advised regarding oral hygiene practice. Cabozantinib treatment should be held at least 28 days prior to scheduled dental surgery or

invasive dental procedures, if possible. Caution should be used in patients receiving medicines associated with ONJ, such as bisphosphonates. Cabozantinib should be discontinued in patients who experience ONJ.

***Palmar-plantar erythrodysesthesia syndrome***

Palmar-plantar erythrodysesthesia 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 medicines 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 medicines that are strong CYP3A4 inducers with cabozantinib should be avoided (see sections 4.2 and 4.5).

***P-glycoprotein substrates***

Cabozantinib was an inhibitor ($IC_{50}$ = 7,0 µM), but not a substrate, of P-glycoprotein (P-gp) transport activities in a bi-directional assay system using MDCK-MDR1 cells. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. Subjects should be cautioned regarding taking a P-gp substrate (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib (see section 4.5).

***MRP2 inhibitors***

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

***Excipient related warnings***

Contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take CABOMETYX.

## 4.5 Interaction with other medicines and other forms of interaction

**Effect of other medicines on cabozantinib**

***CYP3A4 inhibitors and inducers***

Administration of the strong CYP3A4 inhibitor ketoconazole (400 mg daily for 27 days) to healthy volunteers decreased cabozantinib clearance (by 29 %) and increased single-dose plasma cabozantinib exposure (AUC) by 38 %. Therefore, co-administration of strong CYP3A4 inhibitors (e.g., ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) with cabozantinib should be approached with caution.

Administration of the strong CYP3A4 inducer rifampicin (600 mg daily for 31 days) to healthy volunteers increased cabozantinib clearance (4,3-fold) and decreased single-dose plasma cabozantinib exposure (AUC) by 77 %. Chronic co-administration of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing St. John's Wort *[Hypericum perforatum]*) with cabozantinib should therefore be avoided.

***Gastric pH modifying agents***

Co-administration of proton pump inhibitor (PPI) esomeprazole (40 mg daily for 6 days) with a single dose of 100 mg cabozantinib to healthy volunteers resulted in no clinically significant effect on plasma cabozantinib exposure (AUC). No dose adjustment is indicated when gastric pH modifying agents (i.e., PPIs, H2 receptor antagonists, and antacids) are co-administered with cabozantinib.

***MRP2 inhibitors***

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

***Bile salt-sequestering agents***

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

***Effect of cabozantinib on other medicines***

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. Cabozantinib is highly protein bound in vitro in human plasma (≥ 99.7%). A plasma protein displacement interaction with other highly protein-bound drugs (e.g., warfarin) is possible. In case of such combination, INR values should be monitored.

***P-glycoprotein substrates***

Cabozantinib was an inhibitor ($IC_{50}$ = 7,0 µM), but not a substrate, of P-gp transport activities in a bi-directional assay system using MDCK-MDR1 cells. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. Subjects should be cautioned regarding taking a P-gp substrate (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib.

## 4.6 Fertility, pregnancy and lactation

**Women of childbearing potential /Contraception in males and females**

Women of childbearing potential must be advised to avoid pregnancy while on cabozantinib. Female partners of male patients taking cabozantinib must also avoid pregnancy. Effective methods of contraception should be used by male and female patients and their partners during therapy, and for at least 4 months after completing therapy. Because oral

contraceptives might possibly not be considered as “effective methods of contraception”, they should be used together with another method, such as a barrier method (see section 4.5).

**Pregnancy**

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

**Breast-feeding**

It is not known whether cabozantinib and/or its metabolites are excreted in human milk. Because of the potential harm to the infant, mothers should discontinue breast-feeding during treatment with cabozantinib, and for at least 4 months after completing therapy.

**Fertility**

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

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

**a. Summary of the 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 erythrodysesthesia 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 common serious adverse drug reactions in the DTC population (≥1% incidence) are diarrhoea, pleural effusion, pneumonia, pulmonary embolism, hypertension, anaemia, deep vein thrombosis, hypocalcaemia, osteonecrosis of jaw, pain, palmar-plantar erythrodysesthesia 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.

