

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

COMETRIQ 20 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One hard capsule contains cabozantinib (*S*)-malate equivalent to 20 mg cabozantinib. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

The hard capsules are grey with “XL184 20mg” printed in black on the body of the capsule. The capsule contains an off-white to white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COMETRIQ is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.

For patients in whom Rearranged during Transfection (RET) mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision (see important information in sections 4.4 and 5.1).

4.2 Posology and method of administration

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

Posology

The recommended dose of COMETRIQ is 140 mg once daily, taken as one 80 mg orange capsule and three 20 mg grey capsules. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

It should be expected that a majority of patients treated with COMETRIQ will require one or more dose adjustments (reduction and/or interruption) due to toxicity. Patients should therefore be closely monitored during the first eight weeks of therapy (see section 4.4).

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of COMETRIQ therapy. When dose reduction is necessary, it is recommended to reduce to 100 mg daily, taken as one 80 mg orange capsule and one 20 mg grey capsule, and then to 60 mg daily, taken as three 20 mg grey capsules.

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.

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), and gastrointestinal (GI) events (abdominal or mouth pain, mucosal inflammation, constipation, diarrhoea, vomiting).

The occurrence of some serious adverse reactions (like GI fistula) might be dependent on the cumulative dose and might present in a later stage of treatment.

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

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.

Elderly patients

No specific dose adjustment for the use of cabozantinib in older people (≥ 65 years) is recommended. However, a trend in increased rate of SAEs has been observed in subjects aged 75 years and older.

Race

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

Renal impairment

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

Hepatic impairment

In patients with mild or moderate hepatic impairment the recommended dose of cabozantinib is 60 mg once daily. Monitor for adverse events and adjust dose or use dosing interruption 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 aged <18 years have not yet been established. No data are available.

Method of administration

The capsules should be swallowed whole and not opened. Patients should be instructed to not eat anything for at least 2 hours before through 1 hour after taking COMETRIQ.

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

Dose reductions and dose interruptions occurred in 79% and 72%, respectively, of cabozantinib-treated patients in the pivotal clinical trial. Two dose reductions were required in 41% of patients. The median time to first dose reduction was 43 days, and to first dose interruption was 33 days. Close monitoring of patients is therefore recommended during the first eight weeks of therapy (see section 4.2).

Perforations, fistulas, and intra-abdominal abscesses

Serious GI perforations and fistulas, sometimes fatal, and intra-abdominal abscesses have been observed with cabozantinib. Patients who have had recent radiotherapy, have inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, peritonitis, or diverticulitis), have tumour infiltration of trachea, bronchi, or oesophagus, have complications from prior GI surgery (particularly when associated with delayed or incomplete healing), or have complications from prior radiation therapy to the thoracic cavity (including mediastinum) should be carefully evaluated before initiating cabozantinib therapy and subsequently they should be monitored closely for symptoms of perforations and fistulas. Non-GI fistula should be ruled out as appropriate in cases of onset of mucositis after start of therapy. Cabozantinib should be discontinued in patients who experience a GI perforation or a GI or non-GI fistula.

Thromboembolic events

Events of venous thromboembolism 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

Haemorrhage has been observed with cabozantinib. Patients who have evidence of involvement of the trachea or bronchi by tumour or a history of haemoptysis prior to treatment initiation should be carefully evaluated before initiating cabozantinib therapy. Cabozantinib should not be administered to patients with serious haemorrhage or recent haemoptysis.

Wound complications

Wound complications have been observed with cabozantinib. Cabozantinib treatment should be stopped at least 28 days prior to scheduled 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. 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.

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. For invasive dental procedures, cabozantinib treatment should be held at least 28 days prior to scheduled surgery, if possible. Caution should be used in patients receiving agents associated with ONJ, such as bisphosphonates. Cabozantinib should be discontinued in patients who experience ONJ.

Palmar-plantar 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.

Reversible posterior leukoencephalopathy syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS), also known as Posterior Reversible Encephalopathy Syndrome (PRES) has been observed with cabozantinib. 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. Concomitant treatment with strong CYP3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be used with caution.

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.

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.

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 cholestagel may interact with cabozantinib and may impact absorption (or reabsorption) resulting in potentially decreased exposure (see section 5.2). The clinical significance of these potential interactions is unknown.

Effect of cabozantinib on other medicinal products

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

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, 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 a 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 reactions associated with cabozantinib are pneumonia, mucosal inflammation, hypocalcaemia, dysphagia, dehydration, pulmonary embolism, and hypertension. The most frequent adverse reactions of any grade (experienced by at least 20% of patients) included diarrhoea, PPES, weight decreased, decreased appetite, nausea, fatigue, dysgeusia, hair colour changes, hypertension, stomatitis, constipation, vomiting, mucosal inflammation, asthenia, and dysphonia.

The most common laboratory abnormalities were increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased alkaline phosphatase (ALP), lymphopenia, hypocalcaemia, neutropenia, thrombocytopenia, hypophosphataemia, hyperbilirubinemia, hypomagnesaemia, and hypokalaemia.

Tabulated summary of adverse reactions

Adverse reactions are listed in Table 1 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 $< 1/100$), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions reported with cabozantinib

MedDRA System Organ Class	Very Common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Not Known
Infections and infestations		abscess (including visceral, skin, tooth), pneumonia, folliculitis, fungal infection (including skin, oral, genital)	aspergilloma	
Endocrine disorders		hypothyroidism		
Metabolism and nutrition disorders	decreased appetite, hypocalcaemia, hypophosphataemia, hyperbilirubinemia, hypokalaemia, hypomagnesaemia	dehydration, hypoalbuminaemia		
Psychiatric disorders		anxiety, depression, confusional state	abnormal dreams, delirium	
Nervous system disorders	dysgeusia, headache, dizziness	cerebrovascular accident, peripheral neuropathy, paraesthesia, ageusia, tremor	ataxia, disturbance in attention, hepatic encephalopathy, loss of consciousness, speech disorder, posterior reversible encephalopathy syndrome	
Eye disorders		vision blurred	cataract, conjunctivitis	

MedDRA System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Not Known
Ear and labyrinth disorders		ear pain, tinnitus	hearing impairment	
Cardiac disorders		atrial fibrillation	angina pectoris, supraventricular tachycardia	myocardial infarction
Vascular disorders	hypertension	hypotension, venous thrombosis, pallor, peripheral coldness	arterial thrombosis	
Respiratory, thoracic, and mediastinal disorders	dysphonia, oropharyngeal pain	non-gastrointestinal fistula (including tracheal, pneumomediastinum, tracheo-oesophageal), pulmonary embolism, respiratory tract haemorrhage (including pulmonary, bronchial, tracheal), pneumonia aspiration	atelectasis, pharyngeal oedema, pneumonitis	
Gastrointestinal disorders	diarrhoea, nausea, stomatitis, constipation, vomiting, abdominal pain, dyspepsia, dysphagia, glossodynia	gastrointestinal perforation, gastrointestinal haemorrhage, pancreatitis, haemorrhoids, anal fissure, anal inflammation, cheilitis	gastrointestinal fistula, oesophagitis	
Hepatobiliary disorders		cholelithiasis		
Skin and subcutaneous tissue disorders	palmar-plantar erythrodysesthesia syndrome, hair colour changes, rash, dry skin, alopecia, erythema	hyperkeratosis, acne, blister, hair growth abnormal, skin exfoliation, skin hypopigmentation	skin ulcer, telangiectasia	
Musculoskeletal and connective tissue disorders	arthralgia, muscle spasms	musculoskeletal chest pain, osteonecrosis of jaw	rhabdomyolysis	

MedDRA System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Not Known
Renal and urinary disorders		proteinuria, dysuria, haematuria	renal failure acute	
Reproductive system and breast disorders			amenorrhoea, vaginal haemorrhage	
General disorders and administration site conditions	fatigue, mucosal inflammation, asthenia	impaired wound healing, chills, face oedema	cyst, facial pain, localised oedema	
Investigations	weight decreased, serum ALT, AST, and ALP increased, blood LDH increased, blood TSH increased, lymphopenia, neutropenia, thrombocytopenia	blood creatinine phosphokinase increased	activated partial thromboplastin time shortened, eosinophil count increased, platelet count increased	

Description of selected adverse reactions

A thyroid stimulating hormone (TSH) value above normal after first dose was observed in 57% of patients on cabozantinib versus 19% of patients on placebo (regardless of baseline values). Ninety-two percent of patients on the cabozantinib arm had a prior thyroidectomy, and 89% were taking thyroid hormones prior to first dose.

