

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CABOMETYX 20 mg film-coated tablets

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

Excipients with known effect

Each film-coated tablet contains 15.54 mg lactose.

CABOMETYX 40 mg film-coated tablets

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

Excipients with known effect

Each film-coated tablet contains 31.07 mg lactose.

CABOMETYX 60 mg film-coated tablets

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

Excipients with known effect

Each film-coated tablet contains 46.61 mg lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

CABOMETYX 20 mg film-coated tablets

The tablets are yellow round with no score, and debossed with “XL” on one side and “20” on the other side of the tablet.

CABOMETYX 40 mg film-coated tablets

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

CABOMETYX 60 mg film-coated tablets

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

CABOMETYX (cabozantinib) tablets and COMETRIQ (cabozantinib) capsules are not bioequivalent and should not be used interchangeably (see section 5.2). If a patient must switch from cabozantinib capsules to cabozantinib tablets, the patient should continue at a CABOMETYX dose not to exceed 60 mg or the current COMETRIQ dose (whichever is lower).

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

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

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

Table 1: Recommended CABOMETYX dose modifications for adverse reactions

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

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

Concomitant medicinal products

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

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

Special populations

Elderly patients

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

Race

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

Patients with renal impairment

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

Patients with hepatic impairment

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

Patients with cardiac impairment

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

Paediatric population

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

Method of administration

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

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

Perforations and fistulas

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

Thromboembolic events

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

Haemorrhage

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

Wound complications

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

Hypertension

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

Palmar-plantar erythrodysaesthesia syndrome

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

Proteinuria

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

Reversible posterior leukoencephalopathy syndrome

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

Prolongation of QT interval

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

CYP3A4 inducers and inhibitors

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

P-glycoprotein substrates

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

MRP2 inhibitors

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

Excipient related warnings

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

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on cabozantinib

CYP3A4 inhibitors and inducers

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

Administration of the strong CYP3A4 inducer rifampicin (600 mg daily for 31 days) to healthy volunteers increased cabozantinib clearance (4.3-fold) and decreased single-dose plasma cabozantinib exposure (AUC) by 77%. Chronic co-administration of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing St. John's Wort [*Hypericum perforatum*]) with cabozantinib should therefore be avoided.

Gastric pH modifying agents

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

MRP2 inhibitors

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

Bile salt-sequestering agents

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

Effect of cabozantinib on other medicinal products

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

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

P-glycoprotein substrates

Cabozantinib was an inhibitor ($IC_{50} = 7.0 \mu M$), 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, tolcapten) while receiving cabozantinib.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential must be advised to avoid pregnancy while on cabozantinib. Female partners of male patients taking cabozantinib must also avoid pregnancy. Effective methods of contraception should be used by male and female patients and their partners during therapy, and for at least 4 months after completing therapy. Because oral contraceptives might possibly not be considered as “effective methods of contraception”, they should be used together with another method, such as a barrier method (see section 4.5).

Pregnancy

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

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

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

Tabulated list of adverse reactions

Adverse reactions are listed in Table 2 according to MedDRA System Organ Class and frequency categories. Frequencies are based on all grades and defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

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

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

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

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

Description of selected adverse reactions

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

Gastrointestinal (GI) perforation

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

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

Fatal perforations have occurred in the cabozantinib clinical program.

Fistulas

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

Haemorrhage

In the study in RCC following prior VEGF-targeted therapy (METEOR), the incidence of severe haemorrhagic events (Grade \geq 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 \geq 3) was 5.1% (4/78) in cabozantinib-treated RCC patients.

Fatal haemorrhages have occurred in the cabozantinib clinical program.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

No cases of RPLS were reported in the METEOR or CABOSUN studies, but RPLS has been reported in other clinical studies with cabozantinib.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Cabozantinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodeling, drug resistance, and metastatic progression of cancer. Cabozantinib was evaluated for its inhibitory activity against a variety of kinases and was identified as an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors. In addition, cabozantinib inhibits other tyrosine kinases including the GAS6 receptor (AXL), RET, ROS1, TYRO3, MER, the stem cell factor receptor (KIT), TRKB, Fms-like tyrosine kinase-3 (FLT3), and TIE-2.

