EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP)

Active substance (International Nonproprietary Name or common name)	Cabozantinib (INN)
Pharmaco-therapeutic group (Anatomic Therapeutic Chemical (ATC) Code):	Antineoplastic agent, protein kinase inhibitor L01EX07
Name of Marketing Authorisation Holder (MAH) or Applicant:	Ipsen Pharma
Number of medicinal products to which this Risk Management Plan (RMP) refers:	1
Product concerned (brand name):	CABOMETYX

Data lock point (DLP) for this RMP: 28 November 2023
Version Number: 9.0
Date of final sign off: 07 July 2025

Rationale for submitting an updated RMP:

The RMP is updated for submission of a new indication for the treatment of adult patients with unresectable or metastatic, well differentiated extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours who have progressed following at least one prior systemic therapy other than somatostatin analogues, based on results from a pivotal Study ALLIANCE A021602 (CABINET), conducted by the Alliance for Clinical Trials in Oncology as part of the National Cancer Institute-Cancer Therapy Evaluation Programme (NCI-CTEP).

The Study ALLIANCE A021602 (CABINET) is referred to as Study A021602 in the remainder of the document.

Qualified Person for Pharmacovigilance (QPPV) name:

Frédérique Korn

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation QPPV or their deputy. The electronic signature is available on file.

[redacted]

Administrative information on the Risk Management Plan (RMP)

Table 1 Summary of Significant Changes in this RMP

Part	Module/Annex	Significant changes in this RMP
Part I Product(s) Overview		Updated to include the new proposed indication and dosage for the treatment of adult patients with unresectable or metastatic, well differentiated extra-pancreatic and pancreatic neuroendocrine tumours who have progressed to at least one prior systemic therapy other than somatostatin analogues. Product anatomical therapeutic chemical (ATC) code has been updated.
Part II Safety Specification	**Module SI** Epidemiology of the Indication(s) and Target Population(s)	Addition of epidemiology data and target population for the new indication of neuroendocrine tumours.
	Module SII Nonclinical Part of the Safety Specification	Addition of new data for nephrotoxicity, hepatotoxicity, and carcinogenicity from Study A021602.
	Module SIII Clinical Trial Exposure	Addition of clinical trial exposure data from Study A021602.
	Module SIV Populations Not Studied in Clinical Trials	Number of paediatric patients exposed to cabozantinib in the postmarketing setting has been updated. Clinical trial exposure to cabozantinib was updated on the basis of most recent periodic safety update report (PSUR) data. Addition of new exposure data from Study A021602. Addition of new exposure data of special populations from Study A021602.
	Module SV Post-authorisation-authorisation Experience	Post-authorisation exposure was updated on the basis of most recent PSUR data.
	Module SVI Additional European Union (EU) Requirements for the Safety Specification	Addition of central nervous system effects such as dependence, sedation and mood change that would make cabozantinib attractive for misuse for illegal purposes.

Part	Module/Annex	Significant changes in this RMP
	Module SVII Identified and Potential Risks	Addition of new data for important identified and potential risks from Study A021602. Characterisation of important identified and potential risks has been updated based on new data received from Study A021602.
	Module SVIII Summary of the Safety Concerns	No change
Part III Pharmacovigilance Plan (including post-authorisation safety studies)		Removal of the completed post-authorisation safety study (PASS) Study F-FR-60000-001 (CASSIOPE) from additional pharmacovigilance activities.
Part IV Plans for Post-authorisation Efficacy Studies		No change
Part V Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)		Addition of Summary of Product Characteristics (SmPC) Section 4.4 as a routine risk communication for important identified risk of osteonecrosis and package leaflet (PL) Section 2 for important identified of posterior reversible encephalopathy syndrome (PRES).
Part VI Summary of the RMP		Addition of new proposed indication for the treatment of adult patients with unresectable or metastatic well differentiated extra-pancreatic and pancreatic neuroendocrine tumours who have progressed following at least one prior systemic therapy other than somatostatin analogues. Evidence for linking the risks to the medicine has been updated based on new data from Study A021602. Addition of SmPC Section 4.4 as a routine risk communication for important identified risk of osteonecrosis and PL Section 2 for important identified of PRES.
Part VII Annexes	Annex 1 EudraVigilance Interface	No change
	Annex 2 Tabulated Summary of Planned, Ongoing and Completed Pharmacovigilance Study Programme	No change
	Annex 3 Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan	No change

Part	Module/Annex	Significant changes in this RMP
	Annex 4 Specific Adverse Drug Reaction Follow-Up Forms	No change
	Annex 5 Protocols for Proposed and Ongoing Studies in RMP Part IV	No change
	Annex 6 Details of proposed Additional Risk Minimisation Activities (if applicable)	No change
	Annex 7 Other Supporting Data (including referenced material)	Medical Dictionary for Regulatory Activities (MedDRA) terms used for postmarketing surveillance of identified and potential risks has been updated. Addition of new references for the epidemiology data for neuroendocrine tumours. Removal of citations that are not referenced/used in the body of the RMP.
	Annex 8 Summary of Changes to the RMP Over Time	Updated to reflect the above changes made based on addition of new data such as epidemiology of the disease and target population for neuroendocrine tumours, clinical trial exposure data from Study A021602, post-authorisation experience based on most recent PSUR, and characterisation of risks from Study A021602.

Other RMP versions under evaluation:

There are no other RMP versions under evaluation.

Details of the currently approved RMP:

Table 2 Details of the currently approved RMP

Version number	9.0
Approved with procedure	EMEA/H/C/004163/II/0040
Date of approval (opinion date)	19 June 2025

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LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
CNS	Central nervous system
CRPC	Castration-resistant prostate cancer
CSR	Clinical study report
CTEP	Cancer Therapy Evaluation Programme
DLP	Data lock point
DTC	Differentiated Thyroid Carcinoma
EMA	European Medicines Agency
EPAR	European Public Assessment Report
epNET	Extra-pancreatic neuroendocrine tumour
EU	European Union
GAP	Global access programme
HCC	Hepatocellular carcinoma
ICI	Immune checkpoint inhibitor
INN	International Nonproprietary Name
IV	Intravenously
MA	Marketing authorization
MAH	Marketing authorisation holder
MAP	Managed access programme
MedDRA	Medical Dictionary for Regulatory Activities
MTC	Medullary thyroid cancer
NCI	National Cancer Institute
NET	Neuroendocrine tumour
PL	Package leaflet
pNET	Pancreatic neuroendocrine tumour
PRAC	Pharmacovigilance Risk Assessment Committee
PRES	Posterior reversible encephalopathy syndrome
PSUR	Periodic Safety Update Report
qd	Once daily
QPPV	Qualified Person for Pharmacovigilance
Q2W	Every two weeks

Q4W	Every four weeks
RAI	Radioactive iodine
RCC	Renal cell carcinoma
RMP	Risk management plan
ROW	Rest of the world
SAE	Serious adverse event
SmPC	Summary of product characteristics
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

PART I: PRODUCT(S) OVERVIEW

Table 3 Product(s) Overview

Active substance(s) (International Nonproprietary Name (INN) or common name)	Cabozantinib
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agent, protein kinase inhibitor (L01EX07)
Marketing Authorisation Holder	EU MA Holder: Ipsen Pharma 65 quai Georges Gorse 92100 Boulogne-Billancourt France
Medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	CABOMETYX
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class Antineoplastic agent, protein kinase inhibitor
	Summary of mode of action Cabozantinib is a small molecule that inhibits multiple RTKs implicated in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer. Cabozantinib was evaluated for its inhibitory activity against a variety of kinases and was identified as an inhibitor of MET and VEGF receptors. In addition, cabozantinib inhibits other tyrosine kinases including the Gas6 receptor (AXL), RET, ROS1, TYRO3, MER, the stem cell factor receptor (KIT), TrkB, FLT3, and TIE-2.
	Important information about its composition <u>Tablet content:</u> *Active substance:* Cabozantinib *Excipients:* Microcrystalline cellulose Anhydrous lactose Hydroxypropyl cellulose Croscarmellose sodium Colloidal anhydrous silica Magnesium stearate <u>Film-coating:</u> Hypromellose 2910 Titanium dioxide (E171) Triacetin Iron oxide yellow (E172)
Hyperlink to the Product Information	EU Summary of Product Characteristics (SmPC)

Indication(s) in the EEA	Current: Renal Cell Carcinoma (RCC) Cabometyx is indicated as monotherapy for advanced renal cell carcinoma: - as first-line treatment of adult patients with intermediate or poor-risk, - in adults following prior VEGF-targeted therapy. Cabometyx, in combination with nivolumab, is indicated for the first-line treatment of advanced renal cell carcinoma in adults. Hepatocellular Carcinoma (HCC) Cabometyx is indicated as monotherapy for the treatment of HCC in adults who have previously been treated with sorafenib. Differentiated thyroid carcinoma (DTC) Cabometyx is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic DTC, refractory or not eligible to RAI who have progressed during or after prior systemic therapy.
	Proposed: Cabometyx is indicated for the treatment of adult patients with unresectable or metastatic, well differentiated extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours who have progressed following at least one prior systemic therapy other than somatostatin analogues.
Dosage in the EEA	Current: *Cabometyx as monotherapy* For RCC, HCC and DTC, the recommended dose of Cabometyx is 60 mg once daily. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. *Cabometyx in combination with nivolumab in first-line advanced RCC* The recommended dose of Cabometyx is 40 mg once daily in combination with nivolumab administered intravenously at either 240 mg every 2 weeks or 480 mg every 4 weeks. Cabometyx treatment should continue until disease progression or unacceptable toxicity. Nivolumab should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression (see SmPC for posology of nivolumab).
	Proposed: *Cabometyx as monotherapy* For NET, the recommended dose of Cabometyx is 60 mg once daily.
Pharmaceutical form(s) and strengths	Current: Film-coated tablets containing cabozantinib (S)-malate equivalent to either 20 mg, 40 mg or 60 mg cabozantinib.

	Proposed: None
Is/will the product be subject to additional monitoring in the EU?	No

ATC=anatomical therapeutic chemical; DTC=differentiated thyroid carcinoma; EEA=European Economic Area; EU=European Union; FLT3=Fms like tyrosine kinase-3; Gas6= growth arrest-specific gene 6; HCC=hepatocellular carcinoma; INN=international nonproprietary name; MA=marketing authorisation; MET=mesenchymal epithelial transition; NET=neuroendocrine tumour; RAI=radioactive iodine; RCC=renal cell carcinoma; RET=rearranged during transfection; RMP=risk management plan; RTK=receptor tyrosine kinases; SmPC=summary of product characteristics; TrkB=tropomyosin receptor kinase B; VEGF=vascular endothelial growth factor.

PART II: SAFETY SPECIFICATION

Part II: Module SI – Epidemiology of the Indication(s) and Target Population(s)

Indication

The approved indications for Cabometyx are:

- **Renal Cell Carcinoma (RCC)**

Cabometyx is indicated as monotherapy for the treatment of advanced RCC:

- in first-line treatment of adult patients with intermediate or poor-risk,
- in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy.

Cabometyx, in combination with nivolumab, is indicated for the first-line treatment of advanced RCC in adults.

- **Hepatocellular Carcinoma (HCC)**

Cabometyx is indicated as monotherapy for the treatment of HCC in adults who have previously been treated with sorafenib.

- **Differentiated Thyroid Carcinoma (DTC)**

Cabometyx is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic DTC, refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy.

The proposed expanded indication for Cabometyx is:

- **Neuroendocrine Tumours (NET)**

Cabometyx is indicated for the treatment of adult patients with unresectable or metastatic, well differentiated extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours, who have progressed following at least one prior systemic therapy other than somatostatin analogues.

SI.1. Epidemiology of the Disease

SI.1.1. Advanced Renal Cell Carcinoma

The incidence, prevalence, demographics, risk factors, natural history (including mortality and morbidity), treatment options and important co-morbidities of the population of adult patients with advanced RCC are summarised in Table 4.

Table 4 Epidemiology of Patients with Renal Cell Carcinoma

Incidence of target indication	**Advanced RCC in adult patients**
Incidence of target indication	The age-standardised incidence rate of kidney cancer is not evenly distributed around the world, with the highest rate in North America (12.2 per 100,000), followed by Northern Europe (10.3 per 100,000), and the lowest rate in North Middle Africa (1.0 per 100,000) [**Error! Reference source not found.**]. Renal cell carcinoma is the main type of kidney cancer, which comprises more than 90% of kidney cancer [**Error! Reference source not found.**, **Error! Reference source not found.**]. • The global incidence of kidney cancer is approximately 431,000 in 2020 and results in about 179,000 deaths [**Error! Reference source not found.**]. • In the USA, the incidence rate of kidney cancer has generally increased (approximately 0.6% annually) over the past decade. For example, the incidence of kidney cancer was reported as 58,000, with approximately 13,000 deaths in 2010, and the estimated incidence is 79,000 with 13,920 deaths in 2022 [**Error! Reference source not found.**]. • In Europe, the incidence of kidney cancer is approximately 138,000 in 2020 [**Error! Reference source not found.**].
Prevalence of target indication	• The 5-year prevalence numbers were highest in Asia (409,111) and lowest in Oceania (17,044) by GLOBOCAN 2020 [**Error! Reference source not found.**]. • In 2019, 599,072 people were reported living with kidney and renal pelvis cancer in the USA by the SEER programme [**Error! Reference source not found.**]. • According to GLOBOCAN 2020, the 5-year prevalence (all ages) was 405,983 in Europe (all regions) [**Error! Reference source not found.**].
Demographic profile of target population	• The incidence of kidney cancer (of which 90% of cases are RCC, as noted above) increases steadily with age worldwide, and the median age of diagnosis is 75 years. There was a variation of the peak age at diagnosis by geographic location: in UK (74 years), USA (65 years), India (67 years) and China and Italy (82 years) [**Error! Reference source not found.**]. • The incidence of kidney cancer is higher in males (~271,000) than females (~160,000). There is high variation in incidence by ASR among countries by sex. In North America, a higher ASR's is seen among males (16.1 per 100,000) versus females (8.6 per 100,000). These differences are less distinct in Eastern Africa (19. vs 1.4) and Western Africa (1.8 vs 1.6) [**Error! Reference source not found.**]. • In the USA, the incidence rate varies by ethnicity. ASRs were highest among American Indian and Alaska Native, Non-Hispanic (23.9 per 100,000), followed by Black, Non-Hispanic (19.0 per 100,000), Hispanic (17.8 per 100,000), White Non-Hispanic (17.3 per 100,000), and Asian and Pacific Islander, Non-Hispanic (7.9 per 100,000) [**Error! Reference source not found.**].
Risk factors for the disease	As noted above, non-modifiable risk factors for kidney cancer are age, sex, race/ethnicity, and geography. Modifiable risk factors for kidney cancer are obesity, hypertension, chronic kidney disease, lack of exercise, diabetes, smoking and environmental exposure [**Error! Reference source not found.**]. A working group in 2016 from the International Agency for Research on Cancer on Body Fatness based on sufficient evidence supported the temporal association between obesity and kidney cancer [**Error! Reference source not found.**]. Strong evidence from a meta-analysis of 125 articles (18 of which are related to hypertension and the risk of RCC) also demonstrate hypertension increasing the risk of RCC development [**Error! Reference source not found.**]. Chronic kidney disease and end-stage renal disease is attributed in the increased risk of kidney cancer [**Error! Reference source not found.**, **Error! Reference source not found.**]. Additionally a meta-analysis of cohort studies (1996-2010) indicates a positive association between diabetes and kidney cancer with an excess risk of 40% [**Error! Reference source not found.**].