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 cancer patients. This effect was not associated with a change in cardiac wave form morphology or new rhythms. No cabozantinib-treated subjects had a QTcF >500 ms.

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, 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 RET, the GAS6 receptor (AXL), the stem cell factor receptor (KIT), and Fms-like tyrosine kinase-3 (FLT3).

Pharmacodynamic effects

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

Efficacy with cabozantinib was observed in medullary thyroid cancer patients with wild-type or mutant RET.

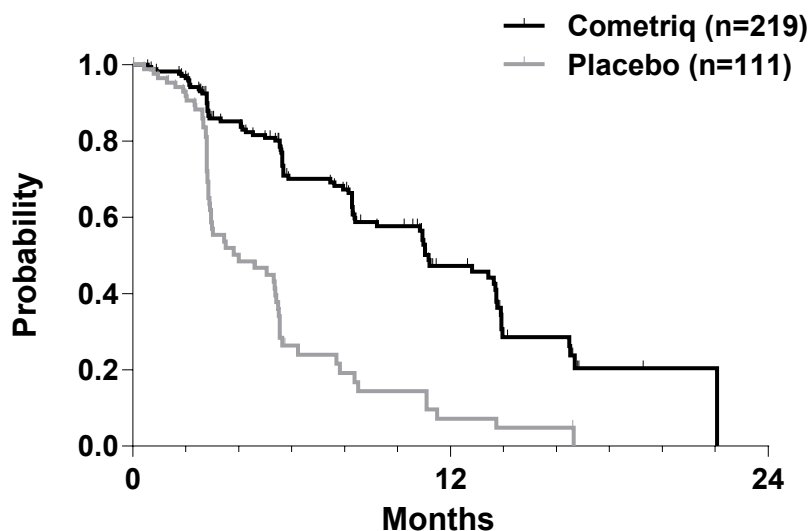
Clinical data in medullary thyroid cancer

A multi-center, randomized double-blind study comparing cabozantinib (N = 219) with placebo (N = 111) was conducted in patients with unresectable locally advanced or metastatic MTC and documented radiographic disease progression within 14 months prior to study entry. The primary objective was to compare progression-free survival (PFS) in patients receiving cabozantinib versus patients receiving placebo. The secondary objectives were to compare overall response rate (ORR) and overall survival (OS). Centralized, independent, blinded review of the imaging data was used in the assessment of PFS and ORR. Patients were treated until disease progression or unacceptable toxicity.

The result of the PFS analysis, based on the central review RECIST assessment, demonstrated a statistically significant difference in the duration of PFS with cabozantinib versus placebo: the median duration was 11.2 months for subjects in the cabozantinib arm versus 4.0 months for subjects in the placebo arm (stratified Hazard Ratio [HR] = 0.28; 95% CI: 0.19, 0.40; $p < 0.0001$; Figure 1). The PFS results were consistent across all baseline and demographic subgroups evaluated, including prior therapy with tyrosine kinase inhibitors (which may have consisted of agents targeting pathways associated with anti-angiogenesis), RET mutational status (including subjects documented not to have RET mutations), prior anticancer or radiotherapy status, or the existence of bone metastases.

The ORR was 27.9% and 0% for subjects in the cabozantinib arm and placebo arm, respectively ($p < 0.0001$; Table 2). The median duration of objective responses was 14.6 months (95% CI: 11.1, 17.5) for subjects in the cabozantinib arm.

Figure 1: Kaplan Meier curve of progression free survival



Number of subjects at risk								
Month	0	3	6	9	12	15	18	21
Cometriq	219	121	78	55	31	12	2	1
Placebo	111	35	11	6	3	2	0	0

The final analysis of OS was conducted after 218 events (deaths) occurred and shows a trend for an increase in median survival of 5.5 months in the cabozantinib arm: median (months) 26.6 cabozantinib vs. 21.1 placebo (HR = 0.85 [95% CI: 0.64, 1.12], p = 0.2409).

Figure 2: Kaplan-Meier curve of overall survival

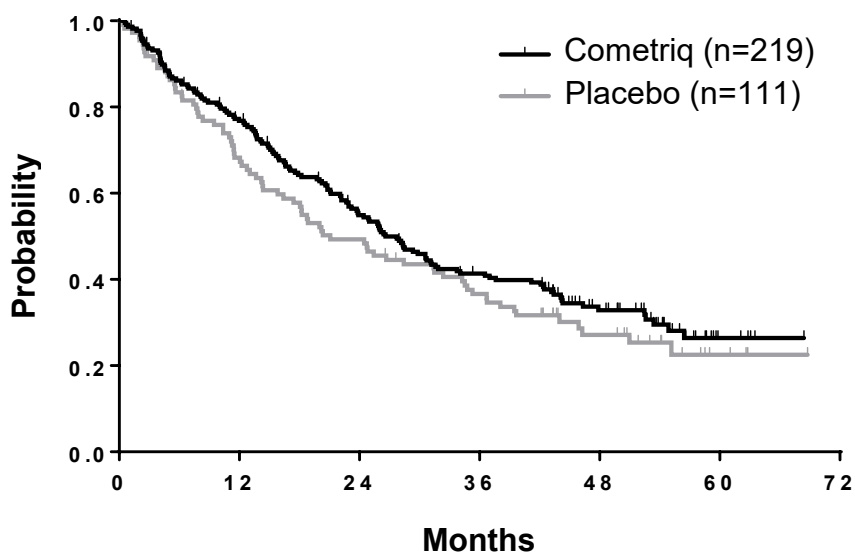


Table 2: Summary of key efficacy findings

	Cabozantinib	Placebo
Median Progression-Free Survival	11.2 months	4.0 months
	HR: 0.28 (0.19, 0.40) p <0.0001	
Median Overall Survival	26.6 months	21.1 months
	HR: 0.85 (0.64, 1.12) p = 0.2409	
Overall Response Rate^a (95% CI)	27.9% (21.9%, 34.5%)	0%
	p <0.0001	
Duration of Response; Median (95% CI)	14.6 months (11.1, 17.5)	N/A
Disease Control Rate^b (95% CI)	55.3% (48.3%, 62.2%)	13.5% (7.6%, 21.6%)
Calcitonin Response^a	47% (49/104) ^c	3% (1/40) ^c
CEA Response^a	33% (47/143) ^c	2% (1/55) ^c

