SUMMARY OF THE RISK MANAGEMENT PLAN FOR COMETRIQ (CABOZANTINIB)

This is a summary of the risk management plan (RMP) for Cometriq. The RMP details important risks of Cometriq, how these risks can be minimised and how more information will be obtained about Cometriq's risks.

Cometriq's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Cometriq should be used.

This summary of the RMP for Cometriq should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Cometriq's RMP.

I The Medicine and What it is Used for

Cometriq is authorised for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma (see SmPC for the full indication). It contains cabozantinib as the active substance and it is given by oral administration.

Further information about the evaluation of Cometriq's benefits can be found in Cometriq's EPAR, including in its plain-language summary, available on the European Medicine's Agency (EMA) website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/cometriq

II Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Cometriq, together with measures to minimise such risks and the proposed studies for learning more about Cometriq's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of Important Risks and Missing Information

Important risks of Cometriq are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Cometriq. Potential risks are concerns for which an association with the use of this medicine is possible based on available data but this

association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks:	• Gastrointestinal perforation • Gastrointestinal and non-gastrointestinal fistula • Thromboembolic events • Haemorrhage (Grade ≥3) • Wound complications • Posterior Reversible encephalopathy syndrome • Osteonecrosis
Important potential risks:	• Renal failure • Hepatotoxicity • Embryotoxicity • Carcinogenicity
Missing information:	None

II.B Summary of Important Risks

Important identified risk – Gastrointestinal perforation	
Evidence for linking the risk to the medicine	The risk of gastrointestinal perforation was initially identified based on cabozantinib clinical studies (Studies XL184-001, XL184-201 and XL184-301). Gastrointestinal perforation is a rare but serious AE and is thought to occur in approximately 3% of cabozantinib-treated patients, consistent with the data generated during the MTC clinical development programme. Vandetanib also carries a warning for GI perforation although the reported incidence is lower than that of cabozantinib at 0.4%. Spontaneous gastric perforation has been reported in patients treated with axitinib (1%), pazopanib (1%) and sorafenib (1%). Sunitinib also carries a warning for GI perforation based on clinical trial data. Gastrointestinal perforation can have debilitating, disabling or fatal outcomes and therefore is an important identified risk for cabozantinib.
Risk factors and risk groups	Patients who have MTC, inflammatory bowel disease (for example, Crohn's disease, ulcerative colitis, carcinomatosis, peritonitis or diverticulitis), have tumour infiltration of the GI viscera or have complications from prior GI surgery (particularly when associated with delayed or incomplete healing) are potentially at higher risk of developing perforation. Individuals with familial MTC may develop GI perforation regardless of whether or not they are taking cabozantinib. Additional risk factors include concurrent use of steroid treatment or nonsteroidal anti-inflammatory drugs.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:**

Important identified risk – Gastrointestinal perforation	
	None

AE=adverse event; GI=gastrointestinal; MTC=medullary thyroid cancer; PL=package leaflet; SmPC=summary of product characteristics.

Important identified risk - Gastrointestinal and non-gastrointestinal fistula	
Evidence for linking the risk to the medicine	The risk of gastrointestinal and non-gastrointestinal fistula was initially identified based on cabozantinib clinical studies (Studies XL184-001, XL184-201 and XL184-301). Gastrointestinal fistula formation in patients with MTC is an uncommon AE reported for cabozantinib, as well as other tyrosine kinase inhibitors (TKIs) such as pazopanib and lenvatinib used for the treatment of thyroid cancer. Non-GI fistula has been reported in patients with thyroid cancer treated with anti-angiogenic TKIs such as sorafenib and sunitinib. Fistula can have a debilitating, disabling or fatal outcome and therefore is an important identified risk for cabozantinib.
Risk factors and risk groups	**GI fistula:** Risk factors for GI fistula are the same as for GI perforations noted above. In addition, RET mutations, MEN 2A or MEN 2B disease and radiation therapy may predispose to fistula formation; complications from prior GI surgery (particularly when associated with delayed or incomplete healing) are potentially at higher risk of developing fistulae. **Non-GI fistula:** Risk factors for these events include infiltration of viscera by tumour (including bronchus and trachea), active complications affecting the viscera from prior radiotherapy and incomplete healing after surgery.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None

AE=adverse event; GI=gastrointestinal; PL=package leaflet; SmPC=summary of product characteristics; TKI=tyrosine kinase inhibitor.