**b. Tabulated summary of adverse reactions**

Adverse reactions reported in the pooled dataset for patients treated with cabozantinib in RCC, HCC and DTC (n=1128) 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**

| System organ class | Frequency | Adverse reactions |
|---|---|---|
| Infections and infestations | Common | Abscess, pneumonia |
| Blood and lymphatic system disorders | Very common | Anaemia, thrombocytopenia |
| | Common | Neutropenia[a], lymphopenia |
| Endocrine disorders | Very common | Hypothyroidism* |
| Metabolism and nutrition disorders | Very common | Decreased appetite, hypomagnesaemia, hypokalaemia, hypoalbuminemia |
| | Common | Dehydration, hypophosphatemia, |

| System organ class | Frequency | Adverse reactions |
|---|---|---|
| | | hyponatraemia, hypocalcaemia, hyperkalaemia, hyperbilirubinemia[c], hyperglycaemia, hypoglycaemia |
| Nervous system disorders | Very common | Dysgeusia, headache, dizziness |
| | Common | Peripheral neuropathy[a] |
| | Uncommon | Convulsion, Cerebro-vascular accident, posterior reversible encephalopathy syndrome. |
| Ear and labyrinth disorders | Common | Tinnitus |
| Cardiac disorders | Not known | Acute Myocardial infarction |
| Vascular disorders | Very common | Hypertension, haemorrhage[b*] |
| | Common | Venous thrombosis[c] |
| | Uncommon | Hypertensive crisis, arterial thrombosis, embolism arterial |
| | Not known | Aneurysms and artery dissections |
| Respiratory, thoracic and mediastinal disorders | Very common | Dysphonia, dyspnoea, cough |
| | Common | Pulmonary embolism |
| | Uncommon | Pneumothorax |

| System organ class | Frequency | Adverse reactions |
|---|---|---|
| Gastrointestinal disorders | Very common | Diarrhoea*, nausea, vomiting, stomatitis, constipation, abdominal pain, dyspepsia |
| | Common | Gastrointestinal perforation*, pancreatitis, fistula*, gastroesophageal reflux disease, haemorrhoids, oral pain, dry mouth, dysphagia |
| | Uncommon | Glossodynia |
| Hepato-biliary disorders | Common | Hepatic encephalopathy* |
| | Uncommon | Hepatitis cholestatic |
| Skin and subcutaneous tissue disorders | Very common | Palmar-plantar erythrodysesthesia syndrome, rash[f] |
| | Common | Pruritus, alopecia, dry skin, dermatitis acneiform, hair colour change, hyperkeratosis |
| | Not Known | cutaneous vasculitis |
| Musculoskeletal and connective tissue disorders | Very common | Pain in extremity |
| | Common | Muscle spasms, arthralgia |
| | Uncommon | Osteonecrosis of the jaw |
| Renal and urinary disorders | Common | Proteinuria |

| System organ class | Frequency | Adverse reactions |
|---|---|---|
| General disorders and administration site conditions | Very common | Fatigue, mucosal inflammation, asthenia, peripheral oedema |
| Investigations | Very common | Weight decreased, serum ALT increased, AST increased |
| | Common | Blood ALP increased, GGT increased, blood creatinine increased, amylase increased, lipase increased, blood cholesterol increased, blood triglycerides increased |
| Injury, poisoning and procedural complications | Uncommon | Wound complications[e] |

*See section 4.8 Description of selected adverse reactions for further characterisation.

[a] including polyneuropathy: peripheral neuropathy is mainly sensory

[b] Including epistaxis as the most commonly reported adverse reaction

[c] All venous thrombosis including deep vein thrombosis

[d] Based on reported adverse reactions

[e] Impaired healing, incision site complication and wound dehiscence

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

**c. Description of selected adverse reactions**

Data for the following reactions are based on patients who received CABOMETYX 60 mg qd po in the pivotal studies in RCC following prior VEGF-targeted therapy and in treatment-naïve RCC in HCC following prior systemic therapy and in DTC in patient refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy (section 5.1).

***Gastrointestinal (GI) perforation (see section 4.4)***

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.