^a Response = CR + PR

^b Disease Control Rate = SD+ ORR

^c Includes patients who were evaluable for response

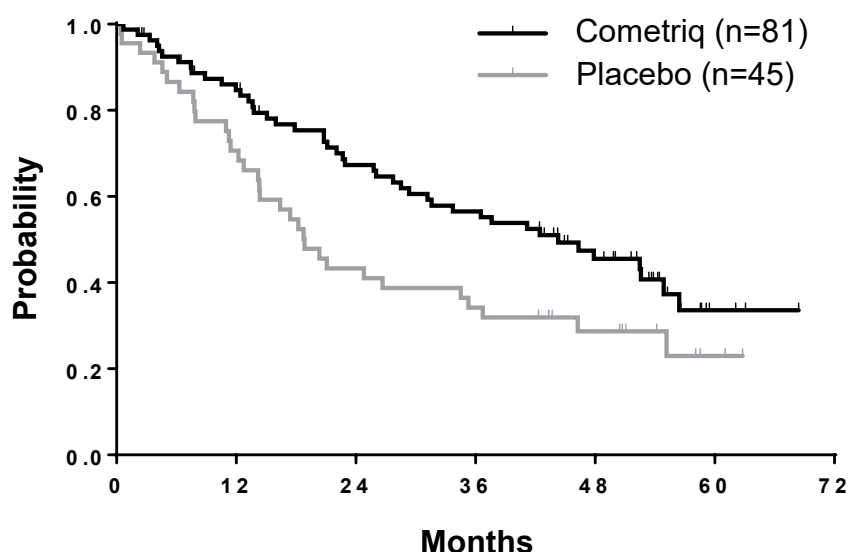
RET mutation status

Of the 215 subjects with sufficient data to determine mutational status, 78.6% (n=169) were classified as *RET* mutation positive (126 of which were positive for the M918T mutation), and 21.4% (n=46) were classified as *RET* mutation negative. For an additional 115 subjects the *RET* mutational status could not be determined or was unclear. All three subgroups showed increased PFS in the cabozantinib arm compared to the placebo arm (HRs of 0.23, 0.53, and 0.30 for *RET* mutation positive, negative, and unknown subgroups, respectively). The objective response rates measured in these subgroups were generally consistent with the PFS results, with the *RET* mutation positive, negative, and unknown subgroups showing tumour response rates of 32%, 22%, and 25%, respectively.

Further genetic analysis showed that a small proportion of patients harboured somatic tumour mutations in *HRAS*, *KRAS*, or *NRAS*. These patients (n=16) showed significant prolongation of PFS (HR of 0.15) and an objective response rate of 31%. *RET* mutation negative patients with no evidence of RAS mutation (n=33) showed a decreased PFS benefit on cabozantinib (HR of 0.87) and a lower response rate of 18% compared to other mutational subgroups.

A significant improvement in OS was observed in the subgroup of *RET* M918T mutation positive patients (n=81/219 cabozantinib arm): 44.3 months in the cabozantinib arm vs. 18.9 months in the placebo arm (HR = 0.60, p = 0.0255). There was no improvement in OS for the *RET* M918T negative and unknown subgroups.

Figure 3: Kaplan-Meier Analysis of OS Among Subjects with a *RET* M918T Mutation



Paediatric population

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

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary

5.2 Pharmacokinetic properties

Absorption

Following oral administration of cabozantinib, peak cabozantinib plasma concentrations are reached at 2 to 5 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.

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/F) is approximately 349 L (SE: $\pm 2.73\%$). 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

The plasma terminal half-life of cabozantinib in single dose studies in healthy volunteers is approximately 120 hours. Mean clearance (CL/F) at steady-state in cancer patients was estimated to be 4.4 L/hr in a population PK analysis. 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

No data are available to determine a difference in PK 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 bile duct hyperplasia. Findings in uterus/ovaries and decreased haematopoiesis appeared to be transient, while effects on bone parameters and liver pigmentation were sustained. Evaluations in juvenile rats (comparable to a <2 year old pediatric population) have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Microcrystalline cellulose
Croscarmellose sodium
Sodium starch glycolate
Silica colloidal anhydrous
Stearic acid

Capsule shell

Gelatin
Black iron oxide (E172)
Titanium dioxide (E171)

Printing ink

Shellac
Black iron oxide (E172)
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25 °C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PE/PCTFE-Al blisters with foil backing, sealed into a secondary heat-sealed card packaging.

Blister cards containing:

21 x 20 mg capsules (60 mg/day dose for a 7-day supply)

28 day pack containing:

84 capsules (4 blister cards of 21 x 20 mg) (60 mg/day dose for a 28 day supply)

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)

EU/1/13/890/001 21 x 20 mg capsules (60 mg/day dose for a 7-day supply)
EU/1/13/890/004 84 capsules (4 blister cards of 21 x 20 mg) (60 mg/day dose for a 28 day supply)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2014
Date of latest renewal: 08 January 2018

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>.

▼ 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

COMETRIQ 20 mg hard capsules
COMETRIQ 80 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One hard capsule contains cabozantinib (*S*)-malate equivalent to 20 mg or 80 mg cabozantinib. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

The hard capsules are grey with “XL184 20mg” printed in black on the body of the capsule. The capsule contains an off-white to white powder.

The hard capsules are orange with “XL184 80mg” printed in black on the body of the capsule. The capsule contains an off-white to white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COMETRIQ is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.

For patients in whom Rearranged during Transfection (RET) mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision (see important information in sections 4.4 and 5.1).

4.2 Posology and method of administration

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

Posology

The recommended dose of COMETRIQ is 140 mg once daily, taken as one 80 mg orange capsule and three 20 mg grey capsules. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

It should be expected that a majority of patients treated with COMETRIQ will require one or more dose adjustments (reduction and/or interruption) due to toxicity. Patients should therefore be closely monitored during the first eight weeks of therapy (see section 4.4).

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of COMETRIQ therapy. When dose reduction is necessary, it is recommended to reduce to 100 mg daily,

taken as one 80 mg orange capsule and one 20 mg grey capsule, and then to 60 mg daily, taken as three 20 mg grey capsules.

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.

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), and gastrointestinal (GI) events (abdominal or mouth pain, mucosal inflammation, constipation, diarrhoea, vomiting).

The occurrence of some serious adverse reactions (like GI fistula) might be dependent on the cumulative dose and might present in a later stage of treatment.

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

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.

Elderly patients

No specific dose adjustment for the use of cabozantinib in older people (≥ 65 years) is recommended. However, a trend in increased rate of SAEs has been observed in subjects aged 75 years and older.

Race

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

Renal impairment

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

Hepatic impairment

In patients with mild or moderate hepatic impairment the recommended dose of cabozantinib is 60 mg once daily. Monitor for adverse events and adjust dose or use dosing interruption as needed (see section 4.2). Cabozantinib is not recommended for use in subjects 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 aged <18 years have not yet been established. No data are available.

Method of administration

The capsules should be swallowed whole and not opened. Patients should be instructed to not eat anything for at least 2 hours before through 1 hour after taking COMETRIQ.

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

Dose reductions and dose interruptions occurred in 79% and 72%, respectively, of cabozantinib-treated patients in the pivotal clinical trial. Two dose reductions were required in 41% of patients. The median time to first dose reduction was 43 days, and to first dose interruption was 33 days. Close monitoring of patients is therefore recommended during the first eight weeks of therapy (see section 4.2).

Perforations, fistulas, and intra-abdominal abscesses

Serious GI perforations and fistulas, sometimes fatal, and intra-abdominal abscesses have been observed with cabozantinib. Patients who have had recent radiotherapy, have inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, peritonitis, or diverticulitis), have tumour infiltration of trachea, bronchi, or oesophagus, have complications from prior GI surgery (particularly when associated with delayed or incomplete healing), or have complications from prior radiation therapy to the thoracic cavity (including mediastinum) should be carefully evaluated before initiating cabozantinib therapy and subsequently they should be monitored closely for symptoms of perforations and fistulas. Non-GI fistula should be ruled out as appropriate in cases of onset of mucositis after start of therapy. Cabozantinib should be discontinued in patients who experience a GI perforation or a GI or non-GI fistula.