Pharmacodynamic effects

Cabozantinib exhibited dose-related tumour growth inhibition, tumour regression, and/or inhibited metastasis in a broad range of preclinical tumour models.

Cardiac electrophysiology

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

Clinical efficacy and safety

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

The safety and efficacy of CABOMETYX for the treatment of renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy were evaluated in a randomized, open-label, multicenter Phase 3 study (METEOR). Patients (N=658) with advanced RCC with a clear cell component who had previously received at least 1 prior VEGF receptor tyrosine kinase inhibitor (VEGFR TKI) were randomized (1:1) to receive CABOMETYX (N=330) or everolimus (N=328). Patients could have received other prior therapies, including cytokines, and antibodies targeting VEGF, the programmed death 1 (PD-1) receptor, or

its ligands. Patients with treated brain metastases were allowed. Progression-free survival (PFS) was assessed by a blinded independent radiology review committee, and the primary analysis was conducted among the first 375 subjects randomized. Secondary efficacy endpoints were objective response rate (ORR) and overall survival (OS). Tumor assessments were conducted every 8 weeks for the first 12 months, then every 12 weeks thereafter.

The baseline demographic and disease characteristics were similar between the CABOMETYX and everolimus arms. The majority of the patients were male (75%), with a median age of 62 years. Seventy-one percent (71%) received only one prior VEGFR TKI; 41% of patients received sunitinib as their only prior VEGFR TKI. According to the Memorial Sloan Kettering Cancer Center criteria for prognostic risk category, 46% were favorable (0 risk factors), 42% were intermediate (1 risk factor), and 13% were poor (2 or 3 risk factors). Fifty-four percent (54%) of patients had 3 or more organs with metastatic disease, including lung (63%), lymph nodes (62%), liver (29%), and bone (22%). The median duration of treatment was 7.6 months (range 0.3 – 20.5) for patients receiving CABOMETYX and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

A statistically significant improvement in PFS was demonstrated for CABOMETYX compared to everolimus (Figure 1 and Table 3). A planned interim analysis of OS was conducted at the time of the PFS analysis and did not reach the interim boundary for statistical significance (202 events, HR=0.68 [0.51, 0.90], p=0.006). In a subsequent unplanned interim analysis of OS, a statistically significant improvement was demonstrated for patients randomized to CABOMETYX as compared with everolimus (320 events, median of 21.4 months vs. 16.5 months; HR=0.66 [0.53, 0.83], p=0.0003; Figure 2). Comparable results for OS were observed with a follow-up analysis (descriptive) at 430 events.

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

Objective response rate findings are summarized in Table 4.