Fatal perforations have occurred in the cabozantinib clinical program.

***Hepatic encephalopathy (see section 4.4)***

In the HCC study (CELESTIAL), hepatic encephalopathy (hepatic encephalopathy, encephalopathy, hyperammonaemic encephalopathy) was reported in 5,6 % of cabozantinib-treated patients (26/467); Grade 3-4 events in 2,8 %, and one (0,2 %) Grade 5 event. Median time to onset was 5,9 weeks.

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

***Diarrhoea (see section 4.4)***

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.

***Fistulas (see section 4.4)***

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 fistula) were reported in 1.8 % (3/170) of the cabozantinib treated patients.

Fatal fistulas have occurred in the cabozantinib clinical program.

***Haemorrhage (see section 4.4)***

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.

Fatal haemorrhages have occurred in the cabozantinib clinical program.

***Posterior reversible encephalopathy syndrome (PRES) (see section 4.4)***

No case of PRES was reported in the METEOR or CABOSUN or CELESTIAL studies, but PRES has been reported in one patient in the DTC study (COSMIC-311) and rarely in other clinical studies (in 2/4872 subjects; 0,04 %).

***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.

***Reporting of suspected adverse reactions***

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to Acino Pharma via email on Drugsafety_ZA@arceralifesciences.com OR SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

### 4.9 Overdose

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

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

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agent, protein kinase inhibitor

ATC code: L01XE07.

**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 efficacy and safety**

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

The safety and efficacy of CABOMETYX for the treatment of renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy were evaluated in a

randomized, open-label, 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 randomized (1:1) to receive cabozantinib (N=330) or comparator (N=328). Patients could have received other prior therapies, including cytokines, and antibodies targeting VEGF, the programmed death 1 (PD-1) receptor, or its ligands. Patients with treated brain metastases were allowed. Progression-free survival (PFS) was assessed by a blinded independent radiology review committee, and the primary analysis was conducted among the first 375 subjects randomized. Secondary efficacy endpoints were objective response rate (ORR) and overall survival (OS). Tumour assessments were conducted every 8 weeks for the first 12 months, then every 12 weeks thereafter.

The baseline demographic and disease characteristics were similar between the cabozantinib and comparator 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 cabozantinib and 4,4 months (range 0,21 – 18,9) for patients receiving comparator.

A statistically significant improvement in PFS was demonstrated for cabozantinib compared to comparator (Figure 1 and Table 3). A planned interim analysis of OS was conducted at the time of the PFS analysis and did not reach the interim boundary for statistical significance (202 events, HR=0,68 [0,51; 0,90], p=0,006). In a subsequent unplanned interim analysis of OS, a

statistically significant improvement was demonstrated for patients randomized to cabozantinib as compared with comparator (320 events, median of 21,4 months vs. 16,5 months; HR=0,66 [0,53; 0,83], p=0,0003; Figure 2). Comparable results for OS were observed with a follow-up analysis (descriptive) at 430 events.

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

Objective response rate findings are summarized in Table 4.