Thromboembolic events

Events of venous thromboembolism 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

Hemorrhage has been observed with cabozantinib. Patients who have evidence of involvement of the trachea or bronchi by tumour or a history of haemoptysis prior to treatment initiation should be carefully evaluated before initiating cabozantinib therapy. Cabozantinib should not be administered to patients with serious haemorrhage or recent haemoptysis.

Wound complications

Wound complications have been observed with cabozantinib. Cabozantinib treatment should be stopped at least 28 days prior to scheduled 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. 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.

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. For invasive dental procedures, cabozantinib treatment should be held at least 28 days prior to scheduled surgery, if possible. Caution should be used in patients receiving agents associated with ONJ, such as bisphosphonates. Cabozantinib should be discontinued in patients who experience ONJ.

Palmar-plantar erythrodysaesthesia syndrome

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

Proteinuria

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

Reversible posterior leukoencephalopathy syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS), also known as Posterior Reversible Encephalopathy Syndrome (PRES) has been observed with cabozantinib. 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. Concomitant treatment with strong CYP3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be used with caution.

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.

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.

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 cholestagel may interact with cabozantinib and may impact absorption (or reabsorption) resulting in potentially decreased exposure (see section 5.2). The clinical significance of these potential interactions is unknown.

Effect of cabozantinib on other medicinal products

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

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, 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 a 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 reactions associated with cabozantinib are pneumonia, mucosal inflammation, hypocalcaemia, dysphagia, dehydration, pulmonary embolism, and hypertension. The most frequent adverse reactions of any grade (experienced by at least 20% of patients) included diarrhoea, PPES, weight decreased, decreased appetite, nausea, fatigue, dysgeusia, hair colour changes, hypertension, stomatitis, constipation, vomiting, mucosal inflammation, asthenia, and dysphonia.

The most common laboratory abnormalities were increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased alkaline phosphatase (ALP), lymphopenia, hypocalcaemia, neutropenia, thrombocytopenia, hypophosphataemia, hyperbilirubinemia, hypomagnesaemia, and hypokalaemia.

Tabulated summary of adverse reactions

Adverse reactions are listed in Table 1 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 $< 1/100$), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions reported with cabozantinib

MedDRA System Organ Class	Very Common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Not Known
Infections and infestations		abscess (including visceral, skin, tooth), pneumonia, folliculitis, fungal infection (including skin, oral, genital)	aspergilloma	
Endocrine disorders		hypothyroidism		
Metabolism and nutrition disorders	decreased appetite, hypocalcaemia, hypophosphataemia, hyperbilirubinemia, hypokalaemia, hypomagnesaemia	dehydration, hypoalbuminaemia		
Psychiatric disorders		anxiety, depression, confusional state	abnormal dreams, delirium	
Nervous system disorders	dysgeusia, headache, dizziness	cerebrovascular accident, peripheral neuropathy, paraesthesia, ageusia, tremor	ataxia, disturbance in attention, hepatic encephalopathy, loss of consciousness,	

MedDRA System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Not Known
			speech disorder, posterior reversible encephalopathy syndrome	
Eye disorders		vision blurred	cataract, conjunctivitis	
Ear and labyrinth disorders		ear pain, tinnitus	hypoacusis	
Cardiac disorders		atrial fibrillation	angina pectoris, supraventricular tachycardia	myocardial infarction
Vascular disorders	hypertension	hypotension, venous thrombosis, pallor, peripheral coldness	arterial thrombosis	
Respiratory, thoracic, and mediastinal disorders	dysphonia, oropharyngeal pain	non-gastrointestinal fistula (including tracheal, pneumomediastinum, tracheo-oesophageal), pulmonary embolism, respiratory tract haemorrhage (including pulmonary, bronchial, tracheal), pneumonia aspiration	atelectasis, pharyngeal oedema, pneumonitis	
Gastrointestinal disorders	diarrhoea, nausea, stomatitis, constipation, vomiting, abdominal pain, dyspepsia, dysphagia, glossodynia	gastrointestinal perforation, gastrointestinal haemorrhage, pancreatitis, haemorrhoids, anal fissure, anal inflammation, cheilitis	gastrointestinal fistula, oesophagitis	
Hepatobiliary disorders		cholelithiasis		
Skin and subcutaneous tissue disorders	palmar-plantar erythrodysesthesia syndrome, hair colour changes, rash, dry skin, alopecia, erythema	hyperkeratosis, acne, blister, hair growth abnormal, skin exfoliation, skin hypopigmentation	skin ulcer, telangiectasia	
Musculoskeletal and connective tissue disorders	arthralgia, muscle spasms	musculoskeletal chest pain, osteonecrosis of jaw	rhabdomyolysis	

MedDRA System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Not Known
Renal and urinary disorders		proteinuria, dysuria, haematuria	renal failure acute	
Reproductive system and breast disorders			amenorrhoea, vaginal haemorrhage	
General disorders and administration site conditions	fatigue, mucosal inflammation, asthenia	impaired wound healing, chills, face oedema	cyst, facial pain, localised oedema	
Investigations	weight decreased, serum ALT, AST, and ALP increased, blood LDH increased, blood TSH increased, lymphopenia, neutropenia, thrombocytopenia	blood creatinine phosphokinase increased	activated partial thromboplastin time shortened, eosinophil count increased, platelet count increased	

Description of selected adverse reactions

A thyroid stimulating hormone (TSH) value above normal after first dose was observed in 57% of patients on cabozantinib versus 19% of patients on placebo (regardless of baseline values). Ninety-two percent of patients on the cabozantinib arm had a prior thyroidectomy, and 89% were taking thyroid hormones prior to first dose.

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 cancer patients. This effect was not associated with a change in cardiac wave form morphology or new rhythms. No cabozantinib-treated subjects had a QTcF >500 ms.

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, 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 RET, the GAS6 receptor (AXL), the stem cell factor receptor (KIT), and Fms-like tyrosine kinase-3 (FLT3).

Pharmacodynamic effects

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

Efficacy with cabozantinib was observed in medullary thyroid cancer patients with wild-type or mutant RET.

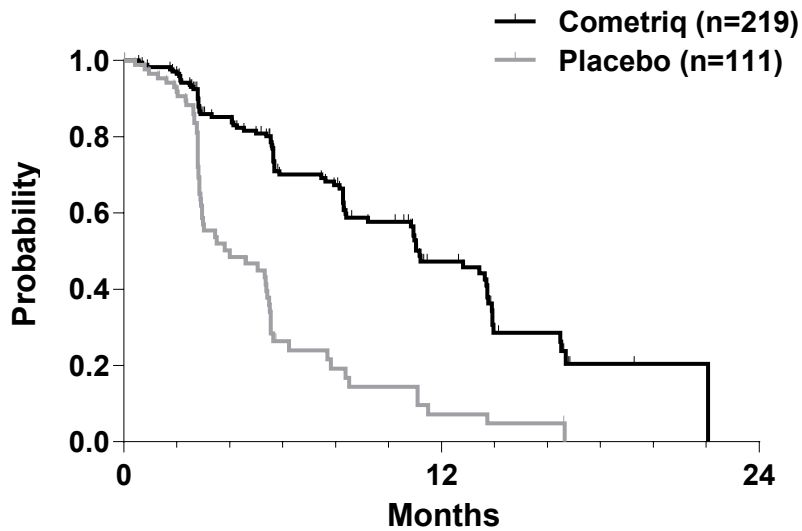
Clinical data in medullary thyroid cancer

A multi-center, randomized double-blind study comparing cabozantinib (N = 219) with placebo (N = 111) was conducted in patients with unresectable locally advanced or metastatic MTC and documented radiographic disease progression within 14 months prior to study entry. The primary objective was to compare progression-free survival (PFS) in patients receiving cabozantinib versus patients receiving placebo. The secondary objectives were to compare overall response rate (ORR) and overall survival (OS). Centralized, independent, blinded review of the imaging data was used in the assessment of PFS and ORR. Patients were treated until disease progression or unacceptable toxicity.