Incidence of target indication	Advanced RCC in adult patients
	Evidence on physical activity and kidney cancer risk are limited and conflicting. Although a pooled analysis (between 2014-2015) of 12 cohort studies in USA and Europe reported a reduced risk of kidney cancer, a 2015 World Cancer Research Fund and American Institute for Cancer Research report concluded there was limited to no link between physical activity and kidney cancer risk [**Error! Reference source not found.**, **Error! Reference source not found.**]. Tobacco smoking is classified as carcinogenic for the kidney cancer by the International Agency for Research on Cancer [**Error! Reference source not found.**]. A systematic review and metanalysis of 56 epidemiological studies in 2019 evaluated the dose-response relationship between cigarette smoking and kidney cancer and concluded a 40% increased risk of kidney cancer secondary to smoking [**Error! Reference source not found.**]. Several studies conclude the risk of alcohol consumption of (moderate intake) is lower compared to non-drinkers or occasional drinkers. cancer [**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**]. Among environmental exposures, trichloroethylene used most as metal cleaner and degreaser is identified as a human carcinogen causing kidney cancer based on sufficient evidence.[**Error! Reference source not found.**] Additionally, other environmental exposures such as the ingestion of Aristolochia plants is historically linked to carcinomas of the urinary tract [**Error! Reference source not found.**]. Majority of the kidney cancers are sporadic with 3-5% with a familial context.[**Error! Reference source not found.**] Autosomal dominant inherited cancer syndromes such as VHL syndrome is most commonly associated with the increased risk for kidney cancer and accounts for 1% of the kidney cancers. [**Error! Reference source not found.**] Genome-wide association studies (GWAS) additionally have identified 13 loci at-risk for the development of kidney cancer [**Error! Reference source not found.**].
Main treatment options	The ESMO guidelines recommend the following medications for treatment of advanced/metastatic RCC: • Adjuvant pembrolizumab should be considered optional for patients with intermediate- or high-risk operable ccRCC (as defined by the study) after careful patient counselling regarding immature OS and potential long-term adverse events. Further data are required in the future including positive OS data. Treatment should start within 12 weeks of surgery and continue for up to 1 year. • Regarding the M1 NED population, systemic therapy with PD-1-based combination therapy is the standard of care for patients who relapse within one year of nephrectomy. • Metastasectomy as an alternative to this systemic therapy in patients with synchronous or early oligometastatic disease is not usually recommended and requires a multidisciplinary team decision. • Adjuvant pembrolizumab can be offered to these patients after complete resection of their oligometastatic disease. • Incomplete resection should not be offered to patients with oligometastatic disease. **First-line advanced/metastatic RCC:** • Lenvatinib–pembrolizumab is now FDA approved but not EMA approved and joins other VEGFR–PD-1 inhibitor-targeted combinations (axitinib-pembrolizumab or cabozantinib–nivolumab) to be recommended for first-line treatment of advanced ccRCC, irrespective of the IMDC risk groups. There is no preferred VEGFR TKIPD-1 inhibitor combination and indirect comparisons across trials are not recommended. • Ipilimumab–nivolumab is recommended as first-line treatment of IMDC intermediate- and poor-risk disease.

Incidence of target indication	Advanced RCC in adult patients
	• Immune checkpoint inhibitor (ICI)-based therapy is particularly active in sarcomatoid renal tumours and should be strongly recommended above single-agent VEGFR TKI. • Sunitinib, pazopanib and tivozanib are alternatives to PD-1 inhibitor-based first-line combinations when immunotherapy is contraindicated or not available. Cabozantinib is also an alternative in IMDC intermediate- and poor-risk disease for those patients who cannot receive first-line PD-1 inhibitor-based therapy. • Sunitinib or pazopanib are potential alternatives to PD-1 inhibitor-based combination therapy in IMDC favourable-risk disease due to a lack of clear superiority for PD-1-based combinations over sunitinib in this subgroup of patients, and the non-inferior effectiveness of sunitinib and pazopanib demonstrated by the COMPARZ trial. • Surveillance is an alternative approach in a small subset of patients. This requires careful consideration. • Only ICI-based combinations with a survival advantage are recommended in the first-line setting. Axitinib–avelumab and bevacizumab–atezolizumab are not yet associated with an OS advantage and are therefore not recommended. • Cessation of ICIs should be considered after two years of therapy. • Lenvatinib–everolimus should not be regarded as a standard first-line treatment of metastatic disease but can be recommended as a subsequent therapy after first-line treatment, along with other agents. **Second-line treatment for ccRCC**: Robust prospective second-line data exclusively after first-line PD-1 inhibitor-based combination therapy is lacking. Prospective data sets exist for axitinib, pazopanib and sunitinib, but they include mixed patient populations and small numbers. **Third-line treatment for ccRCC:** Prospective data on further lines of therapy after first-line PD-1 inhibitor combination therapy and second-line VEGFR-based therapy are lacking. It is likely that sequencing different targeted therapies approved in advanced RCC is beneficial, as was the case in the pre-ICI era. Despite advances in treatment, the vast majority of patients will experience disease progression due to acquired or a priori resistance to VEGFR- or mTOR-targeted therapy [**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**]. Therefore, there is a clear unmet medical need in advanced RCC, and therapies that target important oncogenic drivers in RCC in addition to inhibiting VEGFR may convey important benefit.
Natural history, including mortality and morbidity	• Various imaging studies and histological examination are necessary for an accurate diagnosis of renal cell carcinoma. Approximately, 80% are ccRCC, 10% have pRCC, Type 1 and Type 2, 5% have chRCC. Clear cell renal cell carcinoma occurs primarily in men, usually in the sixth and seventh decades of life. It is haemorrhagic with possible necrosis. Compared to ccRCC, pRCC patients have similar sex and age demographics and is also less vascular than ccRCC and chRCC. Papillary renal cell carcinoma tends to infiltrate the lungs and bones initially. The others are collecting duct renal cell carcinoma, which is rare, most aggressive and is seen among Blacks. Unclassified RCC has features of RCC but does not fit the criteria for ccRCC, pRCC and chRCC and may have sarcomatoid features [**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**]. • Clear cell renal cell carcinoma is linked to mutations on the short arm of chromosome 3(3p). The primary gene implicated in ccRCC is the VHL gene known as pVHL. It is a suppressor protein which undergoes mutation leading to an increase in insulin like growth factor-1, upregulation of hypoxia inducing factor and VEGF, creation of VEGF receptor and angiogenesis resulting in the tumour formation. [**Error! Reference source not found.**] Vascular endothelial

Incidence of target indication	Advanced RCC in adult patients
	growth factor is present in most RCC cells with no difference among the RCC types [**Error! Reference source not found.**]. • Papillary renal cell carcinoma is linked to alterations in chromosomes 7 and 17, a loss of chromosome Yand chRCC to 1,2, 6, 10,13, and 17. Hereditary papillary RCC (HPRCC), leiomyomatosis and RCC (HLRCC-Reeds syndrome), Birt-Hogg-Dube syndrome (BHDS), and tuberous sclerosis (TSC) are other hereditary disorders that make an individual susceptible to a unique type of RCC [**Error! Reference source not found.**]. • The pathological stage of the RCC tumour that combines clinical staging with surgical pathology results is the most important prognostic indicator for patients with RCC and provides a direction for treatment approaches [**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**]. Patients with early stages (I and II) have a five-year survival rate of 80% to 90%. Indicators of poor prognosis are low functional status scores utilising the Karnofsky performance scale or Eastern Cooperative Oncology Group Performance status scale, high levels of serum lactate dehydrogenase, low haemoglobin, high serum corrected levels and history of diabetes [**Error! Reference source not found.**, **Error! Reference source not found.**].
Important co-morbidities	There is sparce published data on the co-morbidities for renal cell carcinoma. However, with regard to the modifiable risk factors the co-morbidities can be attributed to hypertension, obesity, diabetes, chronic kidney disease and end-stage renal disease [**Error! Reference source not found.**, **Error! Reference source not found.**].

ASR=age-standardized rates; BHDS=Birt-Hogg-Dube syndrome; ccRCC=clear cell renal cell carcinoma; chRCC=chromophobe renal cell carcinoma; EMA=European Medicines Agency; ESMO=European Society for Medical Oncology; FDA=Food and Drug Administration; GWAS=genome-wide association study; HPRCC=hereditary papillary renal cell carcinoma; ICI=immune checkpoint inhibitor; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; mTOR=mammalian target of rapamycin; NED=no evidence of disease; OS=overall survival; PD-1=programmed cell death protein 1; pRCC=papillary renal cell carcinoma; RCC=renal cell carcinoma; SEER=surveillance, epidemiology and end results; TKI=tyrosine kinase inhibitor; TSC=tuberous sclerosis; UK=united Kingdom; USA=United States of America; VEGF=vascular endothelial growth factor; VEGFR=vascular endothelial growth factor receptor; VHL syndrome=Von Hippel-Lindau syndrome.

SI.1.2. Hepatocellular Carcinoma

The incidence, prevalence, demographics, risk factors, natural history (including mortality and morbidity), treatment options and important co-morbidities of the population of adult patients with HCC are summarised in Table 5.

Table 5 Epidemiology of Patients with Hepatocellular Carcinoma

Indication/target population	HCC in adult patients
Incidence and prevalence of target indication	The incidence of HCC is not evenly distributed throughout the world, with the highest incidence in regions where infection with HBV and HCV are endemic (Asia and Africa) [**Error! Reference source not found.**, **Error! Reference source not found.**]. • Hepatocellular carcinoma rates were lowest in countries of Northern Europe, the Middle East, Oceania, and North and South America, while intermediate rates occurred in countries in Central Europe [**Error! Reference source not found.**, **Error! Reference source not found.**]. • In the USA, overall annual age-adjusted incidence rates of HCC increased from 4.1/100,000 in 1992 to 9.5/100,000 in 2015 [**Error! Reference source not found.**]. • The incidence in the EU was 87,630 cases in 2020 [**Error! Reference source not found.**, **Error! Reference source not found.**]. The estimated incidence of liver cancer in the USA in 2023 is approximately 41,210 cases [**Error! Reference source not found.**].

Indication/target population	HCC in adult patients
	• The global prevalence of HCC increased from an estimated 437,408 cases in 1990 to 714,600 new cases in 2002 [**Error! Reference source not found.**]. • In 2020, there were an estimated 905,700 cases of liver cancer globally [**Error! Reference source not found.**].
Demographic profile of target population	• The incidence of HCC generally increases with advancing age: the average age at diagnosis is in the mid60s, with a shift over the last decade to diagnosis at an earlier age [**Error! Reference source not found.**, **Error! Reference source not found.**]. • Almost all geographical areas report incidence rates in males that are 2 to 3 fold higher than the rates in females [35], with the largest differences in rates (male: female ratio of >4:1) found in medium-risk European populations [**Error! Reference source not found.**]. • Incidence rates also vary by race/ethnicity. In an analysis of a population-based prospective cohort study, which included data on 168,679 men and women from Hawaii and California, the highest incidence rate of HCC was observed in Latinos (22.5 per 100,000) followed by Native Hawaiians (21.3), Japanese Americans (16.8), African Americans (16.6) and whites (7.5) [**Error! Reference source not found.**]. • In a US population-based study using the SEER registry, the median age at diagnosis of HCC was 62 years. However, the median age at diagnosis varied among people born in different regions of the world. Higher proportions of people born in Africa (particularly West Africa) and Oceania had very early onset HCC (age at diagnosis of <40 years) or early onset HCC (age at diagnosis of <50 years) compared to those born in the USA, Asia and Europe [**Error! Reference source not found.**].
Risk factors for the disease	• Risk factors for HCC are generally conditions that lead to cirrhosis or other liver dysfunction. • Major risk factors include HBV or HCV infection (HBV aetiology appears to lead to shorter survival than HCV related disease; [**Error! Reference source not found.**, **Error! Reference source not found.**]), alcoholic liver disease [**Error! Reference source not found.**] NAFLD such as NASH [**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**], tobacco [**Error! Reference source not found.**, **Error! Reference source not found.**] and genetic susceptibility [**Error! Reference source not found.**, **Error! Reference source not found.**]. • With the incidence of obesity, diabetes and metabolic syndrome continuing to increase in the USA and Europe, NAFLD/NASH is becoming a major cause of HCC in developed countries [**Error! Reference source not found.**]. • Some degree of cirrhosis is present in 80% to 90% of patients with HCC [**Error! Reference source not found.**].
Main treatment options	• Treatment options for HCC depend on tumour stage, patient performance status and liver function reserve. Liver transplantation is potentially curative and is recommended for patients with early-stage HCC. Surgical resection of the tumour is recommended in patients with early-stage disease and preserved liver function [**Error! Reference source not found.**]. • Local ablation of the tumour with radiofrequency is a safe and effective treatment for early-stage HCC, with an estimated 5-year survival rate of 67.9% in one study [**Error! Reference source not found.**]. • Transarterial chemoembolisation is considered a standard treatment for patients with intermediate stage HCC (i.e. large or multinodular HCC and relatively preserved liver function, absence of cancer related symptoms and no evidence of vascular invasion or extrahepatic spread) [**Error! Reference source not found.**]. • Although surgery, percutaneous and transarterial interventions are effective in patients with early-stage disease and compensated underlying liver disease, at the time of diagnosis, more than 80% of patients present with multicentric HCC

Indication/target population	HCC in adult patients
	and advanced liver disease or co-morbidities that restrict treatment to best supportive care [**Error! Reference source not found.**]. • Given the limited therapeutic options available, systemic chemotherapy is also sometimes used. However, HCC is usually resistant to systemic cytotoxic chemotherapy alone, and systemic treatment with chemotherapy is not recommended outside of a clinical trial [**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**]. • Sorafenib is a targeted therapy that is approved for the treatment of HCC. It is a small-molecule inhibitor of VEGFR and other protein kinases, and was shown in a phase III, randomised, placebo-controlled study (SHARP) to improve OS compared with best supportive care in subjects with advanced HCC who had not received previous systemic treatment [**Error! Reference source not found.**]. • Lenvatinib represents a second targeted therapy that has been approved for first-line use in HCC. This is based on the REFLECT trial showing non-inferiority of lenvatinib vs. sorafenib in the primary endpoint overall survival [**Error! Reference source not found.**]. • More recently, the combination of the PD-L1 checkpoint-inhibitor atezolizumab in combination with the VEGF-A targeting antibody bevacizumab has been approved by the EMA. The approval is based on the IMbrave150 trial showing a superior overall and progression free survival (co-primary endpoint) of the combination treatment vs. sorafenib [**Error! Reference source not found.**]. Subsequently, the combination of the PD-L1 checkpoint-inhibitor durvalumab in combination with the CTLA-4 checkpoint-inhibitor tremelimumab has been approved based on the HIMALAYA trial, which showed a superior overall survival compared to sorafenib in front-line HCC [**Error! Reference source not found.**]. • In subsequent lines, the targeted therapies cabozantinib (CELESTIAL trial) [**Error! Reference source not found.**] and regorafenib (RESORCE trial) [**Error! Reference source not found.**] as well as the VEGFR2-targeting antibody ramucirumab (REACH-2 trial) [**Error! Reference source not found.**] have been approved by the EMA after prior treatment with sorafenib. While patients that have tolerated prior sorafenib were eligible for the RESORCE trial and patients showing an elevated AFP level were included in the REACH-2 trial, differences in sorafenib-tolerance or AFP levels were not considered as inclusion criteria for the CELESTIAL trial.
Natural history, including mortality and morbidity	• In 80% to 90% of patients, liver cirrhosis precedes the development of HCC. Dysplastic foci or nodules that arise in the background of cirrhosis are considered precancerous lesions, with high grade dysplastic nodules having the greatest risk of developing into HCC. Early HCCs are characterised by the presence of stromal invasion. Early HCC is classified by small (<2 cm), well differentiated (Grade 1) tumour nodules with indistinct margins [**Error! Reference source not found.**]. • The predominant pathways in HCC pathogenesis include those regulating growth factor signalling (e.g. IGF, EGF, PDGF, FGF and HGF/Met pathways), pathways related to cell differentiation such as the WNT, Hedgehog and Notch pathways and those related to angiogenesis such as the VEGF and FGF pathways [**Error! Reference source not found.**]. • The histopathologic appearance of HCC exhibits substantial heterogeneity, with varied morphologic subtypes observed. Such subtypes include biphenotypic HCCs with combined features of hepatocellular and cholangiocarcinoma, cirrhotomimetic HCC, clear cell HCC, fibrolamellar HCC, granulocyte colony stimulating factor HCC with major neutrophilic infiltrates, lymphocyte-rich HCC, myxoid HCC, sarcomatoid HCC, scirrhous HCC and steatohepatitis HCC [**Error! Reference source not found.**]. • Patients with HCC often experience no symptoms until their disease is advanced. HCC becomes severely debilitating as it progresses: patients may

