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Summary of the risk management plan (RMP) for Cometriq (cabozantinib)

This is a summary of the risk management plan (RMP) for Cometriq, which details the measures to be taken in order to ensure that Cometriq is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Cometriq, which can be found on Cometriq's EPAR page.

Overview of disease epidemiology

Medullary thyroid cancer (MTC) is a disease in which cancer cells form in the thyroid gland. MTC develops in a type of thyroid cells called C cells, which are responsible for producing calcitonin, a hormone that maintains calcium levels in the blood.

Patients may be more likely to develop MTC if they are: female, younger than 65 years old, have a history of goitre (enlarged thyroid gland), or have a family history of MTC or a condition called familial MTC or multiple endocrine neoplasia type 2A or 2B syndrome. The average age at diagnosis is about 50 years of age; fewer than 2000 new cases occur annually in the EU. When first seen, about half of MTC patients have disease just in the thyroid gland, and in about one-third it has spread to surrounding tissues or to lymph nodes. Once MTC has spread to distant parts of the body (metastatic disease), treatment is restricted to surgery, external radiation, targeted therapy including the medicine vandetanib (also known as a tyrosine kinase inhibitor) and chemotherapy (treatment with other cancer medicines). MTC is a life-threatening disease. The average overall survival is less than 2 years from the time of surgery for patients with metastatic disease.

Summary of treatment benefits

Cabozantinib is a restricted prescription medicine used to treat patients with progressive MTC that cannot be removed surgically (known as unresectable disease), has advanced locally or has spread to other parts of the body. Cabozantinib's safety and effectiveness were evaluated in a global, multicentre, controlled study. The study included 330 patients with progressive unresectable, locally advanced or metastatic MTC. Patients were randomly assigned to receive either cabozantinib 140 mg (in 219 patients) or placebo (a dummy treatment, in 111) once a day until their disease progressed or toxicity was experienced.

The objectives of the study were to measure the time until patients' disease progressed, how long patients lived, how many patients experienced a response of their tumour to treatment and how long tumour response lasted. The average time until the disease got worse or patients died was 11.2 months in those given cabozantinib versus 4.0 months in those given placebo, and 47.3% versus 7.2% of patients were alive and had no worsening of disease at 1 year. Tumour response was seen in 27.9% of patients on cabozantinib versus 0% on placebo, and the average duration of tumour response was 14.6 months.

Unknowns relating to treatment benefits

In the main cabozantinib study above nearly all patients were white and most were under age 65. There is no evidence to suggest that results would be any different in non-white patients or in older patients.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Perforation of the gut or stomach	Approximately 3 in 100 patients taking cabozantinib may present with a perforation of the gastrointestinal tract (a tear or hole that develops in their stomach or intestine, which can be life-threatening). Some patients with familial MTC may develop this regardless of whether they are taking cabozantinib.	Yes, this may be mitigated by monitoring patients, especially those at higher risk, for early symptoms, which can include pain in the abdomen, nausea (feeling sick), vomiting, constipation, or fever. Cabozantinib should be stopped if a gastrointestinal perforation occurs.
GI fistulas and non-GI fistulas	Fewer than 1 in 100 patients treated with cabozantinib may present with fistulas (abnormal passages between organs) that if left untreated can be fatal. They may lead to abscess or gut perforation.	Yes, this may be mitigated by monitoring patients, especially those at higher risk, for early symptoms. Symptoms can include pain in the abdomen or other locations (depending on the location of the fistula), nausea, vomiting, constipation, fever, or mucositis (inflammation of the moist body surfaces). Cabozantinib should be stopped if a fistula occurs.
Intra-abdominal abscess	Approximately 3 in 100 patients may present with an abscess inside the abdomen. Patients at risk of abscess include patients with cancer in the area or metastasis (spread) to the area, gastrointestinal ulcers, and those with fistulas.	Yes, this may be mitigated by monitoring patients, especially those at higher risk, for early symptoms. Symptoms include pain in the abdomen, nausea, vomiting, constipation, or fever.
Blood clots (thromboembolism) in the arteries or veins	Approximately 3 in 100 patients may present with serious blood clots in veins or arteries. Patients with cancer are at an increased risk of having blood clots, which could be fatal.	Yes, this may be mitigated by monitoring patients, especially those at higher risk, for early symptoms such as pain and swelling of arms or legs. In addition, patients at risk for clots may be given anti-coagulants (medicines that prevent blood