The result of the PFS analysis, based on the central review RECIST assessment, demonstrated a statistically significant difference in the duration of PFS with cabozantinib versus placebo: the median duration was 11.2 months for subjects in the cabozantinib arm versus 4.0 months for subjects in the placebo arm (stratified Hazard Ratio [HR] = 0.28; 95% CI: 0.19, 0.40; $p < 0.0001$; Figure 1). The PFS results were consistent across all baseline and demographic subgroups evaluated, including prior therapy with tyrosine kinase inhibitors (which may have consisted of agents targeting pathways associated with anti-angiogenesis), RET mutational status (including subjects documented not to have RET mutations), prior anticancer or radiotherapy status, or the existence of bone metastases.

The ORR was 27.9% and 0% for subjects in the cabozantinib arm and placebo arm, respectively ($p < 0.0001$; Table 2). The median duration of objective responses was 14.6 months (95% CI: 11.1, 17.5) for subjects in the cabozantinib arm.

Figure 1: Kaplan Meier curve of progression free survival



Number of subjects at risk								
Month	0	3	6	9	12	15	18	21
Cometriq	219	121	78	55	31	12	2	1
Placebo	111	35	11	6	3	2	0	0

The final analysis of OS was conducted after 218 events (deaths) occurred and shows a trend for an increase in median survival of 5.5 months in the cabozantinib arm: median (months) 26.6 cabozantinib vs. 21.1 placebo (HR = 0.85 [95% CI: 0.64, 1.12], p = 0.2409).

Figure 2: Kaplan-Meier curve of overall survival

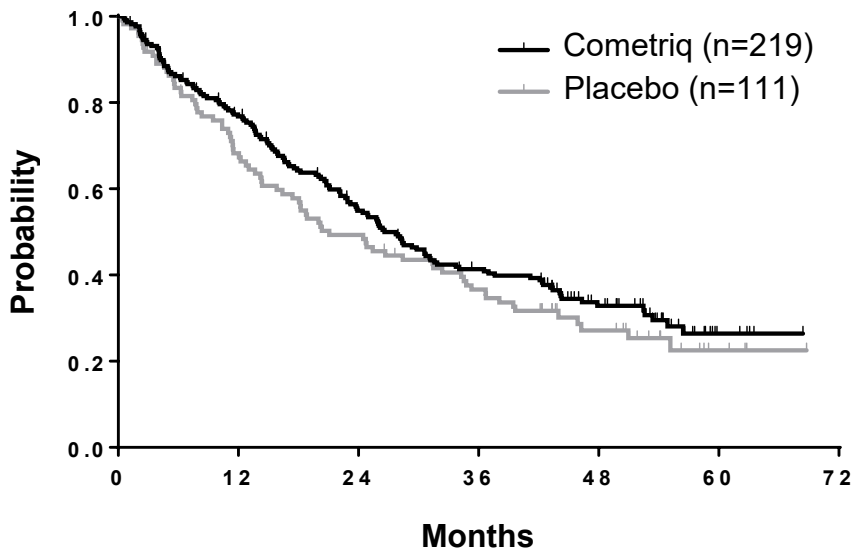


Table 2: Summary of key efficacy findings

	Cabozantinib	Placebo
Median Progression-Free Survival	11.2 months	4.0 months
	HR: 0.28 (0.19, 0.40) p <0.0001	
Median Overall Survival	26.6 months	21.1 months
	HR: 0.85 (0.64, 1.12) p = 0.2409	
Overall Response Rate^a (95% CI)	27.9% (21.9%, 34.5%)	0%
	p <0.0001	
Duration of Response; Median (95% CI)	14.6 months (11.1, 17.5)	N/A
Disease Control Rate^b (95% CI)	55.3% (48.3%, 62.2%)	13.5% (7.6%, 21.6%)
Calcitonin Response^a	47% (49/104) ^c	3% (1/40) ^c
CEA Response^a	33% (47/143) ^c	2% (1/55) ^c

^a Response = CR + PR

^b Disease Control Rate = SD+ ORR

^c Includes patients who were evaluable for response

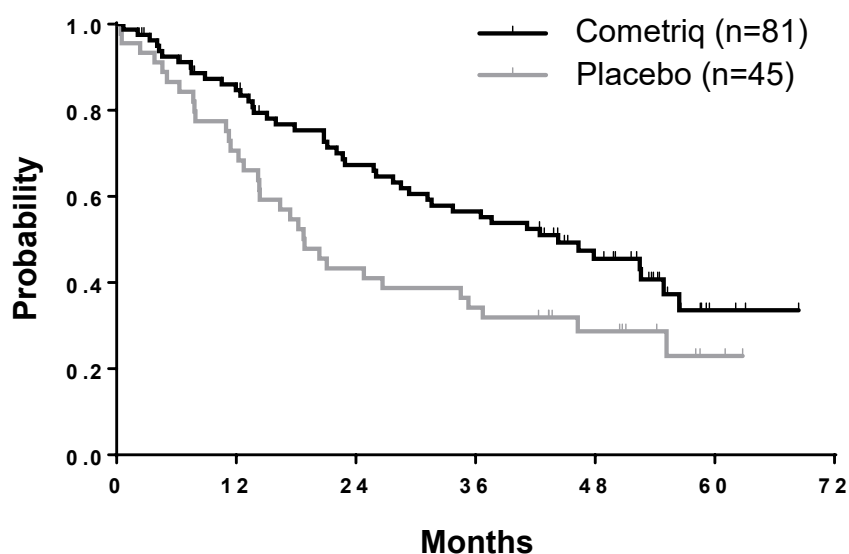
RET mutation status

Of the 215 subjects with sufficient data to determine mutational status, 78.6% (n=169) were classified as *RET* mutation positive (126 of which were positive for the M918T mutation), and 21.4% (n=46) were classified as *RET* mutation negative. For an additional 115 subjects the *RET* mutational status could not be determined or was unclear. All three subgroups showed increased PFS in the cabozantinib arm compared to the placebo arm (HRs of 0.23, 0.53, and 0.30 for *RET* mutation positive, negative, and unknown subgroups, respectively). The objective response rates measured in these subgroups were generally consistent with the PFS results, with the *RET* mutation positive, negative, and unknown subgroups showing tumour response rates of 32%, 22%, and 25%, respectively.

Further genetic analysis showed that a small proportion of patients harboured somatic tumour mutations in *HRAS*, *KRAS*, or *NRAS*. These patients (n=16) showed significant prolongation of PFS (HR of 0.15) and an objective response rate of 31%. *RET* mutation negative patients with no evidence of RAS mutation (n=33) showed a decreased PFS benefit on cabozantinib (HR of 0.87) and a lower response rate of 18% compared to other mutational subgroups.

A significant improvement in OS was observed in the subgroup of *RET* M918T mutation positive patients (n=81/219 cabozantinib arm): 44.3 months in the cabozantinib arm vs. 18.9 months in the placebo arm (HR = 0.60, p = 0.0255). There was no improvement in OS for the *RET* M918T negative and unknown subgroups.

Figure 3: Kaplan-Meier Analysis of OS Among Subjects with a *RET* M918T Mutation



Paediatric population

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

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary

5.2 Pharmacokinetic properties

Absorption

Following oral administration of cabozantinib, peak cabozantinib plasma concentrations are reached at 2 to 5 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.