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

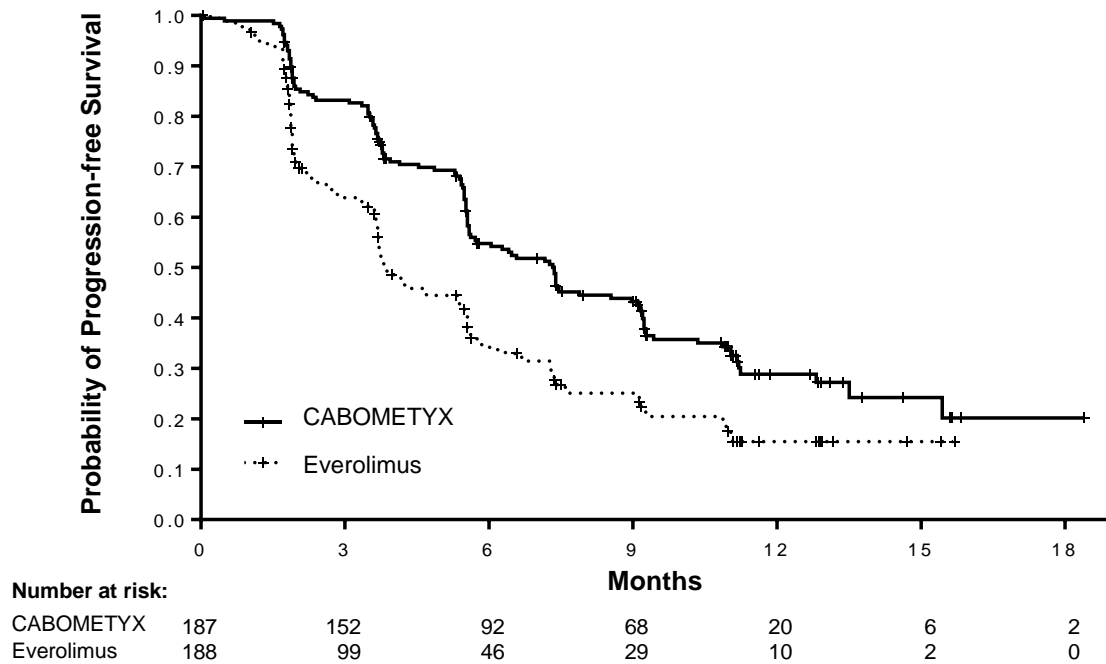


Table 3: Summary of PFS findings by independent radiology review committee in RCC subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy

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

¹ stratified log-rank test

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

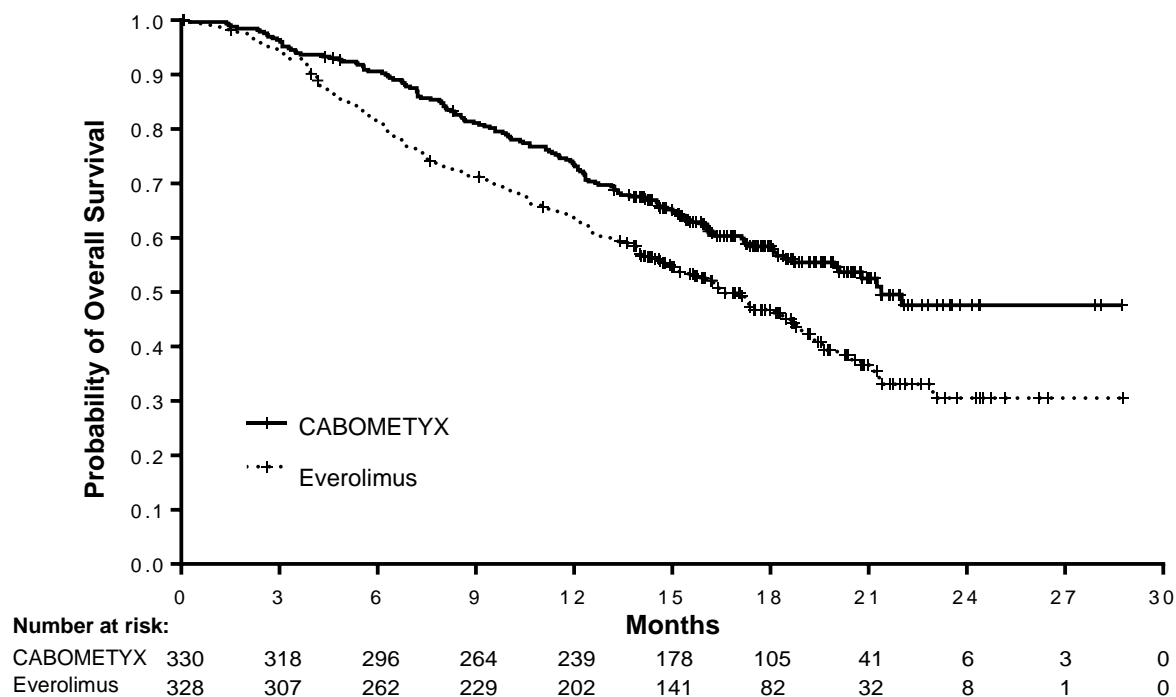


Table 4: Summary of ORR findings per independent radiology committee review (IRC) and investigator review, in RCC subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy

| Endpoint | Primary Analysis ORR Intent-To-Treat Population (IRC) | | ORR per Investigator Review Intent-To-Treat Population | |
|--|---|-----------------|--|-----------------|
| | CABOMETYX | Everolimus | CABOMETYX | Everolimus |
| | N = 330 | N = 328 | N = 330 | N = 328 |
| ORR (partial responses only) (95% CI) | 17% (13%, 22%) | 3% (2%, 6%) | 24% (19%, 29%) | 4% (2%, 7%) |
| p-value ¹ | p<0.0001 | | p<0.0001 | |
| Partial Response | 17% | 3% | 24% | 4% |
| Median time to First Response, months (95% CI) | 1.91 (1.6, 11.0) | 2.14 (1.9, 9.2) | 1.91 (1.3, 9.8) | 3.50 (1.8, 5.6) |
| Stable Disease as Best Response | 65% | 62% | 63% | 63% |
| Progressive Disease as Best Response | 12% | 27% | 9% | 27% |

¹ chi-squared test

Clinical data in treatment-naïve renal cell carcinoma

The safety and efficacy of CABOMETYX for the treatment of treatment-naïve renal cell carcinoma were evaluated in a randomized, open-label, multicenter study (CABOSUN). Patients (N=157) with previously untreated, locally advanced or metastatic RCC with a clear cell component were randomized (1:1) to receive CABOMETYX (N=79) or sunitinib (N=78). Patients had to have intermediate or poor risk disease as defined by the International Metastatic RCC Database Consortium (IMDC) risk group categories. Patients were

stratified by IMDC risk group and presence of bone metastases (yes/no). Approximately 75% of patients had a nephrectomy prior to onset of treatment.

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

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

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

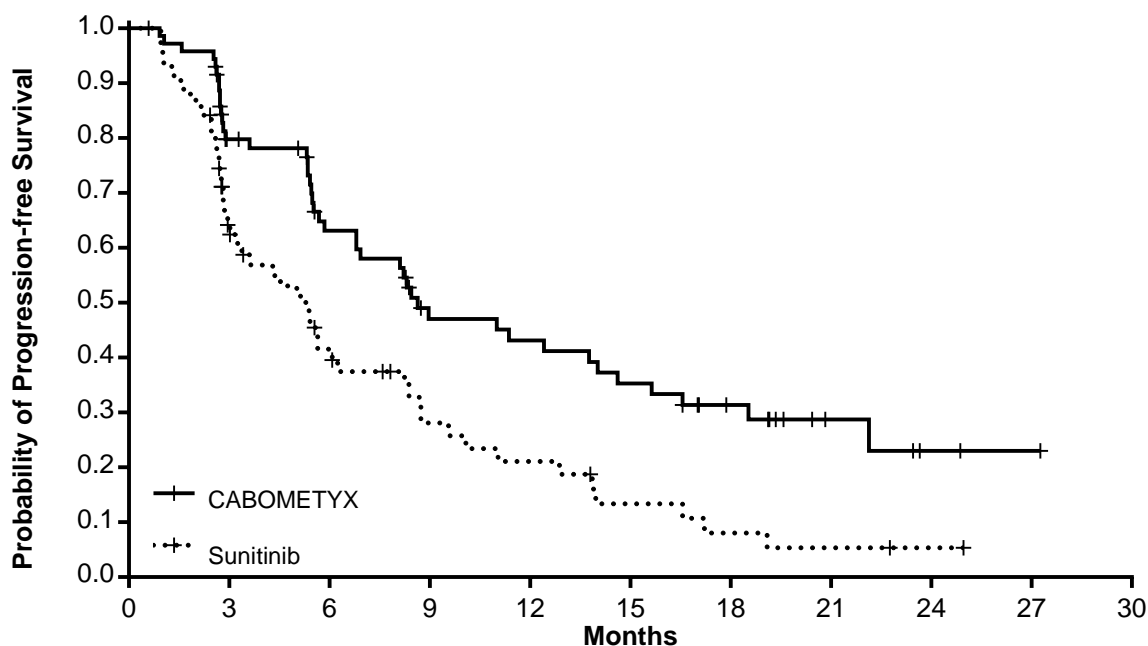
A statistically significant improvement in PFS as retrospectively assessed by a blinded Independent Radiology Committee (IRC) was demonstrated for CABOMETYX compared to sunitinib (Figure 3 and Table 5). The results from the Investigator determined analysis and IRC-determined analysis of PFS were consistent.