Important identified risk – Thromboembolic events	
Evidence for linking the risk to the medicine	The risk of thromboembolic events was initially identified based on cabozantinib clinical studies (Studies XL184-001, XL184-201 and XL184-301). In a meta-analysis of 12 prospective clinical trials evaluating the role of TKI treatment in advanced thyroid cancer, the incidences of high-grade ATEs and VTEs associated with TKIs were 1.4% and 3.3%, respectively (n=1781 subjects). An increased risk of thromboembolic events is shared by various TKIs used in the treatment of thyroid cancer such as lenvatinib, vandetanib and sorafenib, among others. Events as described can have debilitating, disabling or fatal outcomes and so thromboembolic events are an important identified risk of cabozantinib treatment.

Important identified risk – Thromboembolic events	
Risk factors and risk groups	Cancer patients are at high risk for VTE. Cancer growth is associated with the development of a prothrombotic state. Malignant cells can activate blood coagulation in several ways: by producing procoagulant, fibrinolytic and pro-aggregating activities; by releasing proinflammatory and proangiogenic cytokines; and by interacting directly with host vascular and blood cells, such as endothelial cells, leucocytes and platelets, by means of adhesion molecules. The pathogenesis of VTE in cancer patients appears to be multifactorial, with the most important clinical determinants for the risk of VTE including tumour stage at the time of diagnosis, tumour site, anticancer therapy and surgery. Presence of the Virchow's triad predisposes an individual to the development of thrombosis: endothelial injury (damage to the vessel wall), stasis (slowing down of blood flow) and alterations in blood coagulability (inherited or acquired). Most patients with VTE have one or more risk factors. Patients with a history of VTE are more likely to experience additional episodes, particularly if they are exposed to high-risk situations. There are considerably more data on venous thrombosis than for arterial thrombosis in cancer. Increased levels of coagulation molecules, concurrent disease (such as endocarditis), use of growth factors and cytotoxic chemotherapy may increase the risk of arterial thrombosis.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None

ATE=Arterial thromboembolism; PL=package leaflet; SmPC=summary of product characteristics; TKI=tyrosine kinase inhibitor; VTE=venous thromboembolism.

Important identified risk – Haemorrhage (Grade ≥3)	
Evidence for linking the risk to the medicine	The risk of severe haemorrhage (Grade ≥3) was initially identified based on cabozantinib clinical studies (Studies XL184-001, XL184-201 and XL184-301), which is consistent with rates in the published literature of up to 3%. A number of serious and fatal cases of haemorrhage following VEGF-targeting TKIs, including cabozantinib, vandetanib and lenvatinib, for thyroid cancer have been reported. Moreover, Grade ≥3 haemorrhages are seen in 2% to 3% of patients with thyroid cancer treated with the TKIs sorafenib, sunitinib and pazopanib, suggesting that the risk of haemorrhage is an overall risk of this class of drugs. In a meta-analysis of 23 trials, of which four randomised studies were available to analyse data pertaining to bleeding events, the relative risk of bleeding events in cancer patients treated with sorafenib or sunitinib was significantly higher compared to placebo. Haemorrhage may require urgent medical support to prevent loss of life and, therefore, it is an important identified risk of cabozantinib treatment.

Important identified risk – Haemorrhage (Grade ≥3)	
Risk factors and risk groups	Tissues with tumour involvement may potentially be associated with more frequent haemorrhage than uninvolved areas, especially if there is encroachment of blood vessels. The potential patient factors that could be associated with an increased risk of respiratory tract haemorrhage include patients with evidence of tumour infiltration of the trachea or bronchi or a history of haemoptysis prior to treatment. Gastrointestinal haemorrhage could be induced by comedication with nonsteroidal anti-inflammatory medications or corticosteroids. Treatment of thrombotic events with anticoagulation can also predispose to haemorrhage.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None

PL=package leaflet; SmPC=summary of product characteristics; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor.

Important identified risk – Wound complications	
Evidence for linking the risk to the medicine	The risk of wound complications was initially identified based on data from cabozantinib clinical studies where it was experienced by 9/295 cabozantinib-treated subjects in Studies XL184-001, XL184-201 and XL184-301, which is consistent with data from other TKIs such as axitinib (2%). According to drug labels, impaired wound healing is a potential risk following treatment with TKIs such as pazopanib, sorafenib, sunitinib and vandetanib, although no formal studies have been conducted to determine the frequency of wound complications in these populations. These events can have debilitating, disabling or fatal outcomes, and wound complications is therefore an important identified risk for cabozantinib.
Risk factors and risk groups	Patients with wounds from accidents or surgery. Significant risk factors include age over 65 years, wound infection, malignancy, obesity, pulmonary disease, haemodynamic instability, ascites, uraemia, diabetes, and hypertension.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None

PL=package leaflet; SmPC=summary of product characteristics; TKI=tyrosine kinase inhibitor.