Indication/target population	HCC in adult patients
	report symptoms, which are severe enough to affect their quality of life such as sleep disorders, sexual dysfunction, gynaecomastia, pruritus, fatigue and muscle cramps [**Error! Reference source not found.**]. • In 2020, 830,200 deaths due to liver cancer occurred worldwide [**Error! Reference source not found.**]. • The estimated mortality rate of liver cancer in the USA in 2023 will be approximately 29,380 cases [**Error! Reference source not found.**], while mortality in the EU was 78,415 cases in 2020 [**Error! Reference source not found.**]. • In 2020, age-adjusted mortality rates for liver cancer were 8.7/100,000 worldwide. Age-adjusted mortality rates were highest in Eastern Asia (16.1/100,000), Northern Africa (14.5) and South-Eastern Asia (13.2) [**Error! Reference source not found.**]. • Patients who present with advanced disease or those with recurrence after locoregional therapy have a very poor prognosis: the expected median survival time is 6-8 months for patients with cancer related symptoms, macrovascular invasion or extrahepatic spread (lymph node involvement or metastases) [**Error! Reference source not found.**].
Important co-morbidities	• Hepatocellular carcinoma is frequently complicated by the presence of comorbid conditions, which can compromise liver function and affect outcomes [**Error! Reference source not found.**], including liver cirrhosis, infection with HBV or HCV [**Error! Reference source not found.**, **Error! Reference source not found.**], and metabolic co-morbidities, e.g. diabetes mellitus [**Error! Reference source not found.**]. • Liver cirrhosis has multisystem effects and complications. These include hepatopulmonary syndrome, portopulmonary hypertension, hepatic encephalopathy, acquired hepatocerebral degeneration and hepatic myelopathy, prerenal failure, intrinsic renal disease, hepatorenal syndrome, cirrhotic cardiomyopathy and an increased prevalence of gallstones [**Error! Reference source not found.**]. • Thrombotic events, such as portal vein thrombosis occur frequently in patients with HCC. In a retrospective review of 194 subjects with HCC, 60 (31%) subjects had portal vein thrombosis. The presence of portal vein thrombosis was associated with reduced survival and a higher rate of systemic venous thromboembolism compared to patients without portal vein thrombosis [**Error! Reference source not found.**]. • Hepatic encephalopathy can be present in 18% of patients at the initial diagnosis of HCC [**Error! Reference source not found.**], while at the end stages of HCC, intractable encephalopathy almost invariably occurs in most patients [**Error! Reference source not found.**].

AFP=alpha-fetoprotein; EGF=epidermal growth factor; EMA=European Medicines Agency; EU=European Union; FGF=fibroblast growth factor; HBV=hepatitis B virus; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; HGF=hepatocyte growth factor; IGF=insulin like growth factor; Met=hepatocyte growth factor receptor protein; NAFLD=nonalcoholic fatty liver disease; NASH=nonalcoholic steatohepatitis; OS=overall survival; PDGF=platelet-derived growth factor; PD-L1=programmed death-ligand 1; SEER=surveillance, epidemiology and end results programme; USA=United States of America; VEGF= vascular endothelial growth factor; VEGFR=vascular endothelial growth factor receptor; WNT pathway=wingless/integrated pathway.

SI.1.3. Differentiated Thyroid Carcinoma

The incidence, prevalence, demographics, risk factors, natural history (including mortality and morbidity), treatment options and important co-morbidities of the population of adult and adolescent patients with DTC are summarised in Table 6.

Table 6 Epidemiology of Patients with Differentiated Thyroid Carcinoma

Indication/target population	DTC in adult patients
Incidence and prevalence of target indication	Thyroid cancer is the most common endocrine neoplasm with an annual estimate in the US of more than 44,000 newly diagnosed cases and over 2000 deaths; the US annual death rate is approximately 0.6% [**Error! Reference source not found.**]. • In 2020, over 87,000 new cases and over 6,000 deaths were reported in Europe [**Error! Reference source not found.**]; worldwide, there were over 586,000 cases and 43,000 deaths. • Differentiated thyroid cancer (DTC), including papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), and Hürthle cell carcinoma (HTC), are neoplasms originated from follicular cells. Papillary thyroid cancer is the most common histologic subtype of thyroid cancer and has the best prognosis, accounting for ~90% of newly diagnosed thyroid cancers [**Error! Reference source not found.**]. Follicular thyroid cancer is the second most common thyroid cancer and accounts for about 5-15% of DTC cases. Hürthle cell carcinoma, also named oxyphilic or oncocytic cell carcinoma, is considered a variant of FTC and accounts for 3% of thyroid cancers.
Demographic profile of target population	• Although thyroid cancer can occur at any age, approximately 42% of incident cases occur in patients between 45 and 64 years, with a median age at diagnosis of 51 years [**Error! Reference source not found.**]. • Thyroid cancer is about 2.5 times more common in women than in men, and the incidence has doubled from 2000 through 2019 [**Error! Reference source not found.**].
Risk factors for the disease	• Risk factors for DTC include a diet low in iodine and environmental radiation exposure [**Error! Reference source not found.**]. • Inherited conditions such as familial adenomatous polyposis and Cowden's disease have also been linked to thyroid cancers due to certain germline mutations, as well as a family history of the disease [**Error! Reference source not found.**].

Indication/target population	DTC in adult patients
Main treatment options	• Surgical resection by either total thyroidectomy or unilateral lobectomy, with or without lymph node removal, is the main treatment for DTC. Patients with a high-risk of disease recurrence, incompletely resected cancer, or distant metastases, may receive RAI. After thyroidectomy, lifelong thyroid hormone replacement with levothyroxine (LT4) is indicated. Levothyroxine replacement therapy lowers thyroid-stimulating hormone (TSH) levels by negative feedback through the hypothalamic-pituitary axis and helps to prevent the growth of remaining thyroid cancer cells [**Error! Reference source not found.**]. • Patients who develop RAI-refractory DTC have a very poor prognosis with an estimated median survival time of 2.53.5 years [**Error! Reference source not found.**]. • Recent treatment advancements for patients with RAI-refractory DTC include TKIs targeting the VEGFR which inhibits tumour angiogenesis and causes hypoxia in malignant tissue. • Two available multikinase inhibitors (MKIs), sorafenib and lenvatinib are approved for the treatment of unresectable, radioiodine-refractory differentiated thyroid cancer, irrespective of the presence or absence of a RET mutation on the basis of significant improvement in progression free survival (PFS). According to ESMO and National Comprehensive Cancer Network (NCCN) guidelines, lenvatinib has become the preferred treatment option over sorafenib for first-line treatment of DTC [**Error! Reference source not found.**]. • In 2022, the cabozantinib tablet formulation has been approved for the treatment of adult patients with locally advanced or metastatic DTC, refractory or not eligible to RAI who have progressed during or after prior systemic therapy. This approval is based on the COSMIC-311 trial showing a significant benefit in progression free survival of cabozantinib over placebo [**Error! Reference source not found.**, **Error! Reference source not found.**]. • For patients with specific mutations there are additional treatment options in subsequent lines: Selpercatinib has been approved by the EMA for adults with advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib based in the LIBRETTO-001 trial [**Error! Reference source not found.**]. Neurotrophic tyrosine receptor kinase (NTRK)-gene fusions can be targeted by entrectinib or larotrectinib. Both treatments have been approved by EMA in adult and paediatric patients with a solid tumour expressing an NTRK gene fusion if there is no satisfactory treatment option available.
Natural history, including mortality and morbidity	• Surgical resection by either total thyroidectomy or unilateral lobectomy, with or without lymph node removal, is the main treatment for DTC and can be curative [**Error! Reference source not found.**]. However, a considerable number of DTC patients either have inoperable locally advanced disease or have residual or recurrent disease after surgery. Patients with a high-risk of disease recurrence, incompletely resected cancer, or distant metastases may receive adjuvant therapy with RAI. Patients who develop RAI-refractory DTC have a very poor prognosis with an estimated median survival time of 2.5-3.5 years [**Error! Reference source not found.**]. • The age-adjusted death rate was 0.5 per 100,000 men and women per year, based on 2015–2019 cases and 2016–2020 deaths [**Error! Reference source not found.**].
Important co-morbidities	Previous studies suggested that the most frequent co-morbidities in patients with newly diagnosed thyroid cancer include hypertension, other cancers, hypothyroidism, cardiovascular disease, diabetes mellitus [**Error! Reference source not found.**].

Indication/target population	DTC in adult patients

DTC=differentiated thyroid cancer; EMA=European Medicines Agency; ESMO=European Society for Medical Oncology; FTC=follicular thyroid carcinoma; HTC=Hürthle cell carcinoma; LT4=levothyroxine; MKI=multikinase inhibitor; NCCN=National Comprehensive Cancer Network; NTRK=neurotrophic tyrosine receptor kinase; PFS=progression free survival; PTC=Papillary thyroid carcinoma; RAI= radioactive iodine; RET=rearranged during transfection; TKI=Tyrosine kinase inhibitors; TSH=thyroid-stimulating hormone; US(A)=United States (of America); VEGFR=vascular endothelial growth factor receptor.

SI.1.4. Neuroendocrine Tumours

The incidence, prevalence, demographics, risk factors, natural history (including mortality and morbidity), treatment options and important co-morbidities of the population of adult patients with NET are summarised in Table 7.

Table 7 Epidemiology of Patients with Neuroendocrine Tumours

Indication/target population	NETs in adult patients
Incidence and prevalence of target indication	• Gastroenteropancreatic (GEP) neuroendocrine tumours (NETs) incidence appears to be steadily rising and small intestinal and pancreatic NETs tend to be the most prevalent in Europe. Some of the increase may be explained due to more frequent utilisation of cross-sectional imaging and an increased ability to capture occult disease. Differences in more prevalent sites by region may be due to a combination of varied environmental factors and biology across populations [**Error! Reference source not found.**]. • In Germany, using the former East German National Cancer and subsequent Joint Cancer Registry, the crude incidence rate of GEP NETs rose from 0.45 cases per 100,000 in 1976 to 2.5 cases per 100,000 in 2006 [**Error! Reference source not found.**]. • In England, there were 63,949 NEN cases between 1995 and 2018, and the age-adjusted incidence rate increased 3.7-fold from 2.35 to 8.61 per 100,000 from 1995 to 2018. In 2018, the highest incidence occurred in the lungs (1.47 per 100,000), small intestine (1.46 per 100,000), pancreas (1.00 per 100,000), and appendix (0.95 per 100,000). These rates were estimated using the National Cancer Registry and Analysis Service, which captures over 99% of tumours recorded in England's National Health Service and is updated as the histopathological classification systems change [**Error! Reference source not found.**]. • In Norway, there were 10,288 NET cases and 13,982 NECs with incidence rate per 100,000 from 2017-2021 of 9.97 and 9.95 across all sites, respectively. These rates were estimated using the Cancer Registry of Norway and the degree of completeness is estimated to be 98.8% [**Error! Reference source not found.**]. • There is a lack of population-based epidemiologic studies that use standardised data collection methods including an up-to-date pathologic grading system such as the 2019 WHO NET grading criteria and standard metrics (e.g. crude and age-adjusted incidence rates). The heterogeneity in study methodology makes it difficult to make broad conclusions about a region such as Europe [**Error! Reference source not found.**]. • In Norway, the prevalence of NENs increased from 18.2 to 120.9 per 100,000 and from 7.4 to 21.6 for NECs. The prevalence was reported as complete prevalence which represents the proportion of people alive on a certain day who have been diagnosed with the disease, regardless of how long ago the disease was diagnosed, whether the patient is still under treatment or considered cured. The reason why complete prevalence was presented instead of limited duration prevalence, which is most often published, is the long duration of registration in the Cancer Registry of Norway of Norway [**Error! Reference source not found.**].

Indication/target population	NETs in adult patients
Demographic profile of target population	• From 2011-2018, 63,949 patients with NEN had a median age of 67 years (IQR=55-76 years). The patients were 50.2% female and 89.3% White. By site (appendix, caecum, colon, lung, pancreas, rectum, small intestine, stomach) the median age ranged from 61 to 69 years except for appendix, which had a median age of 39 years. Additionally, for NENs in the stomach, pancreas, rectum, small intestine, and colon, males comprised the majority of cases (52.1%-57.2%) as opposed to NENs in the appendix, lung, and caecum (39.3%-45.0%) [**Error! Reference source not found.**]. • Additionally, 10,102 NEN patients from 7 national registries (Belgium, Czech Republic, Germany, Greece, Poland, Spain, Switzerland) had a median age of 60 years (range: 18-102 years) and 48% were female [**Error! Reference source not found.**].
Risk factors for the disease	• A systematic review found a family history of cancer to be the most relevant risk factor of NEN development followed by BMI and diabetes. Cigarette smoking and alcohol consumption were also potential risk factors at select anatomical sites [**Error! Reference source not found.**]. • Several risk factors have been implicated in the potential pathogenesis of NENs including environmental factors, sex, metabolic syndrome and nutrition, lipid homeostasis, vitamin D levels, and microbiota. There is a complex interplay between patient characteristics, environment, and tumour biology which makes it difficult to develop a reliable model of the pathogenesis of NENs [**Error! Reference source not found.**].

Indication/target population	NETs in adult patients
Main treatment options	• Management of NETs is dependent on primary tumour location, grade, presence of symptoms, somatostatin receptor (SSTR) positivity, stage, and disease burden. Locoregional therapies such as surgery and liver-directed therapies may be used for symptom control as well as for curative intent for localised disease [**Error! Reference source not found.**, **Error! Reference source not found.**]. For patients with unresectable or metastatic disease, the management depends on the rate of disease progression in addition to the above factors. Of note, a watch-and-wait strategy may be an option in patients who have low tumour burden, stable disease and a low Ki-67 (<2%) (ESMO Clinical Practice Guidelines, 2020 [**Error! Reference source not found.**]). • Systemic treatment should be given to patients to control tumour-associated clinical symptoms and tumour growth. Somatostatin analogues (SSA) are the standard first-line treatment for patients with hormonal symptoms related to functional tumours. In 70%-80% of cases, patients experience an improvement in symptoms such as flushing and diarrhoea with the use of slow release SSA formulations [**Error! Reference source not found.**]. Telotristat ethyl is an oral inhibitor of tryptophan hydroxylase which is approved for treatment of diarrhoea associated with carcinoid syndrome in patients not adequately controlled with SSA, and it can be used as an add-on treatment to SSA [**Error! Reference source not found.**]. • For patients with progressive pancreatic NET, approved treatment options include the mTOR inhibitor everolimus, the tyrosine kinase inhibitor sunitinib [**Error! Reference source not found.**, **Error! Reference source not found.**] and for patients with SSTR+ disease, the peptide receptor radionuclide therapy (PRRT) lutetium-177 (Lu-177) dotatate [**Error! Reference source not found.**]. For patients with progressive gastrointestinal NET, approved treatment options include everolimus and Lu-177 dotatate for SSTR+ disease [**Error! Reference source not found.**, **Error! Reference source not found.**]. For patients with lung NET, the only approved treatment is everolimus [**Error! Reference source not found.**]. • In addition, cytotoxic chemotherapy including but not limited to temozolomide-based or platinum-based regimens are considered appropriate treatment options for patients with bulky disease, aggressive or symptomatic NETs although these are not specifically approved by EMA [**Error! Reference source not found.**].
Natural history, including mortality and morbidity	• Neuroendocrine tumours are still considered incurable, but treatment options have improved survival of patient's post-diagnosis. The 5-year survival rate for pancreatic NET varies by stage. Localised is 95%, regional is 72%, and distant is 23% with the combined 5-year survival rate being 53% [**Error! Reference source not found.**]. The 5-year survival of GI NET was 98% in localised tumours and 68% in distant [**Error! Reference source not found.**]. The 5-year survival in pulmonary NET was 89% [**Error! Reference source not found.**]. • Prognosis of patients with NET depends in part on disease stage, and site of the primary tumour. In a US retrospective study using data from the Surveillance, Epidemiology and End Results (SEER) 64,971 patients with NETs from 1973 to 2012 were analysed. Survival depended on the stage of their disease with the median overall survival being longest (>30 years) for patients with localised disease, compared to approximately 10 years for patients with regional disease, and approximately 12 months for patients with distant metastatic disease [**Error! Reference source not found.**]. • The speed of tumour growth in general slow for NET with roughly 50% of NET originating within the GI system including the pancreas [**Error! Reference source not found.**]. • Neuroendocrine tumours patients often have symptoms related to hormonal hypersecretion which commonly come in the forms of diarrhoea, flushing, bronchospasm, and hypertension [**Error! Reference source not found.**, **Error! Reference source not found.**].