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

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

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

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



Number at risk:

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

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

| | CABOMETYX (N=79) | Sunitinib (N=78) |
|--|-----------------------------|-----------------------------|
| Progression-free survival (PFS) by IRC ^a | | |
| Median PFS in months (95% CI) | 8.6 (6.2, 14.0) | 5.3 (3.0, 8.2) |
| HR (95% CI); stratified ^{b,c} | 0.48 (0.32, 0.73) | |
| Two-sided log-rank p-value: stratified ^b | p=0.0005 | |
| Progression-free survival (PFS) by Investigator | | |
| Median PFS in months (95% CI) | 8.3 (6.5, 12.4) | 5.4 (3.4, 8.2) |
| HR (95% CI); stratified ^{b,c} | 0.56 (0.37, 0.83) | |
| Two-sided log-rank p-value: stratified ^b | p=0.0042 | |
| Overall Survival | | |
| Median OS in months (95% CI) | 30.3 (14.6, NE) | 21.0 (16.3, 27.0) |
| HR (95% CI); stratified ^{b,c} | 0.74 (0.47, 1.14) | |
| Objective Response Rate n (%) by IRC | | |
| Complete responses | 0 | 0 |
| Partial responses | 16 (20) | 7 (9) |
| ORR (partial responses only) | 16 (20) | 7 (9) |
| Stable disease | 43 (54) | 30 (38) |
| Progressive Disease | 14 (18) | 23 (29) |
| Objective Response Rate n (%) by Investigator | | |
| Complete responses | 1 (1) | 0 |
| Partial responses | 25 (32) | 9 (12) |

| | | |
|------------------------------|---------|---------|
| ORR (partial responses only) | 26 (33) | 9 (12) |
| Stable disease | 34 (43) | 29 (37) |
| Progressive Disease | 14 (18) | 19 (24) |

^a in accord with EU censoring

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

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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with CABOMETYX in all subsets of the paediatric population in treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney) (see section 4.2 for information on paediatric use).

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 ($\geq 99.7\%$). Based on the population-pharmacokinetic (PK) model, the volume of distribution (V_z) is approximately 319 L (SE: $\pm 2.7\%$). Protein binding was not altered in subjects with mild or moderately impaired renal or hepatic function.

Biotransformation

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

Cabozantinib is a substrate for CYP3A4 metabolism *in vitro*, as a neutralizing antibody to CYP3A4 inhibited formation of metabolite XL184 N-oxide by >80% in a NADPH-catalyzed human liver microsomal (HLM) incubation; in contrast, neutralizing antibodies to CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation. A neutralizing antibody to CYP2C9 showed a minimal effect on cabozantinib metabolite formation (ie, a <20% reduction).

