SUMMARY OF THE RISK MANAGEMENT PLAN FOR CABOMETYX (CABOZANTINIB)

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

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

This summary of the RMP for Cabometyx 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 Cabometyx's RMP.

I The Medicine and What it is Used for

Cabometyx is authorised as monotherapy for the treatment of advanced renal cell carcinoma (RCC) as first line treatment of adult patients with intermediate or poor risk and in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy. Cabometyx, in combination with nivolumab, is authorised for the first-line treatment of advanced RCC in adults. Cabometyx is authorised as monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib. Cabomeytx is authorised as monotherapy for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy (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 Cabometyx’s benefits can be found in Cabometyx’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/Cabometyx

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

Important risks of Cabometyx, together with measures to minimise such risks and the proposed studies for learning more about Cabometyx'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 Cabometyx 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 Cabometyx. 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 (GI) perforation was identified from cabozantinib clinical studies. Additional data confirming the risk were from postmarketing use of cabozantinib. GI perforation has been reported in Studies XL184-308, A031203, CA2099ER, XL184-309 and XL184-311, and GI perforation was also seen in published studies with other similar medicines (VEGF-TKIs) in patients with RCC and advanced HCC. 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 inflammatory bowel disease (e.g. Crohn's disease, ulcerative colitis, carcinomatosis, peritonitis, or diverticulitis), gastric ulcer, intestinal obstruction, have tumour infiltration of the GI viscera, or have complications from previous GI surgery (particularly when associated with delayed or incomplete healing) are potentially at higher risk of developing a perforation (hole in the GI tract). Additional risk factors include use of steroid treatment or nonsteroidal anti-inflammatory drugs at the same time and previous use of radiotherapy.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4

Important identified risk – Gastrointestinal perforation	
	SmPC Section 4.8 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None

GI=gastrointestinal; HCC=hepatocellular carcinoma; PL=Patient Leaflet; RCC=renal cell carcinoma; SmPC=summary of product characteristics; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor.

Important identified risk - Gastrointestinal and non-gastrointestinal fistula	
Evidence for linking the risk to the medicine	The risk of fistula was identified from cabozantinib clinical studies. Additional data confirming the risk were from postmarketing use of cabozantinib. Fistula was reported in Studies XL184 308, A031203, CA2099ER, XL184 309, and XL184-311 confirmed by a low frequency of fistula seen in published studies of other VEGF TKIs in metastatic RCC and advanced HCC. Fistula can have a debilitating, disabling or fatal outcome and therefore is an important identified risk for cabozantinib.
Risk factors and risk groups	Risk factors for GI fistula (a connection between the digestive system and adjacent organs) are the same as for GI perforations noted above. In addition, radiation therapy may lead to fistula formation. Patients with complications from previous GI surgery (particularly when associated with delayed or incomplete healing) are potentially at higher risk of developing fistulae. Risk factors for non GI fistulae include infiltration of viscera by tumour (spread of tumour into the abdomen), radiation therapy 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

GI=gastrointestinal; HCC=hepatocellular carcinoma; PL=Patient Information Leaflet; RCC=renal cell carcinoma; SmPC=summary of product characteristics; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor.

Important identified risk – Thromboembolic events	
Evidence for linking the risk to the medicine	The risk of thromboembolic events was identified from cabozantinib clinical studies. Additional data confirming the risk were from postmarketing use of cabozantinib. Thromboembolic events can be arterial (ATE) or venous (VTE) or mixed. ATEs was reported in Studies XL184 308, A031203, CA2099ER, XL184-309 and XL184-311. Events of venous and mixed/unspecified thrombotic events were more frequently reported compared with ATEs in patients treated with cabozantinib in these studies. In the literature there was no increase in

Important identified risk – Thromboembolic events	
	the risk of VTEs for VEGF TKIs compared with controls in the overall population and no increase in the risk of VTEs was found among different VEGF TKIs or tumour types. Although the incidence of these events is generally low, they can have debilitating, disabling or fatal outcomes and therefore thromboembolic events is an important identified risk for cabozantinib.
Risk factors and risk groups	Cancer patients are at high risk for VTE (blood clots in the vein). The development of VTE in cancer patients appears to have many causes, including tumour stage at the time of diagnosis, tumour type and site, anticancer therapy and surgery. The risk of thrombosis is related to endothelial injury (damage to the vessel wall), stasis (slowing down of blood flow), and alterations in blood coagulability (likelihood of clotting) (inherited or acquired). Patients with HCC and macrovascular (large blood vessels) invasion are potentially at higher risk of venous and mixed thrombotic events. 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. Increased levels of coagulation molecules, concurrent disease (such as endocarditis), use of growth factors and cytotoxic chemotherapy may increase the risk of arterial thrombosis (blood clot in the artery).
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 thromboembolic event; PL=Patient Leaflet; RCC=renal cell carcinoma; SmPC=summary of product characteristics; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor; VTE=venous thromboembolic event.