Indication/target population	NETs in adult patients
Important co-morbidities	• Chronic pancreatitis is linked to pancreatic NET, but clear literature is difficult to identify [**Error! Reference source not found.**]. • Diabetes is linked to pancreatic NET and was seen through a meta-analysis that found that diabetes was associated with an odds-ratio (OR) of 2.74 of developing pancreatic NET which highlights a strong correlation between the conditions [**Error! Reference source not found.**].

BMI=body mass index; EMA=European Medicines Agency; ESMO=European Society for Medical Oncology; GEP=gastroenteropancreatic; GI=gastrointestinal; IQR-interquartile range; mTOR=mammalian target of rapamycin; NEC=neuroendocrine carcinoma; NEN=neuroendocrine neoplasm; NET=neuroendocrine tumour; OR=odds-ratio; PRRT=peptide receptor radionuclide therapy; SEER= surveillance, epidemiology and end results; SSA=somatostatin analogues; SSTR=somatostatin receptor; US=United States; WHO=World Health Organization.

Part II: Module SII – Nonclinical Part of the Safety Specification

A summary of the nonclinical findings and their relevance to human usage is outlined in Table 8.

Table 8 Key Nonclinical Safety Findings and Relevance to Human Use

Key safety findings (from nonclinical studies)	Relevance to human usage
• Single dose toxicity Toxicity associated with a single oral dose of cabozantinib in rats was characterised by histopathologic changes in GI tract tissues, bone marrow, lymphoid tissue, and male and female reproductive tissues at plasma concentrations approximately 66-fold higher than expected in humans at the recommended 60 mg dose. Cabozantinib plasma concentrations at the minimal lethal single oral doses of cabozantinib in rats and dogs were ≥75-fold and >22-fold higher, respectively, than expected in humans at the recommended 60 mg dose.	Cabozantinib single dose toxicity is not considered a clinical risk as it occurred at plasma exposures in rats and dogs far greater than expected in humans at the recommended 60 mg dose.
• Repeat-dose toxicity In rats dosed daily for 14 days, microscopic changes occurred in kidney (glomerular membrane thickening, tubular degeneration), ovary (corpora lutea necrosis), pituitary, and adrenal gland (necrosis). In rats dosed daily for 6 months, microscopic changes occurred in kidney (reversible increase in severity and/or incidence of chronic progressive nephropathy (CPN) of aging). Steady-state plasma concentrations were approximately 2-fold higher than expected in humans at the recommended 60 mg dose. Dogs dosed daily for 6 months showed microscopic changes in reproductive tissues (bilateral testicular hypo-spermatogenesis and ovarian corpus luteum absent) at steady-state plasma concentrations approximately 0.2-fold (males) and <0.1-fold (females) of those expected in humans at the recommended 60 mg dose. In a 2-week repeat-dose toxicity study of EXEL-1644, the major metabolite of cabozantinib present in human plasma, no systemic tissue toxicity occurred in rats following daily subcutaneous administration yielding	Nephrotoxic findings in rats following repeat daily dosing of cabozantinib do not appear to represent a marked clinical risk, as they were either reversible with dose discontinuation (glomerular membrane thickening, tubular degeneration), were considered nonadverse (the primary concern of accelerated CPN is animal survivability in longer term studies) and occurred at higher than anticipated clinical exposures. Adrenal and pituitary endocrine tissues did not appear to be cabozantinib target tissues clinically. Microscopic changes in testes and ovaries in rats and dogs correlate with reduced fertility observed in rats administered cabozantinib (see Reproductive Toxicity below) and suggest that cabozantinib has the potential to impair reproductive function and affect fertility in humans at plasma exposures below those expected at the recommended 60 mg dose. Metabolite EXEL-1644 does not appear to represent a significant clinical safety concern based on the absence of systemic toxicity in rats at exposures higher than those expected at the recommended 60 mg cabozantinib dose.

Key safety findings (from nonclinical studies)	Relevance to human usage
steady-state plasma exposures estimated to be >3.5-fold higher than those expected in humans as a metabolite at the recommended 60 mg dose.	
• Reproductive toxicity In rats administered cabozantinib, significantly decreased absolute reproductive tissue weights in testes, epididymis, prostate, and seminal vesicles, and decreased sperm counts occurred following a minimum of 10 weeks of daily dosing. In females, significantly decreased fertility and embryo-foetal viability (pre- and post-implantation loss) occurred following a minimum of 3 weeks of daily dosing. Observed steady-state plasma concentrations were approximately 3-fold (males) and 1-fold (females) of those expected in humans at the recommended 60 mg dose. In a 6-month chronic toxicity study of cabozantinib in dogs, decreased testes and ovarian weights correlated with microscopic changes in these tissues (moderate to severe bilateral hypo-spermatogenesis and a lack of corpora lutea) at steady-state plasma concentrations approximately 0.2-fold (males) and <0.1-fold (females) of those expected in humans at the recommended 60 mg dose.	Cabozantinib has the potential to impair reproductive function and affect fertility in humans, based on results of nonclinical safety studies.
• Developmental toxicity In rats, cabozantinib caused increased post implantation loss at steady-state plasma concentrations ≥0.8-fold of those expected in humans at the recommended 60 mg dose and caused foetal oedema, cleft palate/lip, dermal aplasia, and kinked or rudimentary tail at higher exposures. In rabbits, cabozantinib produced foetal soft tissue changes (reduced spleen size, small or missing intermediate lung lobe) and increased foetal incidence of total malformations at steady-state plasma concentrations approximately 0.2-fold of those expected in humans at the recommended 60 mg dose. Juvenile rats dosed with cabozantinib orally at 2 mg/kg/day starting at PND21 (reflective of a paediatric population >2 years of age) through PND35 or 70 had no unscheduled deaths during the dosing phase, whereas juvenile rat cohorts dosed with cabozantinib orally at 2 mg/kg/day starting at PND12 (reflective of a paediatric population <2 years of age) through PND35 or 70 had unscheduled deaths during the dosing phase. No test article related mortalities were observed in the 1 mg/kg/day cohorts in either study.	Cabozantinib may cause foetal harm at subclinical exposures if administered to a pregnant woman, based on results of nonclinical safety studies. Based on unscheduled deaths in the juvenile rat PND12 cohorts and not in the PND21 cohorts at the 2 mg/kg/day dose, paediatric subjects <2 years of age may be more sensitive to cabozantinib related toxicity than paediatric subjects >2 years of age. Limited safety data are available in paediatric population older than 4 years old (Study ADVL1211 [**Error! Reference source not found.**] and Study ADVL 1622). The safety and efficacy of cabozantinib in children and adolescents aged <18 years have not yet been established.
• Nephrotoxicity Nephrotoxic changes observed in rats dosed daily for 14 days included dose-related effects on kidney weights (slightly increased), urinalysis	Nephrotoxic findings in rats following repeat daily dosing of cabozantinib do not appear to represent a marked clinical risk, as they were reversible with dose discontinuation (glomerular membrane thickening,

Key safety findings (from nonclinical studies)	Relevance to human usage
parameter changes (slightly decreased urine volume and minimally increased urine specific gravity), and microscopic changes (minimal-moderate glomerular basement membrane thickening and tubular degeneration in males and females, reversible). In rats administered cabozantinib daily for 180 days, the sole microscopic treatment related finding was a slight increase in the severity and/or incidence of CPN of aging in males and females, which was reversible upon discontinuation of dosing. Plasma exposures at these nephrotoxic doses in rats in the 2-week and 6-month toxicity studies are approximately 2-fold higher than expected in humans at the recommended 60 mg dose.	tubular degeneration), were considered nonadverse (the primary concern of accelerated CPN is animal survivability in longer term studies) and occurred at higher than anticipated clinical exposures. In the pivotal phase III XL184-308 and XL184-309 studies, the overall frequency of AEs of proteinuria (Grade 3 or 4) was low (<3%) in subjects with either RCC or HCC receiving cabozantinib. Only one cabozantinib-treated subject in Study XL184-308 had renal failure (a Grade 3 SAE that was not treatment related and was ascribed to contrast agent by the investigator), in addition, two subjects had Grade 1 acute renal failure. In the pivotal phase II A031203 study, the overall frequency of AEs of proteinuria (Grade 3 or 4) was low (<3%) in subjects with RCC receiving cabozantinib. A total of seven (9.0%) cabozantinib-treated subjects had AEs of acute renal failure or chronic renal failure (all grades). One subject had Grade 5 acute renal failure. This subject had elevated creatinine at screening and died of acute renal failure following dehydration and the subject refused dialysis. In Study XL184-309, 11 subjects (2.4%) in the cabozantinib arm experienced renal failure-related AEs (four Grade 3 and one Grade 4). A Grade 5 event of prerenal failure was also reported. In Study CA2099ER, the overall frequency of AEs of proteinuria (Grade 3 or 4) was 3.1% in RCC subjects treated with cabozantinib in combination with nivolumab. Twenty-two (6.9%) subjects in the cabozantinib in combination with nivolumab arm in Study CA2099ER experienced renal failure AEs. There were 3 SAEs (0.9%) in the cabozantinib in combination with nivolumab arm. The majority of AEs were of Grade 1 and Grade 2 severity. Grade 3 AEs included renal failure (0.3%) and acute kidney injury (0.6%). Renal failure (including acute kidney injury) and tubulointestinal nephritis are recognised adverse reactions of nivolumab in the OPDIVO SmPC. In Study XL184-311, the overall frequency of AEs of proteinuria (Grade 3 or 4) was 0.8%. Three subjects (2.4%) in the cabozantinib arm experienced renal failure-related AEs (Grade 3 events included acute kidney injury and renal impairment. The Grade 4 event was renal failure. In Study A021602, two subjects (1.0%) in cabozantinib arm experienced renal failure-related AEs of acute kidney injury (both serious, Grade 3). One of the reported Grade 3 event of acute kidney injury was assessed as treatment related.
• Hepatotoxicity Potential evidence of hepatotoxicity occurred in rats dosed with cabozantinib daily for 14 days (decreased total protein and albumin, an enlarged bile duct, and histopathological changes of reversible hepatocellular hypertrophy and vacuolation) and in dogs administered cabozantinib for 5 days (reversible increases in alanine aminotransferase (ALT) and aspartate	Hepatotoxic findings in rats and dogs were not considered primary changes, but rather nonadverse changes, secondary to general drug related systemic toxicity at cabozantinib doses resulting in unscheduled deaths or moribund sacrifices and only at exposures many folds higher than expected at the recommended clinical dose. Therefore, results from nonclinical safety

Key safety findings (from nonclinical studies)	Relevance to human usage
aminotransferase (AST) values, and histopathological changes in gallbladder (accumulation of secretions)) at steady-state plasma concentrations approximately 20-fold higher than expected in humans at the recommended 60 mg dose. The only evidence of possible liver damage associated with cabozantinib administration in chronic toxicity studies in rats and dogs was a minimal, dose-related (2-fold maximum) ALT increase (without correlative microscopic findings) in rats dosed for 180 days at steady-state plasma concentrations approximately 2-fold higher than expected in humans at the recommended 60 mg dose.	studies do not indicate a clinical risk of hepatotoxicity from cabozantinib at clinically-relevant exposures. In Studies XL184-308 and A031203 elevations of liver enzymes were frequent in cabozantinib-treated subjects but there was no evidence of drug-induced liver injury (DILI) with cabozantinib treatment. One cabozantinib-treated subject in Study XL184-308 developed a Grade 4 event of cholestatic hepatitis; the case was confounded by the use of concomitant ciprofloxacin and acetaminophen with an additional potential cause of autoimmune-mediated hepatitis following receipt of nivolumab prior to study entry. In Study CA2099ER the AEs of ALT increased, and AST increased were experienced by 28.1% and 25.3%, respectively in cabozantinib in combination with nivolumab treated subjects. Grade 3 AEs included 5.3% ALT increased and 3.4% AST increased. The majority of AEs were non-serious with only 0.6% SAEs of ALT increased and 0.3% SAE of AST increased. Twenty-nine (9.1%) subjects in the cabozantinib in combination with nivolumab arm in Study CA2099ER experienced hepatotoxicity AEs including 13 (4.1%) Grade 3 AEs and 1 (0.3%) Grade 4 AE. In this study four subjects treated with cabozantinib in combination with nivolumab met Hy's Law criteria of concurrent ALT or AST > 3× upper limit of normal (ULN) with total bilirubin > 2× ULN elevation based on lab results within 30 days of last dose. These 4 subjects also reported concurrent ALT/AST and total bilirubin increases as AEs, of which three subjects had hepatotoxicity reported as an AE. All these 4 cases resolved with the use of corticosteroids. Immune-mediated hepatitis, increased ALT, increased AST, and increased total bilirubin are recognised adverse reactions of nivolumab in the OPDIVO SmPC. In Study XL184-309 all grade AEs of ALT increased, and AST increased were experienced by 17% and 22%, respectively in cabozantinib-treated subjects. Grade 3 or 4 AEs of ALT increased, and AST increased were experienced by 5% and 12%, respectively, of subjects. One SAE of ALT increased, and three SAEs of AST increased were reported. There were no confirmed cases of DILI with cabozantinib treatment in this study. In Study XL184-311, all grade AEs of ALT increased, and AST increased were experienced by 24% and 23% respectively in the cabozantinib-treated patients. Grade 3 or 4 AEs of ALT increased, and AST increased were experienced by 0.8% and 0% subjects respectively. There were no confirmed cases of DILI with cabozantinib treatment in this study. Ten (5.1%) subjects in cabozantinib arm in Study A021602 experienced hepatotoxicity AEs. The majority of AEs were of Grade 3 severity. The Grade 3 AEs included ascites (1.5%), hepatic encephalopathy (0.5%), hepatic failure (0.5%), portal hypertension (0.5%) and spontaneous bacterial peritonitis (0.5%).