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

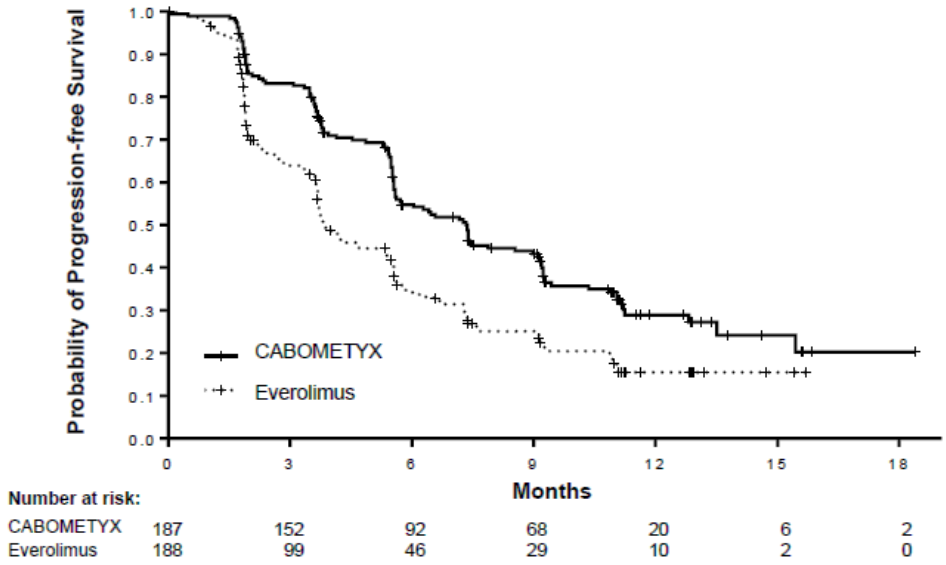



**Table 3: Summary of PFS findings by independent radiology review committee in RCC**

**subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy (METEOR)**

| | Primary PFS analysis Population | | Intent-To-Treat Population | |
|---|---|---|---|---|
| **Endpoint** | **CABOMETYX** | **Comparator** | **CABOMETYX** | **Comparator** |
| | 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)**

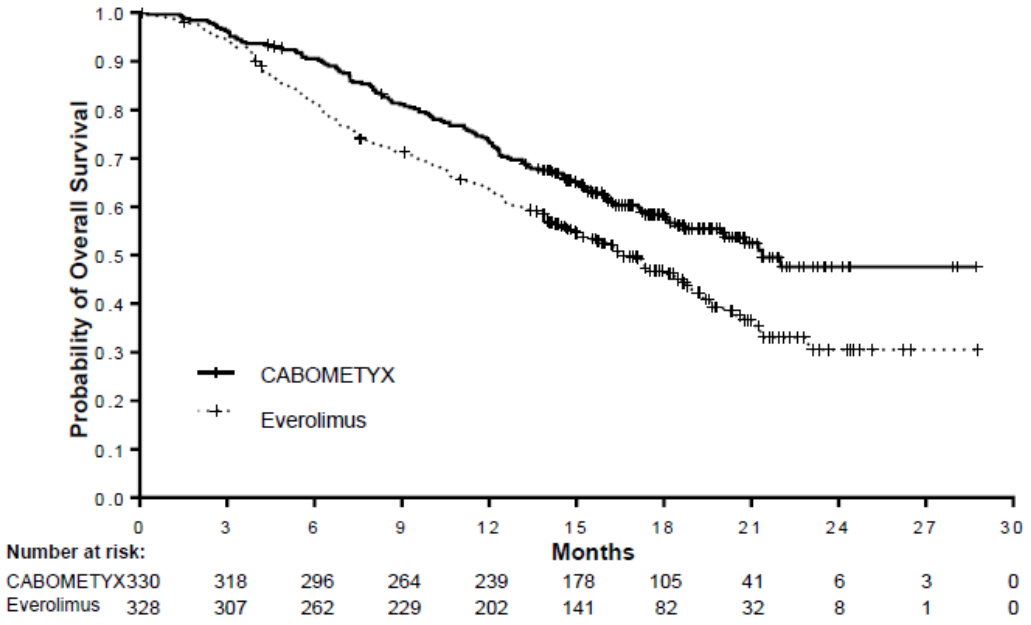


**Table 4: Summary of ORR findings per independent radiology committee review (IRC) and investigator review, in RCC subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy**

| | **Primary Analysis ORR Intent-To-Treat Population (IRC)** | | **ORR per Investigator Review Intent-To-Treat Population** | |
|---|---|---|---|---|
| **Endpoint** | **CABOMETYX** | **Comparator** | **CABOMETYX** | **Comparator** |
| | 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 | 12 % | 27 % | 9 % | 27 % |

| | | | | |
|---|---|---|---|---|
| Best<br><br>Response | | | | |

[1] chi-squared test

**Clinical data in treatment-naïve renal cell carcinoma**

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

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

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

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

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

Patients with both positive and negative MET status showed a favourable effect with cabozantinib compared to sunitinib, with greater activity in patients with a positive MET status compared to patients with a negative MET status (HR=0,32 (0,16 0,63) vs 0,67 (0,37; 1,23)) respectively.