Risk	What is known	Preventability
		clots). Cabozantinib should be stopped in patients with serious events due to clots blocking an artery, such as myocardial infarction (heart attack) or cerebral infarction (stroke).
Haemorrhage (bleeding)	Approximately 3 in 100 patients may experience bleeding that can be serious or life threatening. If the tumour is invading other organs or blood vessels there may be a higher risk of bleeding.	Yes, this can be mitigated by careful monitoring of patients, especially those that are using anticoagulants or have risk factors. Treatment for bleeding events should also be given as medically indicated to prevent a more serious outcome. Cabozantinib should be stopped in patients with severe haemorrhage.
Wound complications	Approximately 1 in 100 patients taking cabozantinib may experience wound closure complications. Poor wound healing can result in infections, bleeding, fistula, or abscess.	Yes, this can be mitigated by not starting cabozantinib treatment within 4 weeks of a surgical incision.
Hypertension (high blood pressure)	Approximately 28 in 100 medullary thyroid cancer patients may experience hypertension when taking cabozantinib. Patients with uncontrolled hypertension or pre-existing hypertension may be at a higher risk of developing severe hypertension.	Yes, this can be mitigated by carefully monitoring patients with existing hypertension and measuring the blood pressure of patients receiving cabozantinib. Hypertension should also be treated as clinically appropriate. Cabozantinib should be stopped in patients with malignant hypertension or hypertensive crisis (very severe or sudden, dangerous increases in blood pressure) or persistent uncontrolled hypertension despite optimal management.
Osteonecrosis	Approximately 1 patient in 100 may experience osteonecrosis (death of bone tissue) in the jaw. Osteonecrosis can result from spread of cancer, osteoporosis (weakening of the bones), or prolonged lack of blood supply (ischaemia) of the bone. Patients with cancer spread to the bone taking bisphosphonates, corticosteroids, chemotherapy,	Yes, the risk of severe osteonecrosis can be mitigated with good oral hygiene. Monitoring after invasive dental procedures can help to recognize early symptoms of osteonecrosis. Cabozantinib should be stopped temporarily 28 days prior to scheduled invasive dental procedures and stopped permanently if osteonecrosis occurs. Osteonecrosis should be

Risk	What is known	Preventability
	radiotherapy to the bone may be at a higher risk.	treated as medically appropriate to avoid a poor outcome.
Posterior reversible encephalopathy syndrome (RPLS)	Fewer than 1 in 100 patients may experience posterior reversible encephalopathy syndrome (RPLS), a serious disease affecting the brain and nervous system that can lead to headache, confusion, seizures (fits), and loss of vision. Risk factors include hypertension, renal failure, and the use of immunosuppressive treatment (medicines that reduce the activity of the immune system). Due to the frequency of hypertension in the MTC population, this population may be at a higher risk.	No. Patients who present with RPLS should stop treatment with cabozantinib
Diarrhoea	Approximately 30 in 100 patients may present with diarrhoea while taking cabozantinib. Diarrhoea is a prevalent condition among patients with MTC, particularly among patients with RET mutations or MEN2A andMEN2B disease. Electrolyte disturbances could result if diarrhoea is prolonged and/or severe (see section below on QTc prolongation). Diarrhoea also can be irritating and may predispose to inflammation of the rectum, perforations, abscesses or fistulas.	Yes, the risk of severe consequences can be mitigated by treating diarrhoea as it occurs.
Palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome, PPES)	Approximately half of the patients taking cabozantinib may present with PPES (rashes and numbness affecting the palms and soles). Only 12 in 100 patients may have a severe form of PPES. Patients may be at higher risk if they are female or have previously had PPES. In addition patients with fewer symptoms and disabilities, and patients with cancer that has spread to lung or liver have a higher chance of getting PPES.	Yes, early intervention to treat PPES as medically indicated may prevent more severe outcomes.
Proteinuria	Approximately 2 in 100 patients treated with cabozantinib may present with proteinuria (the presence of protein in the urine, a	Yes, the risk can be mitigated by carefully monitoring kidney function.

Risk	What is known	Preventability
	sign of possible kidney problems). The number of patients expected to present proteinuria in patients with MTC when untreated is similar. Patients at risk are those with familial MTC, patients with phaeochromocytoma (a tumour of the adrenal glands) or history of kidney failure.	