Important identified risk – Posterior Reversible Encephalopathy syndrome	
Evidence for linking the risk to the medicine	PRES was initially identified as an important identified risk of cabozantinib based on clinical trial data (Studies XL184-001, XL184-201 and XL184-301). Although the overall incidence of PRES is low, there have been several case reports of patients developing this syndrome after treatment with TKIs, including pazopanib, sunitinib, sorafenib and bevacizumab. Although PRES is an infrequent syndrome, these events can have debilitating, disabling or fatal outcomes so PRES is therefore an important identified risk of cabozantinib treatment.
Risk factors and risk groups	Risk factors for PRES in general include hypertensive disorders, renal failure and immunosuppressive therapies. Due to the identified comorbidities of hypertension and phaeochromocytoma among patients with MTC, the population may be at higher risk.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None

ADR=adverse drug reaction; MTC=medullary thyroid cancer; PL=package leaflet; PRES= posterior reversible encephalopathy syndrome; SmPC=summary of product characteristics; TKI=tyrosine kinase inhibitor.

Important identified risk - Osteonecrosis	
Evidence for linking the risk to the medicine	The risk of osteonecrosis was initially identified based on cabozantinib clinical studies (Studies XL184-001, XL184-201 and XL184-301). Osteonecrosis, particularly involving the jaw, is a potentially serious adverse side effect of cabozantinib. A literature review covering 35 patients with medication-related osteonecrosis of the jaw found that three patients had received sunitinib (8.57%), cabozantinib (two patients, 5.71%) or sorafenib (one patient, 2.86%). Medication-related ONJ may be exacerbated by patient risk factors such as dental extraction, mucosal trauma from dentures, chronic periodontal disease and insertion of osteointegrated dental implants. These events can have debilitating, disabling or disfigurement outcomes and osteonecrosis is therefore an important identified risk for cabozantinib.
Risk factors and risk groups	Concurrent treatment with other agents that have been associated with ONJ such as bisphosphonates, prior radiation therapy involving the jaw, prior therapy with other inhibitors of VEGF pathways and invasive dental procedures are possible risk factors. Additional risk factors have been identified such as use of corticosteroids, chemotherapy, local radiotherapy, poor oral hygiene, smoking and dental or orofacial surgery procedures.

Important identified risk - Osteonecrosis	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None

ONJ=osteonecrosis of the jaw; PL=package leaflet; SmPC=summary of product characteristics; VEGF=vascular endothelial growth factor.

Important potential risk – Renal failure	
Evidence for linking the risk to the medicine	Renal failure has initially been identified as a potential risk of cabozantinib based on clinical data (Studies XL184-001, XL184-201 and XL184-301). There are isolated reports of cabozantinib-induced renal thrombotic microangiopathy as well as minimal change nephrotic syndrome or focal and segmental glomerulosclerosis. Review of the package inserts for other TKI medications used in the treatment of MTC and thyroid cancer showed <1% of subjects receiving sorafenib developed renal failure, compared to 3% of placebo-treated subjects. No incidence of renal failure was reported for sunitinib or pazopanib. Although vandetanib has been associated with increased urinary albumin extraction and loss of glomerular endothelial cell integrity in mice and rats, there have been no such reports in humans.
Risk factors and risk groups	Renal failure in the MTC studies was reported concomitantly or shortly after other precipitating events such as dehydration secondary to vomiting and diarrhoea. Renal failure can be secondary to contrast agent toxicity, hypertension, urinary tract infection, and diabetes mellitus.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.8 SmPC Section 5.2 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None

MTC=medullary thyroid cancer; PL=package leaflet; SmPC=summary of product characteristics; TKI=tyrosine kinase inhibitor.