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

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

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

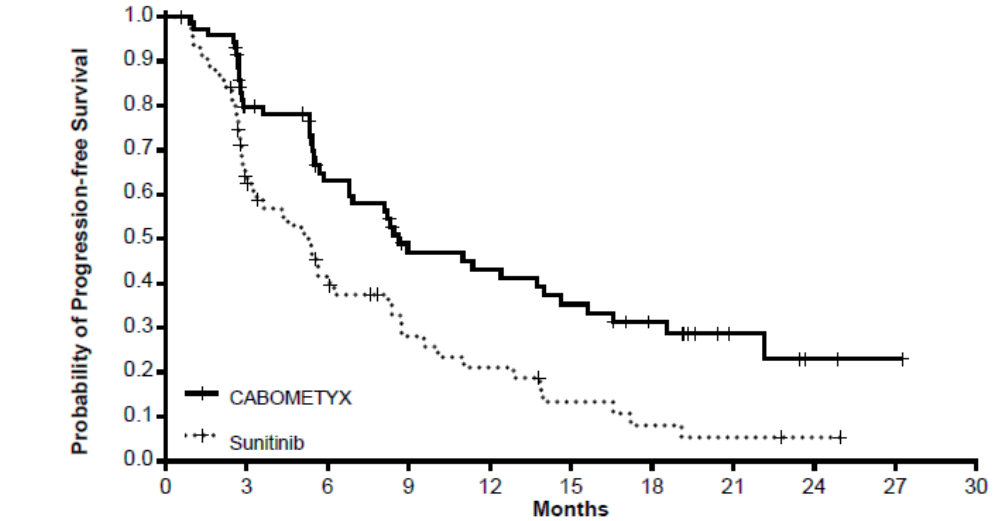


**Table 5: Efficacy results in treatment-naïve RCC subjects (ITT population, CABOSUN)**

| | **CABOMETYX (N=79)** | **Sunitinib (N=78)** |
|---|---|---|
| **Progression-free survival (PFS) by IRC [a]** | | |
| **Median PFS in months (95% CI)** | **8,6 (6,2; 14,0)** | **5,3 (3,0; 8,2)** |
| HR (95 % CI); stratified [b,c] | 0,48 (0,32; 0,73) | |
| Two-sided log-rank p-value: stratified [b] | p=0,0005 | |
| **Progression-free survival (PFS) by Investigator** | | |
| Median PFS in months (95 % CI) | 8,3 (6,5; 12,4) | 5,4 (3,4; 8,2) |
| HR (95 % CI); stratified [b,c] | 0,56 (0,37; 0,83) | |
| Two-sided log-rank p-value: stratified [b] | p=0,0042 | |
| **Overall Survival** | | |
| Median OS in months (95 % CI) | 30,3 (14,6; NE) | 21,0 (16,3; 270) |
| 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) |

| | CABOMETYX (N=79) | Sunitinib (N=78) |
|---|---|---|
| Progressive Disease | 14 (18) | 19 (24) |

[a] in accord with EU censoring

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

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

***Clinical data in 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 randomized (2:1) to receive cabozantinib (N=470) or placebo (N=237). Patients could have received one other prior systemic therapy for advanced disease in addition to sorafenib. Randomization was stratified by aetiology of disease (HBV [with or without HCV], HCV [without HBV], or other), geographic region (Asia, other regions) and by presence of extrahepatic spread of disease and/or macrovascular invasions (Yes, No).

The primary efficacy endpoint was overall survival (OS). Secondary efficacy endpoints were progression-free survival (PFS) and objective response rate (ORR), as assessed by the Investigator using Response Evaluation Criteria in Solid Tumours (RECIST) 1.1. Tumour assessments were conducted every 8 weeks. Subjects continued blinded study treatment after radiological disease progression whilst they experienced clinical benefit or until the need for subsequent systemic or liver-directed local anticancer therapy. Crossover from placebo to cabozantinib was not allowed during the blinded treatment phase.

The baseline demographic and disease characteristics were similar between the cabozantinib and placebo arms and are shown below for all 707 randomised patients:

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 trans arterial embolization or chemo infusion 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 6 and Figure 4).