Important identified risk – Haemorrhage (Grade ≥3)	
Evidence for linking the risk to the medicine	The risk of haemorrhage (Grade ≥3) was identified from cabozantinib clinical studies. Additional data confirming the risk were from postmarketing use of cabozantinib. Haemorrhage (of Grade ≥3 severity) was reported in Studies XL184 308, A031203, CA2099ER, XL184-309 and XL184-311. A similar risk was observed with other cancer medicines where the frequency of bleeding events in cancer patients treated with sorafenib or sunitinib was significantly higher compared to placebo. In another study in patients with advanced RCC, Grade 3 haemorrhage was reported in patients treated with sorafenib but no Grade 4 adverse reactions were observed. In a study in patients with HCC that was not capable of being removed surgically, Grade 3 and 4 adverse reactions of haemorrhage were reported in patients treated with sorafenib. In other noncontrolled studies with VEGF inhibitors a higher frequency of ≥Grade 3 haemorrhage was seen in patients with HCC. These events can have debilitating, disabling or fatal outcomes and haemorrhage (≥Grade 3) is therefore an important identified risk for cabozantinib.
Risk factors and risk groups	Tissues with tumour involvement may potentially be associated with more frequent haemorrhage than areas without tumours, especially if there is encroachment of (advancing towards) blood vessels. The potential factors that could be associated with an increased risk of respiratory tract haemorrhage include patients who experience haemoptysis (coughing blood) before treatment. Gastrointestinal haemorrhage could be caused by some medicines including nonsteroidal anti-inflammatory medications or corticosteroids. Treatment of thrombotic events with medicines to help prevent clots can also result in 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

HCC=hepatocellular carcinoma; PL=Patient Information Leaflet; RCC=renal cell carcinoma; VEGF=vascular endothelial growth factor; SmPC=summary of product characteristics.

Important identified risk – Wound complications	
Evidence for linking the risk to the medicine	The risk of wound complications was identified from cabozantinib clinical studies. Additional data confirming the risk were from postmarketing use of cabozantinib. Wound complications were reported in Studies XL184-308, CA2099ER, XL184-309, and XL184-311, confirmed by wound complications were seen in two published studies of other VEGF-TKIs in metastatic RCC and HCC. Wound complications can have debilitating, disabling or fatal outcomes, and wound complications is therefore an important identified risk for cabozantinib.

Important identified risk – Wound complications	
Risk factors and risk groups	Patients with wounds from accidents or surgery are at risk of wound complications. Significant risk factors include age over 65 years, wound infection, malignancy, obesity, pulmonary (lung) disease, haemodynamic instability (not enough pressure to keep blood flowing to other parts of the body), ascites (build-up of fluid in the abdomen), uraemia (blood in the urea), diabetes, and hypertension (high blood pressure).
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

HCC=hepatocellular carcinoma; PL=Patient Leaflet; RCC=renal cell carcinoma; SmPC=summary of product characteristics; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor

Important identified risk – Posterior Reversible Encephalopathy syndrome	
Evidence for linking the risk to the medicine	The risk of PRES (a neurologic condition with fits, headaches, confusion, or finding it difficult to concentrate) was identified from cabozantinib clinical studies using the cabozantinib capsule but not in Studies XL184-308, A031203, CA2099ER or XL184-309 using the cabozantinib tablet. In Study XL184-311, one case of PRES occurred, Additional data confirm the risk were from postmarketing use of cabozantinib. Although PRES is an infrequent syndrome, these events can have debilitating, disabling or fatal outcomes and PRES is therefore an important identified risk for cabozantinib.
Risk factors and risk groups	Risk factors for PRES in general include hypertensive (high blood pressure) disorders, renal (kidney) failure and immunosuppressive therapies. Hypertension and renal failure are both co-morbidities (disorders that often occur at the same time) in RCC patients.
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

RCC=renal cell carcinoma; PL=Patient Leaflet; PRES=posterior reversible encephalopathy syndrome; SmPC=summary of product characteristics.

Important identified risk - Osteonecrosis	
Evidence for linking the risk to the medicine	The risk of osteonecrosis was identified from cabozantinib clinical studies. Additional data confirming the risk were from postmarketing use of cabozantinib. Osteonecrosis of the jaw (ONJ) (bone damage in the jaw) was reported in Studies XL184-308, CA2099ER and XL184-311. ONJ was not seen in Studies A031203 or XL184-309. ONJ can have debilitating, disabling or disfiguring outcomes and osteonecrosis is therefore an important identified risk for cabozantinib.
Risk factors and risk groups	A study showed that treatment with sunitinib or sorafenib and bisphosphonates at the same time increases the risk of ONJ in RCC patients. Bisphosphonate use is low in RCC patients due to the effect on renal function. The use of bisphosphonates or denosumab (medicines associated with an increased risk of ONJ) is low in patients with RCC due to their known effect on renal function. Additional risk factors for ONJ have been identified such as use of corticosteroids, chemotherapy, local radiotherapy, poor oral hygiene, smoking, and dental or orofacial (mouth, jaws and face) surgery procedures.
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; RCC=renal cell carcinoma; PL=Patient Leaflet; SmPC=summary of product characteristics.