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/F) is approximately 349 L (SE: $\pm 2.73\%$). 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

The plasma terminal half-life of cabozantinib in single dose studies in healthy volunteers is approximately 120 hours. Mean clearance (CL/F) at steady-state in cancer patients was estimated to be 4.4 L/hr in a population PK analysis. 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

No data are available to determine a difference in PK 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 bile duct hyperplasia. Findings in uterus/ovaries and decreased haematopoiesis appeared to be transient, while effects on bone parameters and liver pigmentation were sustained. Evaluations in juvenile rats (comparable to a <2 year old pediatric population) have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Microcrystalline cellulose
Croscarmellose sodium
Sodium starch glycolate
Silica colloidal anhydrous
Stearic acid

Capsule shell

Gelatin
Black iron oxide (E172) (20 mg capsules only)
Red iron oxide (E172) (80 mg capsules only)
Titanium dioxide (E171)

Printing ink

Shellac
Black iron oxide (E172)
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25 °C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PE/PCTFE-Al blisters with foil backing, sealed into a secondary heat-sealed card packaging.

Blister cards containing either:

7 x 20 mg and 7 x 80 mg capsules (100 mg/day dose for a 7-day supply)
21 x 20 mg and 7 x 80 mg capsules (140 mg/day dose for a 7-day supply)

28 day pack containing:

56 capsules (4 blister cards of 7 x 20 mg and 7 x 80 mg) (100 mg/day dose for a 28 day supply)
112 capsules (4 blister cards of 21 x 20mg and 7 x 80 mg) (140 mg/day dose for a 28 day supply)

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)

EU/1/13/890/002	7 x 20 mg and 7 x 80 mg capsules (100 mg/day dose for a 7-day supply)
EU/1/13/890/003	21 x 20 mg and 7 x 80 mg capsules (140 mg/day dose for a 7-day supply)
EU/1/13/890/005	56 capsules (4 blister cards of 7 x 20 mg and 7 x 80 mg) (100 mg/day dose for 28 day supply)
EU/1/13/890/006	112 capsules (4 blister cards of 21 x 20mg and 7 x 80 mg) (140 mg/day dose for 28 day supply)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2014
Date of latest renewal: 08 January 2018

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 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**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Catalent UK Packaging Limited
Lancaster Way, Wingates Industrial Park,
Westboughton, Bolton,
Lancashire, BL5 3XX,
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

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.

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.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
<p>A dose-comparison study (XL-184-401) (140 mg vs 60 mg) in 112 patients with hereditary or sporadic medullary thyroid cancer.</p> <p>Patients with both sporadic and hereditary forms of MTC will be eligible for the study. Fresh tumour samples for tumour genetic analysis from the most recent metastatic site in patients enrolled in the dose-comparison study should be collected.</p> <p>Samples will undergo thorough evaluation for RET and RAS mutations. Tumor tissue samples initially will undergo histological evaluation, manual tumor enrichment, and DNA isolation. The resulting DNA samples will be evaluated for quality by a PCR-based amplification test, and by Sanger sequencing for RET M918T. A replacement sample will be requested if an original sample fails during the PCR quality or the Sanger sequencing tests. Next generation sequencing of RET exons 10, 11, and 13-16 will be performed, which covers the vast majority of known RET mutations. In addition, samples will be evaluated for mutations in RAS gene hotspots (HRAS, KRAS, and NRAS genes).</p> <p>PK assessments will be required for all subjects (both dose groups). Results will be used to evaluate the exposure to cabozantinib at the 60 and 140 mg dose levels and to further characterize the population PK models and exposure response relationships of cabozantinib and possible metabolites in this population.</p>	<p>30 September 2020</p>

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER CARD, 60 mg dose

1. NAME OF THE MEDICINAL PRODUCT

COMETRIQ 20 mg hard capsules
Cabozantinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules
20 mg
60 mg Dose

Pack for the 60 mg daily dose
21 x 20 mg capsules (60 mg/day dose for a 7-day supply)
Each 60 mg daily dose contains three grey 20 mg capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
Package leaflet inside pouch.

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

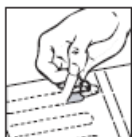
Dispensing instructions

Take all capsules in one row each day without food (patients should fast for at least 2 hours before through 1 hour after taking the capsules). Record date of first dose.

1. Push in tab



2. Peel paper backing



3. Push capsule through foil



8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.
Do not store above 25°C.

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/1/13/890/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

COMETRIQ 20 mg
60 mg/day dose

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF 28 DAY PACK, 60 mg dose (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

COMETRIQ 20 mg hard capsules
Cabozantinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 mg Dose

28 day pack: 84 capsules (4 blister cards of 21 x 20 mg capsules) for the 60 mg daily dose for a 28 day supply.

Each 60 mg daily dose contains a combination of three grey 20 mg capsules.

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

Refer to individual blister cards for dispensing instructions.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.
Do not store above 25°C.

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/1/13/890/004 84 capsules (4 blisters cards of 21 x 20 mg) (60 mg/day dose for 28 day supply)

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

COMETRIQ 20 mg
60 mg/day dose

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BLISTER CARD OF 28 DAY PACK, 60 mg dose (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

COMETRIQ 20 mg hard capsules
Cabozantinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules
20 mg
60 mg Dose

21 x 20 mg capsules (60 mg/day dose for a 7-day supply). Component of a 28 day pack, can't be sold separately.

Pack for the 60 mg daily dose
Each 60 mg daily dose contains three grey 20 mg capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
Package leaflet inside pouch.

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

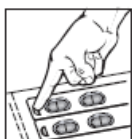
Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Dispensing instructions

Take all capsules in one row each day without food (patients should fast for at least 2 hours before through 1 hour after taking the capsules). Record date of first dose.

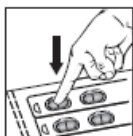
1. Push in tab



2. Peel paper backing



3. Push capsule through foil



8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.
Do not store above 25°C.

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/1/13/890/004 84 capsules (4 blisters cards of 21 x 20 mg) (60 mg/day dose for 28 day supply)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER CARD, 100 mg dose

1. NAME OF THE MEDICINAL PRODUCT

COMETRIQ 20 mg hard capsules
COMETRIQ 80 mg hard capsules
Cabozantinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains cabozantinib (*S*)-malate equivalent to 20 mg or 80 mg of cabozantinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules
20 mg and 80 mg
100 mg Dose

Pack for the 100 mg daily dose
7 x 20 mg capsules and 7 x 80 mg capsules (100 mg/day dose for a 7-day supply).
Each 100 mg daily dose contains a combination of one grey 20 mg capsule and one orange 80 mg capsule.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
Package leaflet inside pouch.

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

Dispensing instructions
Take all capsules in one row each day without food (patients should fast for at least 2 hours before through 1 hour after taking the capsules). Record date of first dose.

1. Push in tab



2. Peel paper backing



3. Push capsule through foil



8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.
Do not store above 25°C.

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/1/13/890/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

COMETRIQ 20 mg
COMETRIQ 80 mg
100 mg/day dose

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF 28 DAY PACK, 100 mg dose (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

COMETRIQ 20 mg hard capsules
COMETRIQ 80 mg hard capsules
Cabozantinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains cabozantinib (*S*)-malate equivalent to 20 mg or 80 mg of cabozantinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

100 mg Dose

28 day pack: 56 capsules (4 blister cards of 7 x 20 mg capsules and 7 x 80 mg capsules) for the 100 mg daily dose for a 28 day supply.

Each 100 mg daily dose contains a combination of one grey 20 mg capsule and one orange 80 mg capsule.

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

Refer to individual blister cards for dispensing instructions.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.
Do not store above 25°C.