PFS and ORR findings are summarized in Table 6.

**Table 6: Efficacy results in HCC (ITT population, CELESTIAL)**

| | **CABOMETYX (N=470)** | **Sunitinib (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) | 16 (20) | 7 (9) |
| ORR (CR + PR) | 16 (20) | 7 (9) |
| p-value[1,4] | p=0,0086 | |
| Stable disease | 282 (60) | 78 (33) |
| Progressive Disease | 98 (21) | 131 (55) |

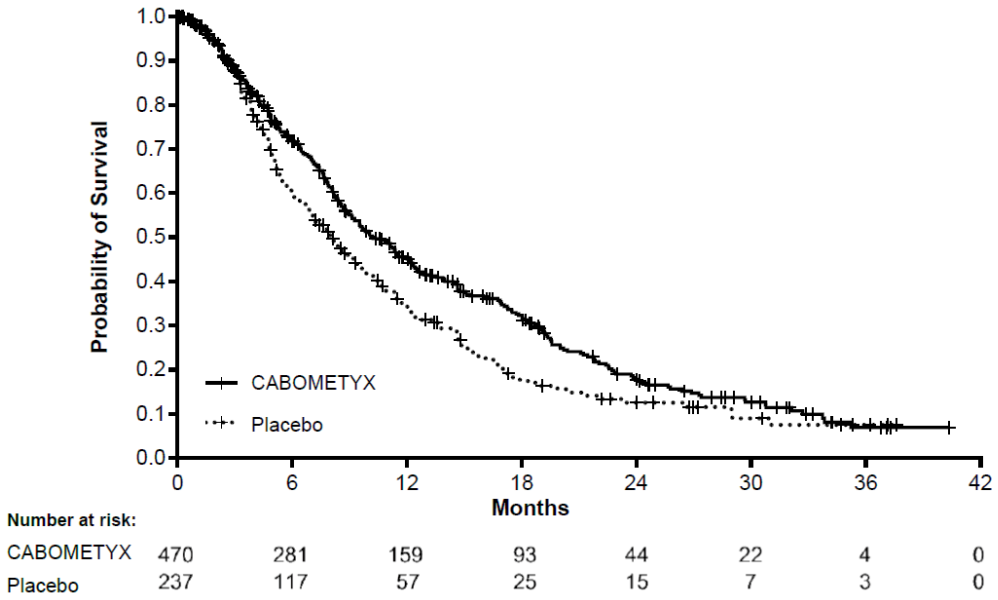
[1] 2-sided stratified log-rank test with aetiology of disease (HBV [with or without HCV], HCV [without HBV], or Other), geographic region (Asia, Other Regions), and presence of extrahepatic spread of disease and/or macrovascular invasion (Yes, No) as stratification factors (per IVRS data)

[2] estimated using the Cox proportional-hazard model

[3] as assessed by investigator per RECIST 1.1

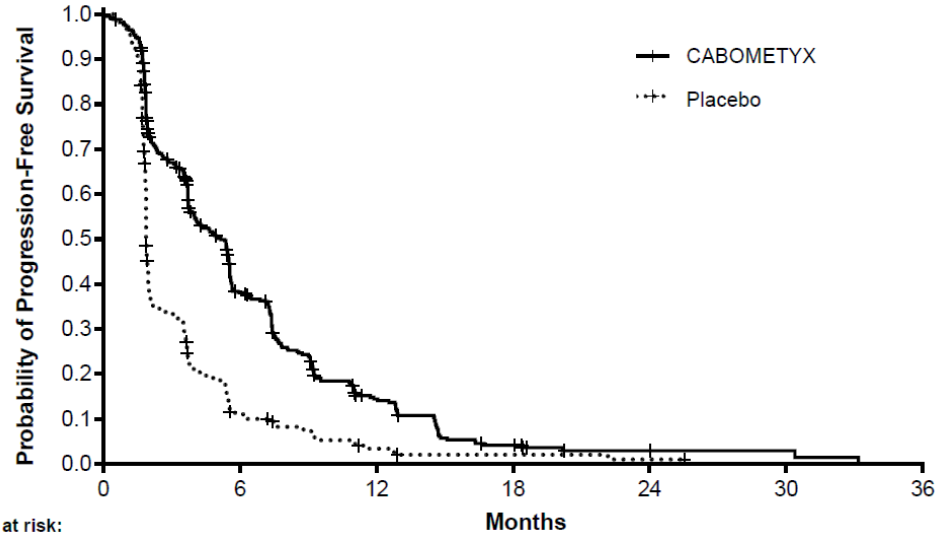
[4] stratified Cochran-Mantel-Haenszel (CMH) test