Elimination

In a population PK analysis of cabozantinib using data collected from 318 patients with RCC and 63 normal healthy volunteers following oral administration of doses of 60 mg, 40 mg, and 20 mg, the plasma terminal half-life of cabozantinib is approximately 99 hours. Mean clearance (CL/F) at steady-state was estimated to be 2.2 L/hr. Within a 48-day collection period after a single dose of 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

Results from a study in patients with renal impairment indicate that the ratios of geometric LS mean for plasma cabozantinib, C_{max} and AUC_{0-inf} were 19% and 30% higher, for subjects with mild renal impairment (90% CI for C_{max} 91.60% to 155.51%; AUC_{0-inf} 98.79% to 171.26%) and 2% and 6-7% higher (90% CI for C_{max} 78.64% to 133.52%; AUC_{0-inf} 79.61% to 140.11%), for subjects with moderate renal impairment compared to subjects with normal renal function. Patients with severe renal impairment have not been studied.

Hepatic impairment

Results from a study in patients with hepatic impairment indicate that exposure (AUC_{0-inf}) increased by 81% and 63% in subjects with mild and moderate hepatic impairment, respectively (90% CI for AUC_{0-inf}: 121.44% to 270.34% for mild and 107.37% to 246.67% for moderate). Patients with severe hepatic impairment have not been studied.

Race

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

5.3 Preclinical safety data

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

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

Cabozantinib has shown no mutagenic or clastogenic potential in a standard battery of genotoxicity assays. The carcinogenic potential of cabozantinib has been evaluated in two species: rasH2 transgenic mice and Sprague-Dawley rats. In the 2-year rat carcinogenicity study, cabozantinib-related neoplastic findings consisted of an increased incidence of benign pheochromocytoma, alone or in combination with malignant pheochromocytoma/complex malignant pheochromocytoma of the adrenal medulla in both sexes at exposures well below the intended exposure in humans. The clinical relevance of the observed neoplastic lesions in rats is uncertain, but likely to be low.

Cabozantinib was not carcinogenic in the rasH2 mouse model at a slightly higher exposure than the intended human therapeutic exposure.

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet content

Microcrystalline cellulose
Anhydrous lactose
Hydroxypropyl cellulose
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

Film-coating

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PCTFE blister with push-through aluminum foil backing containing 7 film-coated tablets. Each carton contains 4 blisters with 28 film-coated tablets.

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Ipsen Pharma
65 quai Georges Gorse
92100 Boulogne-Billancourt
France

8. MARKETING AUTHORISATION NUMBER(S)

Cabometyx 20 mg film-coated tablets

EU/1/16/1136/001

EU/1/16/1136/002

Cabometyx 40 mg film-coated tablets

EU/1/16/1136/003

EU/1/16/1136/004

Cabometyx 60 mg film-coated tablets

EU/1/16/1136/005

EU/1/16/1136/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 September 2016

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Patheon France
40 Boulevard de Champaret
38300 Bourgoin-Jallieu
FRANCE

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

CABOMETYX 20 mg film-coated tablets
cabozantinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
28 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma
65 quai Georges Gorse
92100 Boulogne-Billancourt
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1136/001
EU/1/16/1136/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CABOMETYX 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

CABOMETYX 20 mg film-coated tablets
cabozantinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

CABOMETYX 40 mg film-coated tablets
cabozantinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
28 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma
65 quai Georges Gorse
92100 Boulogne-Billancourt
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1136/003
EU/1/16/1136/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CABOMETYX 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

CABOMETYX 40 mg film-coated tablets
cabozantinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

CABOMETYX 60 mg film-coated tablets
cabozantinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
28 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma
65 quai Georges Gorse
92100 Boulogne-Billancourt
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1136/005
EU/1/16/1136/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CABOMETYX 60 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

CABOMETYX 60 mg film-coated tablets
cabozantinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

CABOMETYX 20 mg film-coated tablets
cabozantinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma
65 quai Georges Gorse
92100 Boulogne-Billancourt
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1136/002

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

CABOMETYX 40 mg film-coated tablets
cabozantinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma
65 quai Georges Gorse
92100 Boulogne-Billancourt
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1136/004

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

CABOMETYX 60 mg film-coated tablets
cabozantinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma
65 quai Georges Gorse
92100 Boulogne-Billancourt
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1136/006

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

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

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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

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

What is in this leaflet

1. What CABOMETYX is and what it is used for
2. What you need to know before you take CABOMETYX
3. How to take CABOMETYX
4. Possible side effects
5. How to store CABOMETYX
6. Contents of the pack and other information

1. What CABOMETYX is and what it is used for

What CABOMETYX is

CABOMETYX is a cancer medicine that contains the active substance cabozantinib. It is used to treat advanced stages of a type of kidney cancer called renal cell carcinoma in adults. .