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/1/13/890/005 56 capsules (4 blisters cards of 7 x 20 mg and 7 x 80 mg) (100 mg/day dose for 28 day supply)

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

COMETRIQ 20 mg
COMETRIQ 80 mg
100 mg/day dose

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BLISTER CARD OF 28 DAY PACK, 100 mg dose (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

COMETRIQ 20 mg hard capsules
COMETRIQ 80 mg hard capsules
Cabozantinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains cabozantinib (S)-malate equivalent to 20 mg or 80 mg of cabozantinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules
20 mg and 80 mg
100 mg Dose

7 x 20 mg capsules and 7 x 80 mg capsules (100 mg/day dose for a 7-day supply). Component of a 28 day pack, can't be sold separately.

Pack for the 100 mg daily dose
Each 100 mg daily dose contains a combination of one grey 20 mg capsule and one orange 80 mg capsule.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
Package leaflet inside pouch.

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

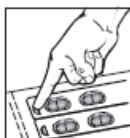
Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

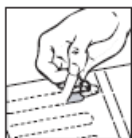
Dispensing instructions

Take all capsules in one row each day without food (patients should fast for at least 2 hours before through 1 hour after taking the capsules). Record date of first dose.

1. Push in tab



2. Peel paper backing



3. Push capsule through foil



8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.
Do not store above 25°C.

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/1/13/890/005 56 capsules (4 blisters cards of 7 x 20 mg and 7 x 80 mg) (100 mg/day dose for 28 day supply)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER CARD 140 mg dose

1. NAME OF THE MEDICINAL PRODUCT

COMETRIQ 20 mg hard capsules
COMETRIQ 80 mg hard capsules
Cabozantinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains cabozantinib (*S*)-malate equivalent to 20 mg or 80 mg of cabozantinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules
20 mg and 80 mg
140 mg Dose

Pack for the 140 mg daily dose
21 x 20 mg capsules and 7 x 80 mg capsules (140 mg/day dose for a 7-day supply)
Each 140 mg daily dose contains a combination of three grey 20 mg capsules and one orange 80 mg capsule.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
Package leaflet inside pouch.

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

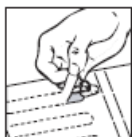
Dispensing instructions

Take all capsules in one row each day without food (patients should fast for at least 2 hours before through 1 hour after taking the capsules). Record date of first dose.

1. Push in tab



2. Peel paper backing



3. Push capsule through foil



8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.
Do not store above 25°C.

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/1/13/890/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

COMETRIQ 20 mg
COMETRIQ 80 mg
140 mg/day dose

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF 28 DAY PACK, 140 mg dose (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

COMETRIQ 20 mg hard capsules
COMETRIQ 80 mg hard capsules
Cabozantinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains cabozantinib (*S*)-malate equivalent to 20 mg or 80 mg of cabozantinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

140 mg Dose

28 day pack: 112 capsules (4 blister cards of 21 x 20 mg capsules and 7 x 80 mg capsules) for the 140 mg daily dose for a 28 day supply.

Each 140 mg daily dose contains a combination of three grey 20 mg capsules and one orange 80 mg capsule.

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

Refer to individual blister cards for dispensing instructions.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.
Do not store above 25°C.

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/1/13/890/006 112 capsules (4 blisters cards of 21 x 20 mg and 7 x 80 mg) (140 mg/day dose for 28 day supply)

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

COMETRIQ 20 mg
COMETRIQ 80 mg
140 mg/day dose

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BLISTER CARD OF 28 DAY PACK, 140 mg dose (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

COMETRIQ 20 mg hard capsules
COMETRIQ 80 mg hard capsules
Cabozantinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains cabozantinib (S)-malate equivalent to 20 mg or 80 mg of cabozantinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules
20 mg and 80 mg
140 mg Dose

21 x 20 mg capsules and 7 x 80 mg capsules (140 mg/day dose for a 7-day supply). Component of a 28 day pack, can't be sold separately.

Pack for the 140 mg daily dose
Each 140 mg daily dose contains a combination of three grey 20 mg capsules and one orange 80 mg capsule.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
Package leaflet inside pouch.

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

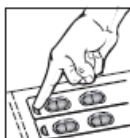
Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

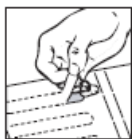
Dispensing instructions

Take all capsules in one row each day without food (patients should fast for at least 2 hours before through 1 hour after taking the capsules). Record date of first dose.

1. Push in tab



2. Peel paper backing



3. Push capsule through foil



8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.
Do not store above 25°C.

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/1/13/890/006 112 capsules (4 blisters cards of 21 x 20 mg and 7 x 80 mg) (140 mg/day dose for 28 day supply)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

COMETRIQ 20 mg hard capsules

COMETRIQ 80 mg hard capsules

Cabozantinib (*S*)-malate

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

1. What COMETRIQ is and what it is used for

COMETRIQ is a medicine used to treat medullary thyroid cancer, a rare type of thyroid cancer, that cannot be removed by surgery or that has spread to other parts of the body.

COMETRIQ may slow or stop the growth of medullary thyroid cancer. It may help shrink tumours associated with this type of cancer.

2. What you need to know before you take COMETRIQ

Do not take COMETRIQ

- 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 COMETRIQ if you:

- have high blood pressure
- have diarrhoea
- have a recent history of coughing up blood or significant bleeding
- have had surgery within the last month (or if surgical procedures are planned), including dental procedures
- have had radiotherapy in the last 3 months

- have inflammatory bowel disease (for example, Crohn's disease or ulcerative colitis or diverticulitis)
- have been told that your cancer has spread to your airway or oesophagus
- have a recent history of blood clot in the leg, stroke, or heart attack
- are taking medicines to control your heart rhythm, have a slow heart rate, have problems with your heart or have problems with the levels of calcium, potassium or magnesium in your blood
- have severe 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 COMETRIQ, or stop treatment altogether. See also section 4 "*Possible side effects*".

You should also tell your dentist that you are taking COMETRIQ. It is important for you to practice good mouth care during treatment with COMETRIQ.

Children and adolescents

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

Other medicines and COMETRIQ

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 COMETRIQ can affect the way some other medicines work. Also, some medicines can affect the way COMETRIQ works. This could mean that your doctor needs to change the dose(s) that you take.

- 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
- Steroids used to reduce inflammation or treat a number of different diseases of the immune system
- 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 ritonavir, maraviroc and emtricitabine
- Medicines used to treat viral infections such as efavirenz
- Medicines used to prevent transplant rejection (cyclosporine) and cyclosporine-based regimens in rheumatoid arthritis and psoriasis

Oral contraceptives

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

Taking COMETRIQ with food

You should not take COMETRIQ with food. You should not eat anything for at least 2 hours before taking COMETRIQ and for 1 hour after taking the medicine. Avoid consuming grapefruit-containing products for as long as you are using this medicine, as it may increase the levels of COMETRIQ in your blood.

Pregnancy, breast-feeding, and fertility

Avoid becoming pregnant while being treated with COMETRIQ. 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 COMETRIQ. See section 2.

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

Talk to your doctor BEFORE taking COMETRIQ 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 COMETRIQ.

Women taking COMETRIQ 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 COMETRIQ may make you feel tired or weak.

3. How to take COMETRIQ

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 experience serious side effects, your doctor may decide to change your dose or stop treatment earlier than originally planned. Your doctor will determine if you need your dose adjusted, particularly during the first eight weeks of therapy with COMETRIQ.

COMETRIQ should be taken once a day. Depending on the dose you were prescribed, the number of capsules to take are as follows:

- 140 mg (1 orange 80 mg capsule and 3 grey 20 mg capsules)
- 100 mg (1 orange 80 mg capsule and 1 grey 20 mg capsule)
- 60 mg (3 grey 20 mg capsules)

Your doctor will decide on the right dose for you.

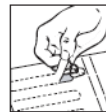
Your capsules will come in a blister card organised by prescribed dose. Each blister card has enough capsules to last for seven days (one week). Your capsules are also available as a 28 day pack, which contains enough capsules to last for 28 days, in 4 blister cards with seven days of capsules on each card.