Key safety findings (from nonclinical studies)	Relevance to human usage
	Grade 4 and Grade 5 events of hepatic failure (one each) were also reported which were assessed as not related to the cabozantinib treatment. Two AEs of ascites were of Grade 2 severity. The AEs of ALT increased and AST increased were experienced by 66% and 72% of subjects, respectively, in cabozantinib arm. Grade 3 AEs of AST increased were experienced by 3.1% and Grade 4 AEs of ALT increased were experienced by 0.5% of the subjects. No Grade 3 AEs were reported for ALT increased. The higher incidence of ALT increased and AST increased in Study A021602 may be because these adverse events are considered expected and their presence/absence should be solicited, per the study protocol. Hepatotoxicity is an important potential risk for cabozantinib and is discussed further in Part II: Module SVII – Identified and Potential Risks.
• Genotoxicity Cabozantinib was negative in in vitro bacterial and mammalian cell and in vivo mouse bone marrow micronucleus genotoxicity bioassays.	Findings from nonclinical studies suggest that cabozantinib poses minimal genotoxic risk to patients with RCC or HCC.
• Carcinogenicity Cabozantinib related neoplastic findings consisted from Study XL184-NC-036 of an increased incidence of benign pheochromocytoma, alone or in combination with malignant pheochromocytoma/complex malignant pheochromocytoma of the adrenal medulla in males administered ≥0.1 mg/kg/day and females administered ≥0.3 mg/kg/day. A cabozantinib related increased incidence of hyperplasia of the adrenal medulla also occurred in females administered ≥0.1 mg/kg/day. At the lowest dose level tested (0.1 mg/kg/day), the Week 26 mean plasma Cmax and AUC0-last values were 187 ng/mL and 2850 ng•hr/mL, respectively, for sexes combined. The exposure in rats dosed at 0.1 mg/kg/day is approximately 0.1 times that of that measured at steady-state in subjects with RCC administered 60 mg cabozantinib daily. Cabozantinib was not carcinogenic in the 26-week 001178-T (hemizygous) rasH2 mouse model. Cabozantinib was negative in all nonclinical genotoxicity bioassays in which it was evaluated (i.e. an in vitro bacterial point mutation assay, an in vitro clastogenicity assay using human peripheral blood lymphocytes, an in vitro mouse lymphoma assay, and an in vivo mouse micronucleus assay). In addition, no preneoplastic lesions were identified in 6-month chronic repeat-dose toxicity studies of cabozantinib in rats and dogs at plasma exposures approximately 2-fold higher than those measured at steady-state in subjects with RCC administered 60 mg cabozantinib daily. Finally, levels of genotoxic impurities in cabozantinib	The carcinogenic potential of cabozantinib in humans is not known. Neoplasia associated with cabozantinib administration to rats for up to 104 weeks was limited to a dose-related increase in benign pheochromocytomas. An increased incidence in pheochromocytomas and adrenal hyperplasia was also reported in a 2-year bioassay in rats administered sunitinib [**Error! Reference source not found.**], a receptor tyrosine kinase inhibitor that also targets the glial cell line derived neurotrophic factor receptor (RET) similar to cabozantinib. No relationship has been identified thus far for chemicals that cause increased incidence of pheochromocytomas in chronic rodent bioassays and with a corresponding increased risk of this tumour type in humans exposed to the same chemical [**Error! Reference source not found.**]. While pheochromocytomas are frequent in rats (up to 20% in males), this is a rare tumour in humans [**Error! Reference source not found.**]. Cabozantinib was not carcinogenic in the 001178-T (hemizygous)rasH2 mouse model. Findings from nonclinical studies suggest that cabozantinib poses minimal carcinogenic risk when administered to patients with RCC or HCC. Four subjects (1.2%) in the cabozantinib arm of Study XL184-308 experienced second primary malignancies that were not related to RCC: one subject each experienced AEs of adenocarcinoma, adenocarcinoma of colon, basal cell carcinoma and chronic lymphocytic leukaemia. Three events were SAEs. No subjects in the cabozantinib arm of Study A031203 experienced second primary malignancies. Six subjects (1.9%) in the cabozantinib in combination with nivolumab arm of Study CA2099ER experienced

Key safety findings (from nonclinical studies)	Relevance to human usage
drug product are also being monitored in order to not exceed specified limits.	second primary malignancies that were not related to RCC. The following second primary malignancies included basal cell carcinoma (2), squamous cell carcinoma (2), bladder neoplasm (1), and keratoacanthoma (1). None of these events were assessed as related to treatment. Three events were SAEs, all reported as resolved. Four subjects (0.9%) in the cabozantinib arm of Study XL184-309 experienced second primary malignancies that were not related to HCC: two subjects experienced AEs of squamous cell carcinoma assessed as not related to cabozantinib, one subject experienced a new onset secondary malignancy of acute lymphocytic leukaemia assessed as not related and one subject with a prior history of breast cancer experienced a new onset second primary malignancy of intraductal proliferative breast lesion assessed as not related. Two events were SAEs. In Study XL184-311, no subjects were identified as developing secondary malignancies. No subjects in the cabozantinib arm of Study A021602 experienced primary or secondary malignancies. Cabozantinib is intended for a patient population with advanced cancer and a short life expectancy. The potential risks should be considered in the context of the potential benefits.
General safety pharmacology Cabozantinib administration resulted in no adverse effects on cardiovascular system functions (including no increase in QTc) in dogs at plasma exposures approximately 4-fold higher than expected at steady-state at the recommended human dose. Cabozantinib administration resulted in no adverse effects on neurobehavioural or respiratory system functions in rats at plasma exposures approximately 60-fold higher than expected at steady-state at the recommended human dose.	Cabozantinib at clinically relevant plasma exposures would appear to represent minimal potential clinical risk of adverse effects on neurobehavioural, respiratory or cardiovascular systems.
Drug interactions • Drug transporter-mediated Cabozantinib appears to be a substrate for transporter MRP2 only, whereas metabolite EXEL-1644 appears to be a substrate for several drug transporters (i.e. OAT3, OATP1B1, OATP1B3, BCRP, and MRP2). Assay data were inconclusive as to whether EXEL-1644 is a P-gp substrate. Cabozantinib demonstrated inhibition of MATE1 and MATE2-K (estimated IC50 values of 5.94 and 3.12 µM, respectively), but no marked inhibition of BCRP, BSEP, MRP2, and P-gp, (i.e. IC50 values >50 µM), or of OAT1, OAT3, OCT1, OATP1B1, and OATP1B3 (i.e. IC50 values >15 µM). Metabolite EXEL-1644 demonstrated most potent inhibition of OAT1, OAT3, and OATP1B1 (IC50 range: 4.3 to	Cabozantinib and EXEL-1644 at clinically-relevant plasma exposures may represent potential risk of a drug transporter DDI. Substrates of P-gp co-administered with cabozantinib should be used with caution. Both cabozantinib and EXEL-1644 have high plasma protein binding yielding low estimated free fraction concentrations at clinically relevant steady-state plasma concentrations, thereby minimising risk of a clinically-relevant DDI with substrates of other drug transporters. However, cabozantinib and EXEL-1644 were both shown to be drug transporter substrates; thus, their plasma PK may also be affected by drugs that inhibit these transporters.

Key safety findings (from nonclinical studies)	Relevance to human usage
6.1 µM), less potent inhibition of BSEP, MRP2, OATP1B3, MATE1, and MATE2-K (IC50 range: 16.7 to 78.5 µM), and no marked inhibition of BCRP, P-gp, OCT1, and OCT2 (i.e. IC50 values exceeded the assay incubation soility limit of 250 µM).	
• CYP-mediated Cabozantinib was determined to be a substrate of CYP isozyme CYP3A4 in vitro using human liver microsomal systems. Cabozantinib and metabolite EXEL-1644 were both shown to most potently inhibit CYP2C8 in an in vitro CYP inhibition panel (CYP2C8, CYP2C9, CYP1A2, CYP2B6, CYP2C19, CYP2D6, and CYP3A4/5 evaluated). In nonclinical studies, XL184 is predicted to be a potential inducer of CYP1A1 in vivo, but not a potent inducer of other CYP isozymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4).	Clinical pharmacology studies in healthy subjects supported the in vitro study findings that cabozantinib is a CYP3A4 substrate: cabozantinib plasma exposure (AUC) was decreased 76% to 77% following CYP3A4 induction by rifampicin, whereas CYP3A4 inhibition by ketoconazole increased cabozantinib plasma exposure 34% to 38%. Concomitant administration of strong CYP3A4 inhibitors with cabozantinib should be done with caution, and concomitant administration of strong CYP3A4 inducers should be avoided. Cabozantinib and EXEL-1644 both appear to represent minimal clinical risk of a DDI by inhibition of CYP isozymes. Cabozantinib and EXEL-1644 each most potently inhibited CYP2C8; however, no effect was observed on the plasma PK of CYP2C8 probe substrate rosiglitazone at clinically relevant steady-state plasma exposures of cabozantinib and metabolite EXEL-1644 in subjects with solid tumours. Thus, cabozantinib and EXEL-1644 would not be considered potential inhibitors of metabolism in vivo for substrates of CYP2C8 and other CYP isozymes with lower in vitro I/Ki values. Based on the low number of concomitant medications metabolised by the CYP1A1 pathway, cabozantinib appears to pose minimal risk of a clinically relevant DDI based on CYP1A1 induction.

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; AUC=area under the plasma drug concentration-time curve; BCRP=breast cancer resistance protein; BSEP=bile salt export pump; C_{max}=maximum plasma concentration; CPN=chronic progressive nephropathy; CYP=cytochrome P450; DDI=drug-drug interaction; GI=gastrointestinal; HCC=hepatocellular carcinoma; IC_{50}=half-maximal inhibitory concentration; Ki=inhibition constant; MATE=multidrug and toxin extrusion protein; MRP2=multidrug resistance associated protein; OAT=organic anion transporter; OATP=organic anion transporter protein; OCT=organic cation transporter; P-gp=P-glycoprotein; PK=pharmacokinetic(s); PND=postnatal day; QTc=corrected QT interval; RCC=renal cell carcinoma; RET=rearranged during transfection; RMP=risk management plan; SAE=serious adverse event; SmPC=summary of product characteristics; ULN=upper limit of normal.

Based on the nonclinical safety characterisation of cabozantinib, the important identified risks (from nonclinical data), the important potential risks (unknown significance), and the important missing information are listed in Table 9.

Table 9 Important Risks and Missing Information

Nonclinical Safety concerns
Important identified risks (from nonclinical data) None
Important potential risks (unknown significance) Embryotoxicity Carcinogenicity
Missing information None

Part II: Module SIII – Clinical Trial Exposure

SIII.1. Brief Overview of Development

During the clinical development of cabozantinib, company sponsored clinical trials explored efficacy and safety across several oncology indications including RCC, glioblastoma, medullary thyroid, prostate, non-small cell lung, small cell lung, pancreatic, ovarian, breast, gastric, and differentiated thyroid cancers.

The approved indications for Cabometyx are:

- **Renal Cell Carcinoma (RCC)**

Cabometyx is indicated as monotherapy for the treatment of advanced RCC:

- in first-line treatment of adult patients with intermediate or poor-risk,
- in adults following prior VEGF-targeted therapy.

Cabometyx, in combination with nivolumab, is indicated for the first-line treatment of advanced RCC in adults.

- **Hepatocellular Carcinoma (HCC)**

Cabometyx is indicated as monotherapy for the treatment of HCC in adults who have previously been treated with sorafenib.

- **Differentiated Thyroid Carcinoma (DTC)**

Cabometyx is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic DTC, refractory or not eligible to RAI who have progressed during or after prior systemic therapy.

The proposed expanded indication for Cabometyx is:

- **Neuroendocrine Tumours (NET)**

Cabometyx is indicated for the treatment of adult patients with unresectable or metastatic, well differentiated extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours who have progressed following at least one prior systemic therapy other than somatostatin analogues.

The original pivotal trials Study XL184-308 (DLP 02 October 2016), Study A031203 (DLP 15 September 2016), Study XL184-309 (DLP 01 June 2017), Study CA2099ER (DLP 30 March 2020) and Study XL184-311 (DLP 08 February 2021) were the basis for the Marketing Authorisation (MA). The MAH proposes to further expand the indication based on pivotal Study A021602 (DLP 24 August 2023), conducted by the Alliance for Clinical Trials in Oncology as part of the NCI-CTEP.

The DLP for post-authorisation exposure was 28 November 2023 (Section SV.1 Post-authorisation Exposure).

The safety profile of cabozantinib is comparable in nature across all clinical development; however, the incidence and severity of adverse events (AEs) may differ across indication. Differences by indication, where relevant, are noted in this RMP.

SIII.2. Clinical Trial Exposure

SIII.2.1. Advanced Renal Cell Carcinoma in Adults Following Prior Vascular Endothelial Growth Factor-targeted Therapy

For the indication of RCC monotherapy, primary safety data are presented for the RCC subjects from the phase III study XL184-308. These subjects received a 60 mg once daily (qd) dose of cabozantinib tablets, which is the marketed dose of cabozantinib. Comparison with XL184-308 data is limited by differences in indications, study populations, and assigned doses. Compared

with the RCC population, the castration-resistant prostate cancer (CRPC) population was more frail and advanced in age and the medullary thyroid cancer (MTC) population had a more extensive history of surgery and radiation treatment, particularly to the head, neck, and upper chest region and received a higher dose.

The majority of the 356 subjects treated with cabozantinib monotherapy in clinical trials for RCC following prior VEGF-targeted therapy received a 60 mg tablet dose daily (n=331) and 25 subjects received 140 mg capsules daily in phase I study XL184-008. Two hundred and fifteen (215) subjects have been treated with cabozantinib 60 mg tablets for more than 6 months and 53 subjects have been treated for more than 12 months. In terms of exposure to cabozantinib by age group, first diagnosis of RCC peaks between the age of 60 to 70 years and exposure to cabozantinib reflects this. Median age of subjects enrolled in the cabozantinib arm of XL184-308 was 62 years (range 32, 84), and approximately 41% of subjects were at least 65 years of age.

The median duration of exposure in the XL184-308 clinical study (RCC) up to the data lock date was 36 weeks, and the maximum duration of exposure was 160 weeks (more than 3 years).The exposure to cabozantinib in Study XL184-308 is summarised by duration (Table 10), by age group and gender (Table 11) and by race (Table 12).

Table 10 Duration of Cabozantinib Exposure in Pivotal Study XL184-308

Duration of exposure	Study XL184-308 N=331	
	Persons n (%)	Person time (person weeks)
Overall exposure		
≥4 weeks	329 (99.4)	16,167
≥8 weeks	312 (94.3)	16,070
≥12 weeks	291 (87.9)	15,869
≥16 weeks	279 (84.3)	15,705
≥20 weeks	245 (74.0)	15,135
≥24 weeks	239 (72.2)	15,007
≥28 weeks	217 (65.6)	14,462
≥32 weeks	202 (61.0)	14,015
≥36 weeks	171 (51.7)	12,999
≥40 weeks	156 (47.1)	12,432
≥44 weeks	147 (44.4)	12,066
≥48 weeks	141 (42.6)	11,785
≥52 weeks	130 (39.3)	11,250
≥56 weeks	119 (36.0)	10,663
≥60 weeks	106 (32.0)	9919
≥64 weeks	97 (29.3)	9366
≥68 weeks	91 (27.5)	8973
≥72 weeks	81 (24.5)	8285
≥76 weeks	77 (23.3)	7988
≥80 weeks	74 (22.4)	7755
≥84 weeks	62 (18.7)	6787
≥88 weeks	57 (17.2)	6359
≥92 weeks	55 (16.6)	6177
≥96 weeks	50 (15.1)	5710
≥100 weeks	44 (13.3)	5127
≥104 weeks	32 (9.7)	3904
≥108 weeks	29 (8.8)	3591
≥112 weeks	24 (7.3)	3043
≥116 weeks	21 (6.3)	2699
≥120 weeks	16 (4.8)	2107

Duration of exposure	Study XL184-308 N=331	
	Persons n (%)	**Person time (person weeks)**
≥124 weeks	12 (3.6)	1619
≥128 weeks	7 (2.1)	986
≥132 weeks	7 (2.1)	986
≥136 weeks	5 (1.5)	721
≥140 weeks	3 (0.9)	447
≥144 weeks	2 (0.6)	306
≥148 weeks	1 (0.3)	160
≥152 weeks	1 (0.3)	160
≥156 weeks	1 (0.3)	160
≥160 weeks	1 (0.3)	160
Total person time	**16,172**	

Table 11 Cabozantinib Exposure by Age Group and Gender

Gender Age group	Study XL184-308 N=331	
	Persons n (%)	**Person time (person weeks)**
Female		
Total	77 (23.3)	3442
<65 years	46 (13.9)	2247
65 to <75 years	25 (7.6)	1039
75 to <85 years	5 (1.5)	96
≥85 years	1 (0.3)	59
Male		
Total	254 (76.7)	12,729
<65 years	151 (45.6)	7121
65 to <75 years	82 (24.8)	4716
75 to <85 years	21 (6.3)	891
≥85 years	0 (0.0)	0

Table 12 Cabozantinib Exposure by Ethnic or Racial Origin

Race	Study XL184-308 N=331	
	Persons n (%)	**Person time (person weeks)**
Total	331 (100.0)	16,172
American Indian or Alaska Native	0 (0.0)	0
Asian	21 (6.3)	1241
Black or African American	6 (1.8)	189
Native Hawaiian or Other Pacific Islander	0 (0.0)	0
White	270 (81.6)	13,382
Other	19 (5.7)	854
Not reported	15 (4.5)	504

SIII.2.2. Advanced Renal Cell Carcinoma in Treatment-naïve Adults with Intermediate or Poor-Risk

Primary safety data are presented for treatment-naïve subjects with advanced RCC with intermediate or poor risk from the phase II study A031203 (CABOSUN). These subjects received a 60 mg qd dose of cabozantinib tablets, which is the marketed dose of cabozantinib.