How CABOMETYX works

CABOMETYX blocks the action of proteins called receptor tyrosine kinases (RTKs), which are involved in the growth of cells and the development of new blood vessels that supply them. These proteins can be present in high amounts in cancer cells, and by blocking their action CABOMETYX can slow down the rate at which the tumour grows and help to cut off the blood supply that the cancer needs.

2. What you need to know before you take CABOMETYX

Do not take CABOMETYX

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

Warnings and precautions

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

- have high blood pressure
- have diarrhoea
- have a recent history of significant bleeding
- have had surgery within the last month (or if surgical procedures are planned), including dental surgery
- have inflammatory bowel disease (for example, Crohn's disease or ulcerative colitis, diverticulitis, or appendicitis)
- have a recent history of blood clot in the leg, stroke, or heart attack
- have liver or kidney disease.

Tell your doctor if any of these affect you.

You may need treatment for them, or your doctor may decide to change your dose of CABOMETYX, or stop treatment altogether. See also section 4 "*Possible side effects*".

Children and adolescents

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

Other medicines and CABOMETYX

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

- Medicines that treat fungal infections, such as itraconazole, ketoconazole, and posaconazole
- Medicines used to treat bacterial infections (antibiotics) such as erythromycin, clarithromycin, and rifampicin
- Allergy medicines such as fexofenadine and ranolazine
- Medicines used to treat epilepsy or fits such as phenytoin, carbamazepine, and phenobarbital
- Herbal preparations containing St. John's Wort (*Hypericum perforatum*), sometimes used for treating depression or depression-related conditions such as anxiety
- Medicines used to thin the blood, such as warfarin
- Medicines to treat high blood pressure or other heart conditions, such as aliskiren, ambrisentan, dabigatran etexilate, digoxin, talinolol, and tolvaptan
- Medicines for diabetes, such as saxagliptin and sitagliptin
- Medicines used to treat gout, such as colchicine
- Medicines used to treat HIV or AIDS, such as efavirenz, ritonavir, maraviroc and emtricitabine
- Medicines used to prevent transplant rejection (cyclosporin) and cyclosporin-based regimens in rheumatoid arthritis and psoriasis

Oral contraceptives

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

Taking CABOMETYX with food

You should not take CABOMETYX with food. You should not eat anything for at least 2 hours before taking CABOMETYX and for 1 hour after taking the medicine. Avoid consuming grapefruit-containing

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

Pregnancy, breast-feeding and fertility

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

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

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

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

Driving and using machines

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

CABOMETYX contains lactose

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

3. How to take CABOMETYX

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

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

CABOMETYX should be taken once a day. The usual dose is 60 mg, however your doctor will decide on the right dose for you.

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

If you take more CABOMETYX than you should

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

If you forget to take CABOMETYX

- If there are still 12 hours or more before your next dose is due, then take the missed dose as soon as you remember. Take the next dose at the normal time.

- If your next dose is due in less than 12 hours, then do not take the dose that you have missed. Take your next dose at the normal time.

4. Possible side effects

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

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

- Symptoms including pain in the abdomen (belly), nausea (feeling sick), vomiting, constipation, or fever. These may be signs of a gastrointestinal perforation, a hole that develops in your stomach or intestine that could be life-threatening.
 - Severe or uncontrollable bleeding with symptoms such as: vomiting blood, black stools, bloody urine, headache, coughing up of blood.
 - Swelling, pain in your hands and feet, or shortness of breath.
 - A wound that does not heal.
- Fits, headaches, confusion, or finding it difficult to concentrate. These may be signs of a condition called reversible posterior leukoencephalopathy syndrome (RPLS). RPLS is uncommon (it affects less than 1 in 100 people).