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
QTc Prolongation (altered electrical activity in the heart that can cause life-threatening abnormalities of heart rhythm)	Cabozantinib (but none of its metabolites) did produce a mild but significant inhibition of one of the pores in heart cells that regulate electrical activity but only at higher concentrations than those that are used to treat patients. During clinical trials a few patients had QTc prolongation, which was not clinically significant. However, QTc prolongation was also seen in patients not taking cabozantinib. Conditions or therapies that lead to electrolyte disturbances such as diarrhoea, vomiting or the use of diuretics (medicines that increase the passage of urine) may be indirect risk factors. Drugs which have the potential to increase the amount of cabozantinib in the body may also increase the risk.
Renal failure (kidney failure)	Renal failure has been reported in some patients with MTC during the development of cabozantinib. Cases of renal failure are uncommon and their relationship to the identified risk of proteinuria or to the underlying disease process is unclear.
Hepatotoxicity (liver damage)	Hepatotoxicity cases are uncommon and relationship to cabozantinib or underlying disease process is unclear. Hepatotoxicity has been reported with other medicines of this class but no direct hepatotoxicity has been identified in patients taking cabozantinib.
Dose-related toxicity	Potential risk based on occurrence of toxicities during the development of cabozantinib in the MTC population exposed to the standard 140 mg dose. Cases of toxicity at the 140 mg dose are very common to common but relationship to the 140 mg dose or underlying disease process is unclear.
Embryotoxicity (damage to a developing unborn baby)	No clinical data exist on events related to embryotoxicity. However, preclinical data suggest that serious effects on a fetus could result from cabozantinib therapy in the mother and could be fatal for the unborn baby. Patients who are pregnant should not take cabozantinib. Patients who are fertile should avoid becoming pregnant while on cabozantinib by using proper and effective contraception for at least 4 months after the last dose of

Risk	What is known (Including reason why it is considered a potential risk)
	cabozantinib. Because it is not known if cabozantinib reduces the effect of oral contraceptives, to ensure effectiveness, they should be used together with another method, such as a barrier method.
Fertility impairment	Cabozantinib administration resulted in reduced fertility in animal studies. Although the mechanism(s) leading to impaired fertility are unknown, these findings are consistent with cabozantinib's mechanism of action.
Medication errors	Potential risk based on occurrence of medication errors during clinical trials for the development of cabozantinib. Five cases of medication error in four subjects were reported during clinical trials where cabozantinib was dispensed in bottles and these included 2 cases of taking the wrong dose after the prescriber reduced the dose, 1 case of taking 2 doses on the same day and 1 case where cabozantinib was not given correctly.
Drug-drug interactions	Cabozantinib is broken down in the body by an enzyme called CYP3A4. Giving cabozantinib with other medicines that strongly reduce the action of CYP3A4 (strong CYP3A4 inhibitors) can result in an increase in levels of cabozantinib in the blood. Therefore, caution is required when giving cabozantinib with strong CYP3A4 inhibitors. Similarly, giving cabozantinib with medicines that strongly increase the action of CYP3A4 can result in a decrease in levels of cabozantinib in the blood and should also be avoided. The effect of cabozantinib on hormonal contraceptives has not been investigated. As contraceptive effect may not be guaranteed, an additional contraceptive method, such as a barrier method, is recommended.
Interaction with food	Taking cabozantinib with food may increase the levels of cabozantinib in the blood. Therefore, it is recommended to take cabozantinib on an empty stomach – to not eat anything for at least 2 hours before taking cabozantinib and for one hour afterwards.

Missing information

Risk	What is known
Use in patients with kidney impairment	No clinical study to evaluate the safety and efficacy of cabozantinib in patients with reduced kidney function has been completed; however, a kidney impairment study is ongoing. Cabozantinib is not extensively metabolised in the kidney. It is not recommended to use cabozantinib in patients with severely reduced kidney function.
Use in liver impaired patients	No clinical study to evaluate the safety and efficacy of cabozantinib in patients with reduced liver function has been completed; however, a liver impairment study is ongoing. Cabozantinib is mainly broken down in the liver. It is not recommended to use

Risk	What is known
	cabozantinib in patients with reduced liver function.
Use in cardiac impaired patients	No clinical study to evaluate the safety and efficacy of cabozantinib in patients with impaired heart function has been completed. The number of patients with heart problems other than hypertension during the development of cabozantinib is limited.
Use in children	No clinical study to evaluate the safety and efficacy of cabozantinib in children has been completed. A paediatric study is ongoing. It is not recommended to use cabozantinib in paediatric patients outside of clinical studies.
Use in patients of ethnicity other than white	The number of non-white patients involved in studies during the development of cabozantinib is limited.
Use in pregnant or lactating women	There are no studies in pregnant women using cabozantinib, and it is not known whether cabozantinib is excreted in human milk. Therefore, pregnant women should not use cabozantinib unless deemed medically necessary, and women should stop breastfeeding while taking cabozantinib.
Drug-drug interactions	The effect of cabozantinib on hormonal contraceptives has not been investigated. As contraceptive effect may not be guaranteed, an additional contraceptive method, such as a barrier method, is recommended. There is the potential that giving cabozantinib with medicines that are removed from the body by the substance P-glycoprotein (known as P-gp substrates, and including, but not limited to, fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) may reduce the effectiveness of the other medicine. Therefore, it is recommended that alternative medications be used. There is also the potential that giving cabozantinib with medicines that alter the acidity of the stomach (eg, some antacids) may alter the effectiveness of cabozantinib. Therefore, it is recommended that alternative medications be used. Giving cabozantinib with other medicines that affect the process of its distribution between the liver and gut may potentially affect the amount of cabozantinib available in the body.
Toxicity of metabolite EXEL-1644	It is unknown whether EXEL-1644 or any of the metabolites (breakdown products) of cabozantinib may have side effects of their own.
Carcinogenicity	Cabozantinib has not been studied to assess whether it can cause cancer.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in

lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Cometriq can be found on Cometriq's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	**Objectives**	**Safety concerns addressed / efficacy issue addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
XL184-003, A Phase 1, Open-Label, Parallel-Group, Single-Dose Study to Assess the Pharmacokinetics of XL184 (Cabozantinib) Capsules in Hepatic Impaired Adult Subjects	Safety and tolerability in hepatic impaired patients	Safety and tolerability in hepatic impaired patients	Ongoing	December 2014 (planned)
XL184-011, A Phase 1 Study of XL184 (Cabozantinib) in Children and Adolescents with Recurrent or Refractory Solid Tumors, including CNS Tumors	PK, safety and tolerability in paediatric patients	Safety and tolerability in paediatric patients	Ongoing	December 2016 (planned per the PIP)
XL184-017, A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Assess the Pharmacokinetics of Cabozantinib (XL184) Capsules in Subjects with Impaired Renal Function	Safety and tolerability in patients with renal impairment	Safety and tolerability in patients with renal impairment	Ongoing	December 2014 (planned)
XL184-NC-039	Assess	P-gp substrate and	Completed	June 2014

Study / activity (including study number)	Objectives	Safety concerns addressed / efficacy issue addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	interactions with P-gp substrates and other individual drug transporters	other drug interactions (PK and safety)		(planned)
XL184-NC-043	Assess interactions with individual drug transporters	Other drug interactions (PK and safety)	Completed	June 2014 (planned)
XL184-018	Assess interactions with drugs affecting gastric pH	Interactions with drugs affecting gastric pH (PK and safety)	Ongoing	December 2014 (planned)
XL184-NC-036	Assess carcinogenicity potential (rat)	Carcinogenic potential	Initiated	October 2016 (planned)
XL184-NC-042	Assess carcinogenicity potential (mouse)	Carcinogenic potential	Planned	October 2015 (planned)
Nonclinical toxicity study EXEL1644-NC-004	Characterisation of specific metabolite toxicity	Potential risks resulting from metabolite not previously characterized in parent (cabozantinib)	Completed	June 2014 (planned)
XL184 NC 034	Bacterial mutagenicity study of metabolites EXEL-1644 and EXEL-1646	Potential mutagenicity of metabolites	Completed	June 2014 (planned)
Millipore EXL084	Kinase panel IC50 determinations for metabolites EXEL-1644 and EXEL-1646	Potential toxicity of metabolites	Completed	June 2014 (planned)
Nonclinical toxicity study XL184-NC-040	Toxicity study of cabozantinib in younger juveniles	Potential risks in paediatric patients (≤2 years)	Initiated	December 2014 (planned)
Enterohepatic recirculation	Evaluation of potential	Potential risks of medicines affecting	Initiated	December 2014 (planned)

Study / activity (including study number)	Objectives	Safety concerns addressed / efficacy issue addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
evaluation in dogs XL184-NC-045	enterohepatic recirculation of cabozantinib in dogs	cabozantinib enterohepatic recirculation and PK		
Enterohepatic recirculation evaluation in rats XL184-NC-046	Evaluation of potential enterohepatic recirculation of cabozantinib in rats	Potential risks of medicines affecting cabozantinib enterohepatic recirculation and PK	Initiated	December 2014 (planned)
XL184-401	Safety, PK, and efficacy at 2 doses, evaluated via a non-inferiority design Guide the development of tablet strengths	Safety at 2 doses Medication errors Similar efficacy outcomes at a lower dose	Planned	March 2019 (planned)

Studies which are a condition of the marketing authorisation

Study / activity (including study number)	Objectives	Safety concerns addressed / efficacy issue addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
XL184-401	Safety, PK, and efficacy at 2 doses, evaluated via a non-inferiority design Guide the development of tablet strengths	Safety at 2 doses Medication errors Similar efficacy outcomes at a lower dose	Planned	March 2019 (planned)

This summary was last updated in 01-2014.