The median (range) age of subjects exposed to cabozantinib in Study A031203 was 63.0 years (40 to 82), and approximately 44% of the subjects were at least 65 years of age. The median

(range) duration of exposure in Study A031203 up to the data lock date for this RMP was 6.5 months (0.2 to 28.7). The exposure to cabozantinib in Study A031203 is summarised by duration (Table 13), by age group and gender (Table 14) and by race (Table 15).

Table 13 Duration of Cabozantinib Exposure in Pivotal Study A031203

Duration of exposure	Study A031203 N=78	
	Persons n (%)	**Person time (person weeks)**
Overall exposure		
≥4 weeks	76 (97.4)	3180
≥8 weeks	68 (87.2)	3137
≥12 weeks	63 (80.8)	3081
≥16 weeks	51 (65.4)	2926
≥20 weeks	49 (62.8)	2888
≥24 weeks	43 (55.1)	2755
≥28 weeks	39 (50.0)	2654
≥32 weeks	37 (47.4)	2594
≥36 weeks	36 (46.2)	2562
≥40 weeks	27 (34.6)	2232
≥44 weeks	26 (33.3)	2189
≥48 weeks	26 (33.3)	2189
≥52 weeks	24 (30.8)	2092
≥56 weeks	21 (26.9)	1930
≥60 weeks	21 (26.9)	1930
≥64 weeks	20 (25.6)	1866
≥68 weeks	20 (25.6)	1866
≥72 weeks	19 (24.4)	1795
≥76 weeks	17 (21.8)	1650
≥80 weeks	16 (20.5)	1571
≥84 weeks	14 (17.9)	1410
≥88 weeks	11 (14.1)	1153
≥92 weeks	9 (11.5)	973
≥96 weeks	9 (11.5)	973
≥100 weeks	7 (9.0)	775
≥104 weeks	5 (6.4)	571
≥108 weeks	3 (3.8)	358
≥112 weeks	3 (3.8)	358
≥116 weeks	3 (3.8)	358
≥120 weeks	1 (1.3)	125
≥124 weeks	1 (1.3)	125

EU=European Union; RCC=renal cell carcinoma; RMP=risk management plan.

Source: Table 1 2017 EU RMP RCC Tables

Table 14 Cabozantinib Exposure by Age Group and Gender

Gender Age group	Study A031203 N=78	
	Persons n (%)	**Person time (person weeks)**
Female		
Total	12 (15.4)	645
<65 years	7 (9.0)	349
65 to <75 years	4 (5.1)	189
75 to <85 years	1 (1.3)	107
≥85 years	0	0
Male		

Gender Age group	Study A031203 N=78	
	Persons n (%)	**Person time (person weeks)**
Total	66 (84.6)	2537
<65 years	37 (47.4)	1479
65 to <75 years	23 (29.5)	897
75 to <85 years	6 (7.7)	161
≥85 years	0	0

EU=European Union; RCC=renal cell carcinoma; RMP=risk management plan.

Source: Table 2 2017 EU RMP RCC Tables

Table 15 Cabozantinib Exposure by Race

Race	Study A031203 N=78	
	Persons n (%)	**Person time (person weeks)**
Total	78 (100.0)	3183
American Indian or Alaska Native	1 (1.3)	12
Asian	1 (1.3)	4
Black or African American	3 (3.8)	126
Native Hawaiian or Other Pacific Islander	0	0
White	69 (88.5)	2949
Other	0	0
Multiple	1 (1.3)	37
Not reported	3 (3.8)	54

EU=European Union; RCC=renal cell carcinoma; RMP=risk management plan.

Source: Table 3 2017 EU RMP RCC Tables

SIII.2.3. Advanced Renal Cell Carcinoma in Combination with Nivolumab in Treatment-naïve Adults

Primary safety data are presented for subjects treated with cabozantinib in combination with nivolumab (first-line) in advanced or metastatic RCC from the phase III study CA2099ER (CheckMate 9ER). These subjects received a 40 mg qd dose of cabozantinib tablets combined with nivolumab 240 mg intravenously (IV) every two weeks (Q2W) or 480 mg IV every four weeks (Q4W).

The median (range) age of all subjects exposed to cabozantinib in Study CA2099ER was 62 years (29 to 90), and approximately 41% of all the subjects were at least 65 years of age. The median (range) duration of exposure to cabozantinib in Study CA2099ER up to the data lock date was 13.8 months (0.2 to 27.3).

The exposure to cabozantinib in Study CA2099ER is summarised by duration (Table 16), by age group and gender (Table 17) and by race (Table 18).

Table 16 Duration of Cabozantinib Exposure in Pivotal Study CA2099ER

Duration of exposure	Study CA2099ER N=320	
	Persons n (%)	**Person time (person weeks)**
Overall exposure		
≥4 weeks	314 (98.1)	17593
≥8 weeks	303 (94.7)	17534
≥12 weeks	287 (89.7)	17380
≥16 weeks	279 (87.2)	17270
≥20 weeks	274 (85.6)	17186

Duration of exposure	Study CA2099ER N=320	
	Persons n (%)	**Person time (person weeks)**
≥24 weeks	265 (82.8)	16991
≥28 weeks	252 (78.8)	16668
≥32 weeks	237 (74.1)	16221
≥36 weeks	232 (72.5)	16048
≥40 weeks	221 (69.1)	15633
≥44 weeks	206 (64.4)	15005
≥48 weeks	191 (59.7)	14320
≥52 weeks	183 (57.2)	13917
≥56 weeks	171 (53.4)	13270
≥60 weeks	160 (50.0)	12629
≥64 weeks	137 (42.8)	11216
≥68 weeks	113 (35.3)	9640
≥72 weeks	92 (28.8)	8175
≥76 weeks	83 (25.9)	7512
≥80 weeks	70 (21.9)	6504
≥84 weeks	58 (18.1)	5522
≥88 weeks	48 (15.0)	4667
≥92 weeks	38 (11.9)	3770
≥96 weeks	22 (6.9)	2264
≥100 weeks	12 (3.8)	1291
≥104 weeks	8 (2.5)	884
≥108 weeks	6 (1.9)	674
≥112 weeks	3 (0.9)	344
≥116 weeks	1 (0.3)	119
≥120 weeks	0 (0.0)	0
Total person time	**17,606**	

RMP=risk management plan.

Source: Table 2.1 15 JUN 2020 CheckMate 9ER RMP Tables

Table 17 Cabozantinib Exposure by Age Group and Gender

Gender Age group	Study CA2099ER N=320	
	Persons n (%)	**Person time (person weeks)**
Female		
Total	73 (22.8)	3607
<65 years	32 (10.0)	1955
65 to <75 years	29 (9.1)	1269
75 to <85 years	11 (3.4)	363
≥85 years	1 (0.3)	20
Male		
Total	247 (77.2)	13999
<65 years	157 (49.1)	9251
65 to <75 years	73 (22.8)	3934
75 to <85 years	16 (5.0)	805
≥85 years	1 (0.3)	9

RMP=risk management plan.

Source: Table 2.2 12 JUN 2020 CheckMate 9ER RMP Tables

Table 18 Cabozantinib Exposure by Ethnic or Racial Origin

Race	Study CA2099ER N=320	
	Persons n (%)	**Person time (person weeks)**
Total	320 (100.0)	17606
American Indian or Alaska Native	3 (0.9)	124
Asian	26 (8.1)	1063
Black or African American	1 (0.3)	102
White	264 (82.5)	14926
Other	26 (8.1)	1391

RMP=risk management plan.

Source: Table 2.3 12 JUN 2020 CheckMate 9ER RMP Tables

SIII.2.4. Hepatocellular Carcinoma

For use of cabozantinib as monotherapy for the treatment of HCC in adults who have previously been treated with sorafenib, primary safety data are presented for subjects with advanced HCC who had progressed following at least one prior systemic therapy regimen for advanced HCC, from the phase III study XL184-309 (CELESTIAL). These subjects received a 60 mg qd dose of cabozantinib tablets, which is the cabozantinib dose marketed for the HCC indication.

The median (range) age of subjects exposed to cabozantinib in Study XL184-309 was 64.0 years (22 to 86), and approximately 49% of subjects were at least 65 years of age. The median (range) duration of exposure in Study XL184-309 up to the DLP for this study was 3.8 months (0.1 to 37.3). The exposure to cabozantinib in Study XL184-309 is summarised by duration (Table 19), by age group and gender (Table 20), and by race (Table 21).

Table 19 Duration of Cabozantinib Exposure in Pivotal Study XL184-309

Duration of exposure	Study XL184-309 N=467	
	Persons n (%)	**Person time (person weeks)**
Overall exposure		
Total	467 (100.0)	11,923
≥4 weeks	441 (94.4)	11,857
≥8 weeks	374 (80.1)	11,460
≥12 weeks	279 (59.7)	10,603
≥16 weeks	248 (53.1)	10,182
≥20 weeks	201 (43.0)	9376
≥24 weeks	177 (37.9)	8852
≥36 weeks	105 (22.5)	6770
≥48 weeks	76 (16.3)	5570
≥72 weeks	31 (6.6)	3021
≥96 weeks	12 (2.6)	1435
≥120 weeks	4 (0.9)	599
≥160 weeks	1 (0.2)	162

RMP=risk management plan.

Source: Duration of Cabozantinib exposure, CELESTIAL study, RMP Analyses.

Table 20 Cabozantinib Exposure by Age Group and Gender

Gender Age group	Study XL184-309 N=467	
	Persons n (%)	**Person time (person weeks)**
Female		

Gender Age group	Study XL184-309 N=467	
	Persons n (%)	**Person time (person weeks)**
Total	91 (19.5)	2142
<65 years	51 (10.9)	1177
65 to <75 years	25 (5.4)	536
75 to <85 years	13 (2.8)	421
≥85 years	2 (0.4)	8
Male		
Total	376 (80.5)	9781
<65 years	188 (40.3)	4818
65 to <75 years	131 (28.1)	3729
75 to <85 years	54 (11.6)	1198
≥85 years	3 (0.6)	35

RMP=risk management plan.

Source: Cabozantinib exposure by age group and gender, CELESTIAL study, RMP Analyses.

Table 21 Cabozantinib Exposure by Race

Race	Study XL184-309 N=467	
	Persons n (%)	**Person time (person weeks)**
Total	467 (100.0)	11,923
Asian	156 (33.4)	3988
Black or African American	8 (1.7)	198
Native Hawaiian or Other Pacific Islander	3 (0.6)	96
Other	5 (1.1)	278
White	264 (56.5)	6617
Not reported	31 (6.6)	746

RMP=risk management plan.

Source: Cabozantinib exposure by ethnic or racial origin, CELESTIAL study, RMP Analyses.

SIII.2.5. Differentiated Thyroid Carcinoma

Phase III study XL184-311 involved the use of cabozantinib as monotherapy for the treatment of DTC in subjects ≥16 years of age with RAI-refractory DTC who had progressed during or after prior Vascular endothelial growth factor receptor (VEGFR)-targeted therapy (including either sorafenib or lenvatinib). Primary safety data are presented. There were no subjects under 18 years of age enrolled in the study. A total of 258 subjects received cabozantinib in study XL184-311 (including 170 initially randomised to cabozantinib and 88 subjects in the context of cross over after they had been randomised and had received placebo). In this RMP, the 170 subjects initially randomised in cabozantinib only arm were considered for the below exposure data. However, there were 210 subjects in total who received cabozantinib which included 170 subjects initially randomised in cabozantinib only arm and 40 subjects randomised to placebo crossed over to receive open-label cabozantinib. Subjects received a 60 mg qd dose of cabozantinib tablets, which is the cabozantinib dose marketed. The median (range) age of subjects exposed to cabozantinib in Study XL184-311 was 65.0 years (31 to 85), and approximately 50% of subjects were at least 65 years of age. The median (range) duration of exposure in Study XL184-311 up to the DLP (08 February 2021) for this study was 6.03 months (0.2 to 18.8). Maximum treatment duration was 18.8 months.

The exposure to cabozantinib in Study XL184-311 is summarised by duration (Table 22), by age group and gender (Table 23) and by race (Table 24).

Table 22 Duration of Cabozantinib Exposure in Pivotal Study XL184-311

Duration of exposure	Study XL184-311 N=170	
	Persons n (%)	**Person time (person weeks)**
Overall exposure		
Total person time	170 (100.0%)	5202
≥4 weeks	164 (96.5%)	5187
≥8 weeks	150 (88.2%)	5102
≥12 weeks	138 (81.2%)	4984
≥16 weeks	123 (72.4%)	4781
≥20 weeks	107 (62.9%)	4503
≥24 weeks	96 (56.5%)	4253
≥28 weeks	81 (47.6%)	3871
≥32 weeks	71 (41.8%)	3573
≥36 weeks	56 (32.9%)	3068
≥40 weeks	52 (30.6%)	2918
≥44 weeks	50 (29.4%)	2831
≥48 weeks	35 (20.6%)	2143
≥52 weeks	27 (15.9%)	1745
≥56 weeks	21 (12.4%)	1426
≥60 weeks	20 (11.8%)	1370
≥64 weeks	16 (9.4%)	1123
≥68 weeks	9 (5.3%)	661

DLP=data lock point; RMP=risk management plan.

Source: Duration of Cabozantinib exposure, XL184-311 study, RMP Analyses (DLP 08 February 2021).

Table 23 Cabozantinib Exposure by Age Group and Gender

Gender Age group	Study XL184-311 N=170	
	Persons n (%)	**Person time (person weeks)**
Female		
Total	87 (51.2%)	2667
<8 years	0 (0.0%)	0
18 to <65 years	45 (26.5%)	1343
65 to <75 years	34 (20.0%)	1026
75 to <85 years	7 (4.1%)	266
≥85 years	1 (0.6%)	33
Male		
Total	83 (48.8%)	2535
<18 years	0 (0.0%)	0
18 to <65 years	38 (22.4%)	1205
65 to <75 years	33 (19.4%)	988
75 to <85 years	12 (7.1%)	342
≥85 years	0 (0.0%)	0

DLP=data lock point; RMP=risk management plan.

Source: Cabozantinib exposure by age group and gender, XL184-311 study, RMP Analyses (DLP 08 February 2021)

Table 24 Cabozantinib Exposure by Race

Race	Study XL184-311 N=170	
	Persons n (%)	**Person time (person weeks)**
Total	170 (100.0%)	5202
White	121 (71.2%)	3684

Race	Study XL184-311 N=170	
	Persons n (%)	Person time (person weeks)
Black or African American	2 (1.2%)	34
Asian	29 (17.1%)	975
American Indian or Alaska native	4 (2.4%)	117
Native Hawaiian or other Pacific Islander	0 (0.0%)	0
Other	2 (1.2%)	86
Not reported	10 (5.9%)	264
Missing	2 (1.2%)	41

DLP=data lock point; RMP=risk management plan.