Other side effects include:

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

- Stomach upset, including diarrhoea, nausea, vomiting, constipation, indigestion, and abdominal pain
- Blisters, pain of the hands or soles of the feet, rash or redness of the skin, dry skin, skin inflammation with eruptions and flat or raised skin bumps
- Decreased appetite, weight loss, altered sense of taste
- Fatigue, weakness, headache, dizziness, numbness, tingling, burning sensation, pain in the limbs
- Hypertension (increase in blood pressure)
- Anaemia (low levels of red blood cells)
- Reduction in platelets (which increase the risk of bleeding or bruising)
- Reduction in white blood cell count
- Redness, swelling or pain in the mouth or throat, difficulty in speaking, hoarseness, cough, dry mouth
- Changes in blood tests used to monitor general health and function of your organs (including the liver)
- Low levels of electrolytes in the blood (like magnesium, calcium, phosphate, sodium, or potassium)
- High blood potassium levels
- Increase in the level of bilirubin in your blood (which may result in jaundice/yellow skin or eyes)
- Decrease in blood level of certain type of protein (hypoalbuminaemia)
- Changes in blood tests used to monitor function of your pancreas (including increase in levels of lipase and amylase)
- Increase in blood creatinine (a chemical product of muscle activity excreted by the kidneys)
- Increase or decrease in blood sugar levels
- Increase in blood cholesterol level
- Pain in arms, legs and joints, muscle spasms
- Shortness of breath
- Protein in urine (seen in tests)
- Reduced thyroid activity; symptoms can include: tiredness, weight gain, constipation, feeling cold and dry skin

- Dehydration (lack of fluids)
- Alopecia (hair loss and thinning), hair colour change

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

- Abscess (collection of pus, with swelling and inflammation)
- Ringing in ears
- Blood clots in the veins, arteries and lungs
- Inflammation of the pancreas
- Pain in the upper part of the abdomen
- Gastro-oesophageal reflux disease (bringing up stomach acid)
- Haemorrhoids (piles)
- Itch
- Swelling in your legs, feet, arms and hands
- Wound complications

Uncommon side effects (may affect 1 in 100 people)

- Fits
- A painful tear or abnormal connection of the tissue in your anus
- Decrease in bile flow from the liver
- Bone damage in the jaw

Not known (unknown frequency)

- Stroke
- Heart attack

Reporting of side effects

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

5. How to store CABOMETYX

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

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

This medicinal product does not require any special storage conditions.

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

6. Contents of the pack and other information

What CABOMETYX contains

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

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

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

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

The other ingredients are:

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

What CABOMETRYX looks like and contents of the pack

CABOMETRYX 20 mg film-coated tablets are yellow, round with no score, and identified with “XL” on one side and “20” on the other side.

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

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

CABOMETRYX tablets are available in packs containing either 4 blisters with 7 tablets each (28 total), or one plastic bottle with 30 tablets.

Not all pack sizes may be marketed in your country.

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Other sources of information

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

Annex IV

Scientific conclusions and grounds for the variation to the terms of the marketing authorisations

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSURs for cabozantinib, the scientific conclusions of CHMP are as follows:

A review of thromboembolic events showed that cerebrovascular accident, myocardial infarction and venous and arterial thrombosis occur following cabozantinib use in clinical trial and/or post-marketing setting. Although information on cases is limited or confounding factors are present in some cases, a causal relationship cannot be excluded. In addition, the literature indicates an increased risk of (arterial) thromboembolic events with VEGFR-TKIs. Therefore, it is recommended to update the product information with these events.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisations

On the basis of the scientific conclusions for cabozantinib the CHMP is of the opinion that the benefit-risk balance of the medicinal products containing cabozantinib is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisations should be varied.