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




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

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




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

The incidence of systemic non-radiation and local liver-directed systemic non-protocol anticancer therapy (NPACT) was 26 % in the cabozantinib arm and 33 % in the placebo arm. Subjects receiving these therapies had to discontinue study treatment. An exploratory OS analysis censoring for the use of NPACT supported the primary analysis: the HR, adjusted for stratification factors (per IxRS), was 0,66 (95 % CI: 0,52; 0,84; stratified logrank p-value = 0,0005). The Kaplan- Meier estimates for median duration of OS were 11,1 months in the cabozantinib arm versus 6,9 months in the placebo arm, an estimated 4,2-month difference in the medians.

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

*Differentiated thyroid carcinoma (DTC)*

*Placebo -Controlled study in adult patients who have received prior systemic therapy and are refractory or not eligible to radioactive iodine (COSMIC-311)*

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

Randomisation was stratified by prior receipt of lenvatinib (yes vs. no) and age ($\leqslant$ 65 years vs. > 65 years). Eligible patients randomised to placebo were allowed to cross-over to

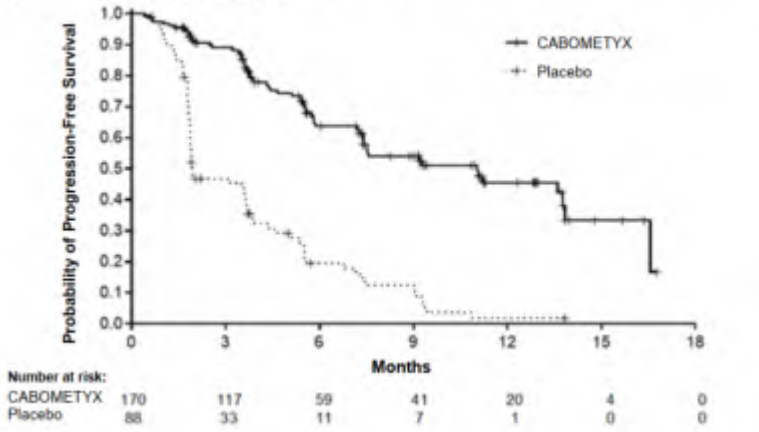
cabozantinib upon confirmation of progressive disease by blinded independent radiology review committee (BIRC). Subjects continued blinded study treatment as long as they experienced clinical benefit or until there was unacceptable toxicity. The primary efficacy outcome measures were progression-free survival (PFS) in the ITT population, and objective response rate (ORR) in the first 100 randomised patients, as assessed by BIRC per RECIST 1.1. Tumour assessments were conducted every 8 weeks after randomisation during the first 12 months on study, then every 12 weeks thereafter. Overall survival (OS) was an additional endpoint.

Table 9: Efficacy Results from COSMIC-311

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

* The primary analysis of PFS included censoring for new anti-cancer treatment. Results for PFS with and without censoring for new anti-cancer treatment were consistent. CI, confidence interval; NE, not evaluable 1 The cut-off date of the primary analysis is 19 August 2020. 2 The cut-off date of the secondary analysis is 08 February 2021. 3 Estimated using the Cox proportional-hazard model. 4 Log-rank test stratified by receipt of prior lenvatinib (yes vs. no) and age (⩽ 65 years vs. > 65 years) as stratification factors (per IXRS data). 5 Based on the first 100 patients included in the study with a median follow-up of 8.9 months, n=67 in CABOMETYX group and n=33 in placebo group. The improvement in ORR was not statistically significant.