Source: Cabozantinib exposure by ethnic or racial origin, XL184-311 study, RMP Analyses (DLP 08 February 2021).

SII.2.6. Neuroendocrine Tumours

Phase III Study A021602 involved the use of cabozantinib for the treatment of adult patients with advanced extra-pancreatic neuroendocrine tumour (epNET; i.e. carcinoid tumours) and pancreatic neuroendocrine tumour (pNET) whose disease had progressed after prior systemic therapy. Primary safety data are presented. There were no subjects under 18 years of age enrolled in the study. In this RMP, the 195 subjects initially randomised in cabozantinib arm were considered for the below exposure data. However, there were 227 subjects in total who received cabozantinib which included 195 subjects initially randomised in cabozantinib arm and 32 subjects who were randomised to the placebo arm crossed over to receive open-label cabozantinib at disease progression. The subjects received a 60 mg qd dose of cabozantinib tablets, which is the approved dose of cabozantinib as monotherapy. For epNET, the median (range) age of subjects in cabozantinib arm was 66.0 years, and 55% of subjects were ≥65 years of age. For pNET, the median age of the subjects was 60.0 years in the cabozantinib arm and majority of subjects (62%) were <65 years of age. The median (range) duration of exposure in Study A021602 up to the DLP (24 August 2023) was 5.52 months (0.1 to 37.8). The maximum duration of exposure was 164 weeks (more than 3 years).

The exposure to cabozantinib in Study A021602 is summarised by duration (Table 25), by age group and gender (Table 26) and by race (Table 27).

Table 25 Duration of Cabozantinib Exposure in Pivotal Study A021602

Duration of exposure	Study A021602 N=195	
	Persons n (%)	Person time (person weeks)
Overall exposure		
Total person time	195 (100.0%)	6496
≥4 weeks	175 (89.7%)	6450
≥8 weeks	157 (80.5%)	6350
≥12 weeks	139 (71.3%)	6166
≥16 weeks	125 (64.1%)	5986
≥20 weeks	110 (56.4%)	5724
≥24 weeks	99 (50.8%)	5477
≥28 weeks	89 (45.6%)	5220
≥32 weeks	83 (42.6%)	5041
≥36 weeks	77 (39.5%)	4842
≥40 weeks	64 (32.8%)	4362
≥44 weeks	59 (30.3%)	4151
≥48 weeks	53 (27.2%)	3876
≥52 weeks	45 (23.1%)	3482

Duration of exposure	Study A021602 N=195	
	Persons n (%)	Person time (person weeks)
≥56 weeks	41 (21.0%)	3265
≥60 weeks	39 (20.0%)	3148
≥64 weeks	27 (13.8%)	2415
≥68 weeks	24 (12.3%)	2215
≥72 weeks	23 (11.8%)	2147
≥76 weeks	20 (10.3%)	1927
≥80 weeks	17 (8.7%)	1695
≥84 weeks	13 (6.7%)	1367
≥88 weeks	9 (4.6%)	1027
≥92 weeks	7 (3.6%)	848
≥96 weeks	6 (3.1%)	756
≥100 weeks	5 (2.6%)	657
≥104 weeks	5 (2.6%)	657
≥108 weeks	3 (1.5%)	443
≥112 weeks	3 (1.5%)	443
≥116 weeks	3 (1.5%)	443
≥120 weeks	3 (1.5%)	443
≥124 weeks	3 (1.5%)	443
≥128 weeks	3 (1.5%)	443
≥132 weeks	3 (1.5%)	443
≥136 weeks	3 (1.5%)	443
≥140 weeks	2 (1.0%)	305
≥144 weeks	1 (0.5%)	164
≥148 weeks	1 (0.5%)	164
≥152 weeks	1 (0.5%)	164
≥156 weeks	1 (0.5%)	164
≥160 weeks	1 (0.5%)	164
≥164 weeks	1 (0.5%)	164
≥168 weeks	0	0

DLP=data lock point; RMP=risk management plan.

Source: Duration of cabozantinib exposure, A021602 study, RMP Analyses (DLP 24 August 2023).

Table 26 Cabozantinib Exposure by Age Group and Gender

Gender Age group	Study A021602 N=195	
	Persons n (%)	Person time (person weeks)
Female		
Total	100 (51.3%)	2971
<18 years	0	0
18 to <65 years	50 (25.6%)	1441
65 to <75 years	41 (21.0%)	1290
75 to <85 years	9 (4.6%)	240
≥85 years	0	0
Male		
Total	95 (48.7%)	3525
<18 years	0	0
18 to <65 years	49 (25.1%)	1921
65 to <75 years	35 (17.9%)	1315
75 to <85 years	10 (5.1%)	284
≥85 years	1 (0.5%)	4

DLP=data lock point; RMP=risk management plan.

Source: Cabozantinib exposure by age group and gender, A021602 study, RMP Analyses (DLP 24 August 2023).

Table 27 Cabozantinib Exposure by Race

Race	Study A021602 N=195	
	Persons n (%)	**Person time (person weeks)**
Total	195 (100.0%)	6496
White	167 (85.6%)	5769
Black or African American	11 (5.6%)	171
Asian	7 (3.6%)	264
American Indian or Alaska Native	1 (0.5%)	12
Native Hawaiian or Other Pacific Islander	1 (0.5%)	2
Multiple	1 (0.5%)	48
Not Reported	2 (1.0%)	79
Unknown	5 (2.6%)	151

DLP=data lock point; RMP=risk management plan.

Source: Cabozantinib exposure by ethnic or racial origin, A021602 study, RMP Analyses (DLP 24 August 2023).

Part II: Module SIV – Populations Not Studied in Clinical Trials

Subjects recruited into the clinical development programme for cabozantinib were representative of the intended population for the product. Common and indication-specific exclusion criteria for subjects in the cabozantinib clinical studies are summarised in Table 28.

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Table 28 Important Exclusion Criteria in Pivotal Clinical Studies

Exclusion criteria	Reason for exclusion	Missing Information (Yes/No)	Is it considered to be missing information? If No, rationale
Common exclusion criteria for all indications			
Hypersensitivity or allergy to active substance or any of the excipients listed	Such patients would have been at-risk of serious ADRs. Cabozantinib is contraindicated in individuals with hypersensitivity to the active substance or to any of the excipients.	No	Cabometyx is contraindicated in these patients (SmPC Section 4.3).
Concomitant treatment with therapeutic doses of oral anticoagulants (except low-dose LMWH/warfarin/aspirin)	Criterion was used as a preventive measure to reduce the occurrence of haemorrhages	No	Certain patients may need anticoagulant therapies for treatment of thromboembolic events. Haemorrhage and thromboembolic events are described as risks in the warnings and precautions in Section 4.4 of the SmPC. The interaction of cabozantinib with warfarin is provided in Section 4.5 of the SmPC: The effect of cabozantinib on the pharmacokinetics of warfarin has not been investigated. An interaction with warfarin may be possible. In case of such combination, INR values should be monitored.

Exclusion criteria	Reason for exclusion	Missing Information (Yes/No)	Is it considered to be missing information? If No, rationale
Pregnant or breastfeeding females	Due to potential embryotoxicity of cabozantinib, pregnant and/or breastfeeding females were excluded from studies	No	There are no studies in pregnant women using cabozantinib and it is not known whether cabozantinib and/or its metabolites are excreted in human milk (SmPC Section 4.6).
Paediatric age patients (<18 years old)	There is no cabozantinib experience in the paediatric population.	No	The safety and efficacy of cabozantinib in children and adolescents <18 years is limited. Studies in paediatric varied indications have been conducted and are ongoing in the context of the Paediatric Investigation Plan. A phase I dose finding study (ADVL 1211) conducted in children and adolescents has been completed in various malignant solid tumours. Thirty-nine subjects globally, aged 4 years old or more, suffering from sarcomas, CNS malignant diseases, medullary thyroid cancer, RCC, hepatoblastoma or epithelial-myoepithelial carcinoma were exposed to cabozantinib. The safety profile observed in this study appeared to be qualitatively similar with the safety profile of cabozantinib as observed in adults. Cumulatively, a combined 276 paediatric patients exposed to cabozantinib in the postmarketing setting suggest that the safety profile in a paediatric population does not differ significantly from the one observed in adults (cabozantinib PSUR DLP 28 November 2023).

Exclusion criteria	Reason for exclusion	Missing Information (Yes/No)	Is it considered to be missing information? If No, rationale
Uncontrolled, serious intercurrent illness, such as cardiovascular disorders (including uncontrolled hypertension, stroke or thromboembolic events); fistulas, GI disorders associated with a high-risk of perforation; major surgery within 2 months prior to randomisation; clinically significant haemorrhage; cavitating pulmonary lesions or lesions invading major pulmonary blood vessels; active infection; serious nonhealing wound or fracture; malabsorption syndrome; uncompensated symptomatic hypothyroidism requirement for dialysis, solid organ transplant	To optimise the benefit-risk balance for the patient and to not confound clinical trial data due to co-morbidities.	No	Important co-morbidities are described in Section 4.4 of the SmPC (Special warnings and precautions for use) as conditions that may put a patient at risk for a serious adverse reaction.
Moderate to severe hepatic impairment (Child Pugh B or C)	To optimise the benefit-risk balance for the patient and to not confound clinical trial data due to co-morbidities.	No	Since only limited data are available for patients with moderate hepatic impairment (Child Pugh B), no dose recommendations can be provided, and close monitoring of overall safety is recommended in these patients (SmPC Sections 4.2 and 5.2). As there is no clinical experience in patients with severe hepatic impairment (Child Pugh C), cabozantinib is not recommended for use in these patients (SmPC Section 4.2).
Prior anticancer treatment (including radiation therapy and cabozantinib) within a specified time period before study entry.	Criterion was used to avoid potential safety and efficacy confounders of the pivotal study.	No	In order to better assess the PK, safety and efficacy profile of cabozantinib in clinical studies, a washout period was required. This is not necessary in a marketed setting.
Cardiac impairment (congestive heart failure, serious cardiac arrhythmia or unstable angina, myocardial infarction within 6 months)	To optimise the benefit-risk balance for the patient and to not confound clinical trial data due to co-morbidities.	No	There are limited data in patients with cardiac impairment. No specific dosing recommendations can be made (SmPC Section 4.2).

Exclusion criteria	Reason for exclusion	Missing Information (Yes/No)	Is it considered to be missing information? If No, rationale
Inability to swallow tablets.	Criterion was used to assure cabozantinib absorption and exposure.	No	As with any oral medication it is routine practice for the physician to assess if the patient is able to swallow tablets.
QTcF >500 msec or history of congenital long QT syndrome	To avoid patients with cardiac disease and potential concurrent cardiac complications.	No	QT prolongation is unlikely to be clinically significant at the 60 mg dose in patients with RCC and HCC or at the 40 mg dose in combination with nivolumab in patients with RCC. 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 Electrocardiogram (ECGs) and electrolytes (serum calcium, potassium, and magnesium) should be considered (SmPC Section 4.4).
Subjects with untreated brain metastases/cranial epidural disease or treated brain metastases requiring systemic corticosteroids. For subjects with HCC, these must have been stable for at least 3 months before randomisation.	Criterion was used to exclude patients for whom brain metastases were an uncontrolled, significant illness requiring systemic treatment and to reduce the risk of premature withdrawal from the study for reasons not related to study medication.	No	The clinical benefit for patients with brain metastases outweighs the risk associated with the study treatment.
Diagnosis of another malignancy within 2 years before randomisation, except for superficial skin cancers, or localised, low-grade tumours deemed cured and not treated with systemic therapy. For subjects with RCC treated with cabozantinib in combination with nivolumab prior malignancy active within the previous 3 years except for locally curable cancers.	To optimise the benefit-risk ratio for the patient and to not confound clinical trial data due to co-morbidities.	No	The clinical benefit for these patients outweighs the risk associated with study treatment.

Exclusion criteria	Reason for exclusion	Missing Information (Yes/No)	Is it considered to be missing information? If No, rationale
Exclusion criteria specific to indications			
Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308)			
Concomitant treatment with therapeutic doses of oral platelet inhibitors	Criterion was used as a preventive measure to reduce the occurrence of haemorrhages	No	Certain patients may need anticoagulant therapies for treatment of thromboembolic events. Haemorrhage and thromboembolic events are described as risks in the warnings and precautions in Section 4.4 of the SmPC.
Chronic treatment with corticosteroids or other immunosuppressive agents (with the exception of inhaled or topical corticosteroids or corticosteroids with a daily dosage equivalent ≤10 mg prednisone if given for disorders other than renal cell cancer).	Criterion was used to avoid confounding efficacy and safety in the trial due to corticosteroid induced immunosuppression as everolimus is an immunosuppressant.	No	The clinical benefit of concomitant corticosteroid use outweighs the risk for cabozantinib-treated patients.
Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203)			
Prior systemic treatment for RCC	This was not the intended population for the study.	No	This was not the intended population.
Chronic concomitant treatment with strong CYP3A4 inducers or inhibitors	Cabozantinib is a CYP3A4 substrate, so concurrent administration of CYP3A4 inhibitors may result in a decrease in cabozantinib plasma exposure.	No	Warnings regarding the concomitant use of medicinal products that are strong inhibitors of CYP3A4 are provided in Sections 4.2, 4.4 and 4.5 of the SmPC.

Exclusion criteria	Reason for exclusion	Missing Information (Yes/No)	Is it considered to be missing information? If No, rationale
Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER)			
Any active, known or suspected autoimmune disease with the exception of Type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger (e.g. celiac disease)	Nivolumab, a human immunoglobulin G4 monoclonal antibody which binds to the programmed death-1 (PD-1) receptor thereby potentiating an immune response to tumour cells, is associated with immune-related adverse reactions. These patients were excluded to prevent confounding of the safety assessment in the study.	No	Warnings regarding the minimisation and management of immune-related adverse reactions are provided in Sections 4.2 and 4.4 of the OPDIVO SmPC as they are recognised adverse reactions of nivolumab and not with cabozantinib. For liver enzymes elevations for RCC patients treated with cabozantinib in combination with nivolumab, Section 4.2 of the Cabometyx SmPC advises that corticosteroid therapy may be considered if immune-mediated reaction is suspected and to refer to the nivolumab SmPC.
Any condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomisation. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.	To avoid confounding the efficacy and safety assessment in the study as nivolumab is recognised to cause immune-related adverse reactions that often require corticosteroid treatment.	No	Immune-related adverse reactions requiring corticosteroid treatment are recognised to occur with nivolumab but not with cabozantinib. Patients are advised in the OPDIVO SmPC not to resume treatment with nivolumab while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. The Cabometyx SmPC advises that corticosteroid therapy may be considered if immune-mediated reaction is suspected for liver enzymes elevations for RCC patients treated with cabozantinib in combination with nivolumab and to refer to the nivolumab SmPC. The clinical benefit of administering cabozantinib in combination with nivolumab to patients requiring systemic corticosteroids or immunosuppressive medications is likely to outweigh the risks and would need to be considered on an individual patient basis in clinical practice.