Important potential risk - Hepatotoxicity	
Evidence for linking the risk to the medicine	The risk of hepatotoxicity was initially identified based on cabozantinib clinical studies (Studies XL184-001, XL184-201 and XL184-301). A recently published comprehensive literature review on hepatotoxicity and TKI treatments, including cabozantinib, concluded that there is an increased risk of drug induced liver injury associated with this class of drugs with no findings for cabozantinib. Across clinical trials of TKIs, this review reported an overall incidence of high grade ALT/AST elevations (Grade 3 or higher) that ranged from 0 to 14% of patients. However, as such events can have debilitating, disabling or fatal outcomes, hepatotoxicity is considered an important potential risk for cabozantinib.
Risk factors and risk groups	A comprehensive meta-analysis of 12 published placebo-controlled phase II and III trials found a significant overall increase in the odds of developing high-grade (Grade 3 or above) hepatotoxicity with the use of TKIs compared to the control arms. This finding was confirmed by Ghatalia et al who demonstrated an increased relative risk of all grade ALT, AST and total bilirubin in patients exposed to VEGFR-TKIs compared to nonexposed controls. There is at present no evidence to suggest that hepatotoxicity is an on-target effect linked to TKI efficacy and therefore its appearance calls for adjustment of therapy when it is severe enough.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 5.2 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None

ALT=alanine aminotransferase; AST=aspartate aminotransferase; TKI=tyrosine kinase inhibitor; PL=patient leaflet; SmPC=summary of product characteristics; TKI=tyrosine kinase inhibitor; VEGFR= vascular endothelial growth factor.

Important potential risk -Embryotoxicity	
Evidence for linking the risk to the medicine	The risk of embryotoxicity was initially identified based on nonclinical data. There was one partner pregnancy reported in Study XL184-301, with no reported AEs. Serial ultrasound examinations at Weeks 16, 23, and 36 revealed adequate foetal growth and no foetal structural malformations. There was a follow-up report on the continued monitoring of the infant up to 6 months of age; at approximately 5 months of age the baby was assessed as healthy. No cases of pregnancy or pregnancy in partner have been described for cabozantinib during postmarketing experience through to the DLP of 28 November 2018. In definitive reproductive and developmental toxicity studies, XL184 was embryotoxic and produced foetal malformations in rats and foetal soft-tissue malformations, but no foetal external or skeletal malformations, in rabbits. In a review of the literature on pregnancy and cancer, Doll et al reported that the incidence of foetal malformations with first trimester chemotherapy exposure with a variety of agents ranged from 14% to 19%. Exposure in the second and third trimester was associated with an incidence of foetal malformations of 1.3%. Similar findings were reported in a review of 376 foetuses exposed to chemotherapy in utero, the majority of which were exposed after organogenesis. Nine of the 11 reported malformations occurred in patients receiving chemotherapy in the first trimester.
Risk factors and risk groups	The 'at risk' group for experiencing cabozantinib related embryotoxicity comprises female patients of childbearing potential or female partners of male patients treated with cabozantinib. **Risk factor in cancer patients receiving chemotherapy:** Treatment with chemotherapy in the first trimester, during organogenesis, substantially increases the risk of foetal malformation compared to exposure to chemotherapy in the second and third trimesters of pregnancy.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.5 SmPC Section 4.6 SmPC Section 5.3 PL Section 2 Restricted medical prescription **Additional risk minimisation measures:** None

AE=adverse event; DLP=data lock point; PL=package leaflet; SmPC=summary of product characteristics.

Important potential risk – Carcinogenicity	
Evidence for linking the risk to the medicine	The potential risk of carcinogenicity was identified based on nonclinical data. Administration of cabozantinib in rats daily at doses of 0.1, 0.3 and 1 mg/kg for up to 104 weeks resulted in benign phaeochromocytoma, alone or in combination with malignant phaeochromocytoma of the adrenal medulla in males administered ≥0.1 mg/kg/day and females administered ≥0.3 mg/kg/day, together with hyperplasia of the adrenal medulla in females administered ≥0.1 mg/kg/day (Study XL184-NC-036). No clinical cases of phaeochromocytoma have occurred through the DLP of 28 November 2020. However, as any type of carcinoma can have debilitating, disabling or fatal outcome, carcinogenicity is considered an important potential risk for cabozantinib.
Risk factors and risk groups	Prior anticancer therapies and radiation may contribute to the risk in a particular patient. The risk of developing carcinoma is likely to be multifactorial in origin. Immune deficiency has been linked to increased risk of second cancers. Factors thought to play a role are age at diagnosis, prior anticancer therapies, radiation, environmental or lifestyle exposures and genetic susceptibility. In humans, both MEN 2A and MEN 2B predispose patients to phaeochromocytoma.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 5.3 Restricted medical prescription **Additional risk minimisation measures:** None

DLP=data lock point; MEN=multiple endocrine neoplasia; SmPC=summary of product characteristics.

II.C Postauthorisation Development Plan

II.C.1 *Studies which are Conditions of the Marketing Authorisation*

There are no planned or ongoing studies that are conditions of the marketing authorisation or that are specific obligations.

II.C.2 *Other Studies in Postauthorisation Development Plan*

Not applicable.