Each day, take all the capsules across the row. More information on the blister cards including how many capsules you will take and how many capsules there are in total in each blister card are described below in section 6. To help you remember your doses, write the date when you took your first dose in the space next to the capsules. To remove the capsules for your dose:

1. Push in tab



2. Peel paper backing



3. Push capsule through foil



COMETRIQ should **not** be taken with food. You should not eat anything for at least 2 hours before taking COMETRIQ and for 1 hour after taking the medicine. Swallow the capsules one at a time with water. Do not open them.

If you take more COMETRIQ than you should

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

If you forget to take COMETRIQ

- 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 COMETRIQ at a lower dose. Your doctor may also prescribe other medicines to help control your side effects.

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

- Symptoms including pain in the abdomen, nausea, 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.
- Swelling, pain in your hands and feet, or shortness of breath.
- A wound that does not heal.
- Vomiting or coughing up blood, which may be bright red or look like coffee grounds.
- Pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs of bone damage in the jaw (osteonecrosis).
- Seizures, 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

- Blister, pain of the hands or soles of the feet, rash or redness of the skin, dry skin
- Decreased appetite, weight loss, altered sense of taste
- Fatigue, weakness, headache, dizziness
- Hair colour changes (lightening), hair loss
- Hypertension (increase in blood pressure)
- Redness, swelling or pain in the mouth or throat, difficulty in speaking, hoarseness
- Changes in blood tests used to monitor general health and the liver, low levels of electrolytes (like magnesium, calcium or potassium)
- Joint pain, muscle spasms
- Swollen lymph glands

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

- Anxiety, depression, confusion
- Generalised pain, chest or muscle pain, ear pain, ringing in ears
- Weakness or reduced sensation or tingling in the limbs
- Chills, tremors
- Dehydration
- Inflammation of the abdomen or pancreas
- Inflammation of the lips and corners of the mouth
- Inflammation at the root of your hair, acne, blisters (on parts of your body other than the hands or feet)
- Swelling in the face and in other parts of the body
- Loss of taste
- Hypotension (decrease in blood pressure)
- Atrial fibrillation (a fast and erratic heartbeat)
- Lightening of skin, flakey skin, unusual pale skin
- Abnormal hair growth
- Haemorrhoids
- Pneumonia
- Pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth
- Reduced thyroid activity; symptoms can include: tiredness, weight gain, constipation, feeling cold and dry skin
- Tear or hole or bleeding in your stomach or intestine, inflammation or tear of anus, , bleeding in lungs or trachea (airway)
- Abnormal connection of the tissue in your trachea (airway), oesophagus, or lungs
- Abscess (collection of pus, with swelling and inflammation) in the abdomen or pelvis area or in your teeth/gums
- Blood clots in the veins and the lungs
- Stroke
- Fungal infection that can be in the skin, mouth, or genitals
- Wounds that have difficulties healing
- Protein or blood in the urine, gallstones, painful urination
- Blurred vision
- Increase in the level of bilirubin in your blood (which may result in jaundice/yellow skin or eyes)
- Decrease in the levels of protein in your blood

Uncommon side effects (may affect 1 in 100 people)

- Inflammation of the oesophagus; symptoms can include heartburn, chest pain, feeling sick, altered taste, bloating, belching and indigestion
- A tear or abnormal connection of the tissue in your digestive system; symptoms can include severe or persistent stomach ache
- Infection and inflammation in the lung, collapse of lung
- Skin ulcers, cysts, red spots on the face or thighs

- Facial pain
- Changes in test results that measure blood clotting or blood cells
- Loss of coordination in your muscles, damage to skeletal muscles
- Loss of attention, loss of consciousness, changes in speech, delirium, abnormal dreams
- Blood clots in the arteries
- Chest pain due to blockage in arteries, rapid heartbeat
- Liver damage, kidney failure
- Impaired hearing
- Inflammation in the eye, cataracts
- Stopping menstruation, vaginal bleeding
- A condition called posterior reversible encephalopathy syndrome (PRES) or reversible posterior leukoencephalopathy syndrome (RPLS), which has symptoms such as seizures, headaches, confusion, or finding it difficult to concentrate

Not Known (unknown frequency)

- 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 COMETRIQ

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 card after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C. Store in the original package in order to protect from moisture.

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 COMETRIQ contains

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

The COMETRIQ 20 mg capsules contain cabozantinib (*S*)-malate equivalent to 20 mg of cabozantinib. The COMETRIQ 80 mg capsules contain cabozantinib (*S*)-malate equivalent to 80 mg of cabozantinib.

The other ingredients are:

- **Capsule contents:** microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, silica colloidal anhydrous, and stearic acid
- **Capsule shell:** gelatin, and titanium dioxide (E171)
 - The 20 mg capsules also contain black iron oxide (E172)
 - The 80 mg capsules also contain red iron oxide (E172)
- **Printing ink:** shellac glaze, black iron oxide (E172), and propylene glycol

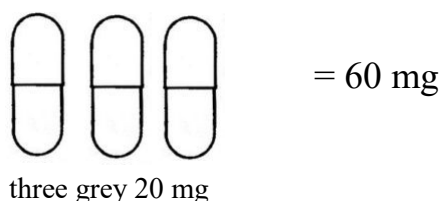
What COMETRIQ looks like and contents of the pack

COMETRIQ 20 mg capsules are grey and have “XL184 20mg” printed on one side.

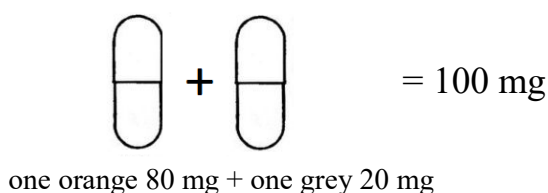
COMETRIQ 80 mg capsules are orange and have “XL184 80mg” printed on one side.

COMETRIQ capsules are packaged in blister cards organised by prescribed dose. Each blister card contains enough medicine for 7 days. Each row of the blister card contains the daily dose.

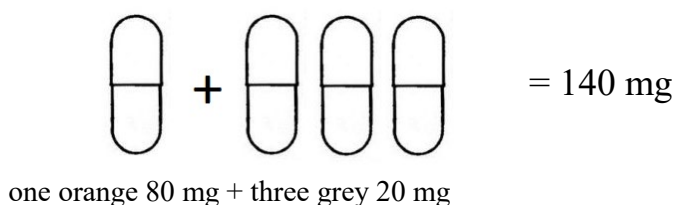
The 60 mg daily dose blister card contains twenty-one 20 mg capsules as 7 daily doses in total. Each daily dose is given in one row and contains three 20 mg capsules:



The 100 mg daily dose blister card contains seven 80 mg capsules and seven 20 mg capsules as 7 daily doses in total. Each daily dose is provided in one row and contains one 80 mg capsule and one 20 mg capsule:



The 140 mg daily dose blister card contains seven 80 mg capsules and twenty one 20 mg capsules as 7 doses in total. Each daily dose is provided in one row and contains one 80 mg capsule and three 20 mg capsules:



COMETRIQ capsules are also available in 28 day packs:

84 capsules (4 blister cards of 21 x 20 mg) (60 mg/day dose)

56 capsules (4 blister cards of 7 x 20 mg and 7 x 80 mg) (100 mg/day dose)

112 capsules (4 blister cards of 21 x 20 mg and 7 x 80 mg) (140 mg/day dose)

Each 28 day pack contains enough medicine for 28 days.

Marketing Authorisation Holder

Ipsen Pharma
65 quai Georges Gorse
92100 Boulogne-Billancourt
France

Manufacturer

Catalent UK Packaging Limited
Lancaster Way
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United Kingdom

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This leaflet was last revised in

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.