Important potential risk – Renal failure	
Evidence for linking the risk to the medicine	The risk of renal (kidney) failure was identified from cabozantinib clinical studies. Additional data confirming the risk were from postmarketing use of cabozantinib. Renal failure was reported in Studies XL184 308, A031203, CA2099ER and XL184-309 and XL184-311. One patient died of acute renal failure in Study A031203; however, this patient had elevated creatinine at screening and died of acute renal failure following dehydration and after refusing dialysis.
Risk factors and risk groups	Renal failure can be caused by conditions such as dehydration secondary to vomiting or diarrhoea, drug toxicity such as from contrast agents, hypertension, urinary tract infections, diabetes mellitus, and underlying disease of RCC.
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

PL=Patient Leaflet; RCC=renal cell carcinoma; SmPC=summary of product characteristics.

Important potential risk - Hepatotoxicity	
Evidence for linking the risk to the medicine	The risk of hepatotoxicity was identified from the cabozantinib clinical studies. Additional data confirming the risk were from postmarketing use of cabozantinib. Elevations of liver enzymes were reported in cabozantinib treated patients in Studies XL184 308, A031203, XL184 309, XL184-311. There were, however, no confirmed cases of drug induced liver injury in these studies. In Study CA2099ER elevations of liver enzymes and hepatotoxicity were reported in patients treated with cabozantinib in combination with nivolumab. Four patients had multiple elevations of liver enzymes that could indicate a risk of severe or fatal liver injury caused by a drug. All 4 patients recovered with the use of corticosteroids. While patients treated with cabozantinib in combination with nivolumab have an increased risk of hepatotoxicity compared to cabozantinib treatment alone, this was found to be manageable with patient monitoring, use of corticosteroids as treatment and dose changes of cabozantinib and nivolumab. Immune-mediated hepatitis is a recognised side effect of nivolumab. Hepatotoxic events can have debilitating, disabling or fatal outcomes. In the published literature, a large study reported elevations in liver enzymes in patients treated with VEGF-TKIs medicines compared to controls.
Risk factors and risk groups	Published clinical studies found an overall increase in the risk of developing high-grade (Grade 3 or above) hepatotoxicity with VEGF-TKI medicines compared to placebo treated patients. This finding was confirmed in another study which found an increased frequency of all grade elevations of liver enzymes (ALT, AST and total bilirubin) in patients exposed to VEGF TKIs compared to controls.
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 identified based on nonclinical data. No cases of pregnancy or pregnancy in partner have been described for cabozantinib during postmarketing experience through to 28November 2020. In nonclinical studies, cabozantinib was embryotoxic and produced foetal malformations in rats and foetal soft tissue malformations, but no foetal external or skeletal malformations, in rabbits. A review of the literature on pregnancy and cancer chemotherapy found that foetal malformations can occur if the medicine is used during the first trimester of pregnancy. Exposure in the second and third trimester was associated with a reduced frequency of foetal malformations. Similar findings were reported in another review in which the majority of 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

PL=package leaflet; SmPC=summary of product characteristics.

Important potential risk – Carcinogenicity	
Evidence for linking the risk to the medicine	The risk of carcinogenicity was identified based on nonclinical data. Administration of cabozantinib to rats resulted in benign pheochromocytoma (a rare tumour of adrenal gland tissue), alone or in combination with malignant pheochromocytoma. In the clinical studies new second cancers following treatment with cabozantinib was very low, which was similar to the Cabometyx postmarketing experience. No clinical cases of pheochromocytoma have occurred up to 28November 2020. A study found that the risk of developing subsequent cancers is about 10% for patients with kidney cancer and about 1% for patients with liver cancer. Carcinogenicity is therefore an important potential risk for cabozantinib.

Important potential risk – Carcinogenicity	
Risk factors and risk groups	Immune deficiency has been linked to increased risk of second cancers. Age and initial tumour size can be important risk factors. Younger patients, who were less than 30 years of age when they were first diagnosed with RCC, were nearly four times more likely than older patients to develop a second cancer. Smaller initial tumours (less than 10 cm) also increase the risk of a second cancer, particularly in the kidney and endocrine glands. In addition to cancer treatment, other risk factors for multiple primary cancers are patient age, environmental and lifestyle exposures, and genetic susceptibility.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 5.3 Restricted medical prescription **Additional risk minimisation measures:** None

RCC=renal cell carcinoma; SmPC=summary of product characteristics.

II.C Postauthorisation Development Plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Cabometyx.

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

There are no studies required for Cabometyx.