**Figure 6: Kaplan-Meier Curve of Progression-Free Survival in COSMIC-311 (updated analysis [cut-off date: 08 February 2021], N=258)**




**Paediatric population**

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

## 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 (dose not recommended for CABOMETYX*)*. 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.

**Biotransformation**

Cabozantinib was metabolized *in vivo*. Four metabolites were present in plasma at exposures (AUC) greater than 10 % of parent: XL184-N-oxide, XL184 amide cleavage product, XL184 monohydroxy sulfate, and 6-desmethyl amide cleavage product sulfate. Two non-conjugated metabolites (XL184-N-oxide and XL184 amide cleavage product), which possess <1 % of the on-target kinase inhibition potency of parent cabozantinib, each represent <10 % of total drug-related plasma exposure.

Cabozantinib is a substrate for CYP3A4 metabolism *in vitro*, as a neutralizing antibody to CYP3A4 inhibited formation of metabolite XL184 N-oxide by >80 % in a NADPH-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).

**Elimination**

In a population PK analysis of cabozantinib using data collected from 1883 patients and 140 healthy volunteers following oral administration of a range of doses from 20 to 140 mg, the plasma terminal half-life of cabozantinib is approximately 110 hours. Mean clearance (CL/F) at steady-state was estimated to be 2,48 L/hr. Within a 48-day collection period after a single dose of $^{14}$C-cabozantinib in healthy volunteers, approximately 81 % of the total administered radioactivity was recovered with 54 % in faeces and 27 % in urine.

**Pharmacokinetics in special patient population**

***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**

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

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

Cabozantinib has shown no mutagenic or clastogenic potential in a standard battery of genotoxicity assays. The carcinogenic potential of cabozantinib has been evaluated in two species: rasH2 transgenic mice and Sprague-Dawley rats. In the 2-year rat carcinogenicity study, cabozantinib-related neoplastic findings consisted of an increased incidence of benign pheochromocytoma, alone or in combination with malignant pheochromocytoma/complex malignant pheochromocytoma of the adrenal medulla in both sexes at exposures well below the intended exposure in humans. The clinical relevance of the observed neoplastic lesions in rats is uncertain, but likely to be low.
Cabozantinib was not carcinogenic in the rasH2 mouse model at a slightly higher exposure than the intended human therapeutic exposure.

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

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

Juvenile rats (comparable to a >2 year-old paediatric population) administered cabozantinib showed increased WBC parameters, decreased haematopoiesis, pubescent/immature female reproductive system (without delayed vaginal opening), tooth abnormalities, reduced bone mineral content and density, liver pigmentation and lymph node lymphoid hyperplasia.

Findings in uterus/ovaries and decreased haematopoiesis appeared to be transient, while effects on bone parameters and liver pigmentation were sustained. Juvenile rats (correlating to a <2- year paediatric population) showed similar treatment-related findings with additional findings in male reproductive system (degeneration and/or atrophy of seminiferous tubules in testes, reduced luminal sperm in epididymis), and appeared to be more sensitive to cabozantinib-related toxicity at comparable dose levels.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

*Tablet content:*

Anhydrous lactose

Colloidal anhydrous silica

Croscarmellose sodium

Hydroxypropyl cellulose

Magnesium stearate

Microcrystalline cellulose

*Film-coating:*

Hypromellose 2910

Iron oxide yellow (E172)

Titanium dioxide (E171)

Triacetin (E1518)

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

4 years.

### 6.4 Special precautions for storage

Store at or below 25 ºC.

### 6.5 Nature and contents of container

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

### 6.6 Special precautions for disposal and other handling

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

## 7 HOLDER OF CERTIFICATE OF REGISTRATION

**Acino Pharma (Pty) Ltd**

106 16th Road

Midrand

1686

South Africa

Tel: 087 742 1860

## 8 REGISTRATION NUMBERS

CABOMETYX 20 mg – 55/26/0756

CABOMETYX 40 mg – 55/26/0757

CABOMETYX 60 mg – 55/26/0758

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 December 2023

## 10 DATE OF REVISION OF THE TEXT

15 September 2026