Exclusion criteria	Reason for exclusion	Missing Information (Yes/No)	Is it considered to be missing information? If No, rationale
Any tumour invading the superior vena cava (SVC) or other major blood vessels or invading the GI tract or any evidence of endotracheal or endobronchial tumour within 30 days prior to randomisation	To avoid confounding the efficacy and safety assessment in the study.	No	The clinical benefit of administering cabozantinib in combination with nivolumab in these populations is likely to outweigh the risks and would need to be considered on an individual patient basis in clinical practice.
Uncontrolled adrenal insufficiency	To avoid confounding the efficacy and safety assessment in the study as nivolumab is recognised to cause immune-related adverse reactions including immune-related endocrinopathies.	No	Immune-related endocrinopathies including adrenal insufficiency are recognised to occur with nivolumab but not with cabozantinib. The clinical benefit of administering cabozantinib in combination with nivolumab to these patients is likely to outweigh the risks and would need to be considered on an individual patient basis in clinical practice.
Any radiologic or clinical evidence of pancreatitis within 30 days prior to randomisation	To avoid confounding the efficacy and safety assessment in the study as cabozantinib and nivolumab monotherapies are both recognised to cause pancreatitis.	No	Pancreatitis is a recognised adverse reaction of cabozantinib and nivolumab monotherapies and for cabozantinib in combination with nivolumab with frequencies of uncommon in both SmPCs.
Prior treatment with VEGF, MET, AXL, KIT, or RET targeted therapy (including, but not limited to, sunitinib, pazopanib, axitinib, tivozanib, sorafenib, lenvatinib, bevacizumab, and cabozantinib)	To avoid confounding the efficacy and safety assessment in the study.	No	The intended population is treatment-naïve adults.
Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways	To avoid confounding the efficacy and safety assessment in the study.	No	The intended population is treatment-naïve adults.

Exclusion criteria	Reason for exclusion	Missing Information (Yes/No)	Is it considered to be missing information? If No, rationale
Prior radiotherapy to the thoracic cavity or abdomen within 4 weeks prior to randomisation, to bone lesions within 2 weeks prior to randomisation, or to any other site within 4 weeks prior to randomisation (in all cases, there must be complete recovery and no ongoing complications from prior radiotherapy)	To avoid confounding the efficacy and safety assessment in the study.	No	The clinical benefit of administering cabozantinib in combination with nivolumab in this population is likely to outweigh the risks and would need to be considered on an individual patient basis in clinical practice.
Participants who have received a live/attenuated vaccine within 30 days of first treatment.	To avoid confounding the efficacy and safety assessment in the study.	No	Patients treated with nivolumab may be at increased risk for immune-related adverse reactions following a live attenuated vaccine. There are extensive warnings in the OPDIVO SmPC on how to minimise and manage immune-related adverse reactions.
HCC in adults who have previously been treated with sorafenib (Study XL184-309)			
Fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma	This was not the intended population for the study.	No	This was not the intended population.
Receipt of more than two prior systemic therapies for HCC	This was not the intended population for the study.	No	This was not the intended population.
Untreated or incompletely treated varices with bleeding or high-risk for bleeding	To optimise the benefit-risk balance for the patient and to not confound clinical trial data due to co-morbidities.	No	Important co-morbidities are described in Section 4.4 of the SmPC (Special warnings and precautions for use) as conditions that may put a patient at risk for a serious adverse reaction.
Moderate or severe ascites	To optimise the benefit-risk balance for the patient and to not confound clinical trial data due to co-morbidities.	No	Important co-morbidities are described in Section 4.4 of the SmPC (Special warnings and precautions for use) as conditions that may put a patient at risk for a serious adverse reaction.

ADR=adverse drug reaction; CD=cluster of differentiation; CNS=central nervous system; CTLA-4=cytotoxic T-lymphocyte-associated protein 4; CYP=cytochrome P450; GI=gastrointestinal; HCC=hepatocellular carcinoma; LMWH=low molecular weight heparin; MET=mesenchymal epithelial transition factor; PD-1=programmed death-1; PD-L1=programmed death-ligand 1; PD-L2=programmed death-ligand 2; PK=pharmacokinetic(s); PSUR=periodic safety update report; QTcF=corrected QT interval by the Fridericia formula; RCC=renal cell carcinoma; RET=rearranged during transfection; SmPC=summary of product characteristics; SVC=superior vena cava; VEGF=vascular endothelial growth factor.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as very rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. A total of 1355 subjects received cabozantinib monotherapy in Studies XL184-308 (n=331), A031203 (n=78), XL184-309 (n=509), XL184-311 (n=210) and A021602 (n=227). A total of 320 subjects received cabozantinib in combination with nivolumab in Study CA2099ER. Adverse drug reactions (ADRs) occurring in the RCC monotherapy population with a frequency less than approximately 1 in 136, in the RCC combination therapy with nivolumab population with a frequency less than approximately 1 in 107, in the HCC population with a frequency less than approximately 1 in 156 and in the DTC population with a frequency less than approximately 1 in 48 based on DLP at initial submission would be unlikely to be detected with a data set of this size. Rare ADRs may occur in a data set of any size, but their incidence cannot be quantified unless an appropriately large data set has been studied. Globally since the developmental international birth date of cabozantinib, 6367 subjects have been exposed to cabozantinib (including 1313 in combination with immune checkpoint inhibitor (ICIs)) in Exelixis sponsored clinical trials allowing detection of rare events across all studied indications (cabozantinib periodic safety update report (PSUR) DLP 28 November 2023). The total number of subjects exposed in the RCC, HCC, DTC, and NET monotherapy indications, which forms the basis of the pooled safety data used for ADR frequency calculation in European Union (EU) Summary of product characteristics (SmPC), is 1355.

One hundred and forty-one (141) subjects (42.6%) in Study XL184-308, 26 subjects (33.3%) in Study A031203 and 76 subjects (16.3%) in Study XL184-309, 35 subjects (20.6%) in Study XL184-311 and 53 subjects (27.2%) in Study A021602 had exposure to cabozantinib ≥48 weeks, while 239 (72.2%) subjects in Study XL184-308, 43 subjects (55.1%) in Study A031203 177 subjects (37.9%) in Study XL184-309, 96 subjects (56.5%) in study XL184-311 and 99 subjects (50.8%) in Study A021602 had exposure to cabozantinib ≥6 months (≥24 weeks). In Study CA2099ER, 191 subjects (59.7%) had exposure to cabozantinib in combination with nivolumab ≥48 weeks and 265 subjects (82.8%) for ≥6 months (≥24 weeks).

The maximum duration of exposure to cabozantinib was 160 weeks as of the DLP of 02 October 2016 for Study XL184-308, 125 weeks as of the DLP of 15 September 2016 for Study A031203, 116 weeks as of the DLP of 30 March 2020 for Study CA2099ER, 188 weeks as of the DLP of 01 December 2017 in Study XL184-309, 68 weeks as of the DLP of 08 February 2021 for study XL184-311 and 164 weeks as of the DLP of 24 August 2023 for the Study A021602. Adverse drug reactions in subjects with previously treated RCC, which require an exposure of longer than 160 weeks to develop, will not be detected in the safety data set, while ADRs in subjects with treatment-naïve RCC, which require an exposure of longer than 125 weeks to develop, will not be detected in the safety data sets. Adverse drug reactions in subjects with previously treated HCC, which require an exposure of longer than 162 weeks to develop, will not be detected in the safety data set.

While the maximum duration of exposure to cabozantinib may have been more than 160 weeks (Study XL184-308), 125 weeks (Study A031203), 161 weeks (Study CA2099ER), 188 weeks (Study XL184-309), 68 weeks (Study XL184-311) or 164 weeks (Study A021602), the probability of detecting ADRs due to exposures of this duration will diminish in proportion to the number of subjects treated for prolonged periods. This is because there are fewer subjects exposed for longer periods than for shorter periods in clinical development studies. Adverse drug reactions occurring in the previously treated RCC population treated with cabozantinib for

more than 6 months with a frequency less than approximately 1 in 80 (239/3) would be unlikely to be detected with a data set of this size, ADRs occurring in the treatment-naïve RCC population treated with cabozantinib for more than 6 months with a frequency less than approximately 1 in 14 (43/3) would be unlikely to be detected with a data set of this size, ADRs occurring in the treatment-naïve RCC population treated with cabozantinib in combination with nivolumab for more than 6 months with a frequency less than approximately 1 in 88 (265/3) would be unlikely to be detected with a data set of this size, and ADRs occurring in the previously treated HCC population treated with cabozantinib for more than 6 months with a frequency less than approximately 1 in 60 (177/3) would be unlikely to be detected. In Study A021602, 192 ADRs (98.5%) were reported.

Cabozantinib is not known to cause ADRs due to cumulative effects.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Some specific patient populations are routinely excluded from clinical studies to ensure patient safety, thus limiting experience in these patients. Exposure in selected special populations is summarised in Table 29.

Table 29 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant or lactating women	No clinical studies with cabozantinib have been conducted in pregnant or lactating women. No clinical data on exposure during pregnancy or lactation are available. It is not known whether cabozantinib is excreted in human milk. Therefore, lactating females were excluded from clinical trials of cabozantinib. Due to the important potential risk of embryotoxicity, Section 4.6 of the SmPC has a requirement for women of child-bearing potential to avoid pregnancy while on cabozantinib and states precautions for women who are breastfeeding.
Patients with relevant co-morbidities	
Patients with renal impairment	Study XL184-017 evaluated the safety and PK of cabozantinib in subjects with mild or moderate renal impairment. The single oral dose of 60 mg cabozantinib (capsule formulation) appeared to be generally well tolerated in subjects with mild and moderate impaired renal function and healthy control subjects; no subjects with severe renal impairment were enrolled in the study. Overall, there were no new safety signals. The results from the renal impairment study indicate that, based on the ratios of geometric LS mean for plasma cabozantinib, Cmax and AUC (AUC0-t and AUC0-inf) values, exposures were 19% and 30% higher, respectively, for subjects with mild renal impairment compared to subjects with normal renal function. Both Cmax and AUC values (AUC0-t and AUC0-inf) of cabozantinib appeared to be similar between the moderate impairment and the matched control cohorts (differences: less than 3% and 7%, respectively). The upper 90% CI values for geometric LS mean ratios for plasma cabozantinib AUC0-inf for subjects with mild or moderate renal impairment relative to matched healthy subjects were lower than the 200% threshold. Therefore, it can be concluded that plasma exposure of cabozantinib was not affected by mild or moderate renal impairment in a clinically significant manner. Based on these results, no dosage adjustment or special precaution for use is needed for cabozantinib administration in patients having mild or moderate renal impairment. Cabozantinib is not recommended for use in patients with severe renal impairment. Dosing recommendations for patients with renal impairment are included in the SmPC Section 4.2.

Type of special population	Exposure
Patients with hepatic impairment	Based on an integrated population PK analysis of cabozantinib in healthy subjects and cancer patients (including HCC), no clinically significant differences in the mean cabozantinib plasma exposure were observed amongst subjects with normal liver function (total bilirubin and AST ≤ULN, n=1425), mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >1.0 to 1.5×ULN and any AST value, n=558), and moderate hepatic impairment (total bilirubin >1.5 to ≤3×ULN and any AST value, n=15). The pooled analysis included 391 patients with HCC of whom 128, 308, and 11 were categorised as having normal liver function, mild hepatic impairment, and moderate hepatic impairment, respectively. The PK of cabozantinib were not evaluated in patients with severe hepatic impairment (total bilirubin >3×ULN and any AST value). Only limited data are available for patients with moderate hepatic impairment (Child Pugh B) and therefore close monitoring in these patients is recommended. Cabometyx is not recommended for use in patients with severe hepatic impairment.
Patients with cardiovascular impairment	Patients with symptomatic CHF, serious cardiac arrhythmia, or unstable angina were excluded from clinical studies as were patients with a myocardial infarction within 6 months. Thus, no specific dosing recommendations can be made.
Immunocompromised patients	These patients were not included in the clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trials	<u>Advanced RCC in adults following prior VEGF-targeted therapy</u> In the cabozantinib arm of Study XL184-308, 165 subjects had an ECOG PS of 0 and 157 subjects had an ECOG PS of ≥1. There was no indication of safety differences based on ECOG status. <u>Advanced RCC in treatment-naïve adults with intermediate or poor-risk</u> In the cabozantinib arm of Study A031203, 36 subjects had an ECOG PS of 0, 32 subjects had an ECOG PS of 1 and 10 subjects had an ECOG PS of 2. Events that were reported more frequently in subjects who had a baseline ECOG PS of 0 compared to subjects who had a baseline ECOG PS of 1 or 2 were hypertension, fatigue and hypophosphataemia. There were no AEs or events to monitor (ETMs) that were reported markedly more frequent in subjects who had a baseline ECOG PS of 1 or 2 than in subjects who had a baseline ECOG PS of 0. <u>Advanced RCC in combination with nivolumab in treatment-naïve adults</u> In the cabozantinib in combination with nivolumab arm of Study CA2099ER Karnofsky Performance Status was reported as 70 in 14 subjects (4.4%), 80 in 52 subjects (16.3%), 90 in 109 subjects (34.1%) and 100 in 145 subjects (45.3%) at baseline. Study participants were required to have Karnofsky Performance Status (KPS) >70%. Overall, the ETMs in the cabozantinib in combination with nivolumab arm were comparable for subjects with KPS ≤80 (75.8%), 90 (71.6%), and 100 (84.1%). <u>HCC in adults who have previously been treated with sorafenib</u> In the cabozantinib arm of Study XL184-309, 244 subjects had an ECOG PS of 0 and 222 subjects had an ECOG PS of 1. Most subjects (395) had extrahepatic spread and/or macrovascular invasion at baseline, which is associated with advanced disease and poor prognosis. There were no notable ECOG-related differences in AEs or ETMs. The incidence of ≥Grade 3 haemorrhage ETMs and VTEs was higher in subjects who had extrahepatic spread and/or macrovascular invasion at baseline compared to those who did not. <u>DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine</u>

Type of special population	Exposure
	In the cabozantinib arm of Study XL184-311, 59 subjects had an ECOG PS of 0 and 66 subjects had an ECOG PS of 1. Most subjects (117 [94%]) had metastatic disease at baseline, which is associated with advanced disease and poor prognosis. There were no notable ECOG-related differences in AEs or ETMs. <u>Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy</u> In the cabozantinib arm of Study A021602, 83 subjects had an ECOG PS of 0, 110 subjects had an ECOG PS of 1 and two subjects had an ECOG PS ≥2. At baseline, most subjects (≥90%) in both treatment arms of both cohorts had an ECOG performance status of ≤1. There were no notable ECOG related differences in AEs or ETMs. The incidence of VTEs ETMs was higher in subjects with ECOG PS of 1. No ATEs ETMs were reported in subjects with ECOG PS of 0, whereas the incidence of Grade 4 and Grade 3 ATEs ETMs was 1.8% and 0.9%, respectively, in subjects with ECOG PS of 1.
Patients with relevant demographic/baseline characteristics	
Population with relevant different ethnic origin	<u>Advanced RCC and HCC in adults</u> Clinical information is limited. A population PK analysis did not identify clinically relevant differences in the PK of cabozantinib based on race. <u>Advanced RCC in adults following prior VEGF-targeted therapy</u> In the cabozantinib arm of Study XL184-308, baseline subject demographics included subjects mostly of White race (81%) with a minority of other races (Asian 7.1%; Black or African American 1.4%; other race 4.9%). Given the data available, there is no indication of safety differences between racial categories, but information is limited and considered missing for racial origins other than White. <u>Advanced RCC in treatment-naïve adults with intermediate or poor-risk</u> Most subjects in Study A031203 (88% of those exposed to cabozantinib) were White, with a minority of other races (Asian 3%; Black or African American 4%; other race 6%). The small number of subjects in other racial categories does not allow meaningful safety conclusions to be drawn based on race. <u>Advanced RCC in combination with nivolumab in treatment-naïve adults</u> In the cabozantinib in combination with nivolumab arm of Study CA2099ER, baseline subject demographics included subjects mostly of White race (82.5%) with a minority of other races (Asian 8.1%; Black or African American 0.3%; American Indian or Alaska native 0.9%; other race 8.1%). <u>HCC in adults who have previously been treated with sorafenib</u> In the cabozantinib arm of Study XL184-309, baseline subject demographics included subjects mostly of White (57%) or Asian (33%) race with a minority of other races (Black or African American 2%; Native Hawaiian/Other Pacific Islander 0.6%; other race 1%). <u>DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine</u> In the cabozantinib arm of Study XL184-311, baseline subject demographics included subjects mostly of White (72%) or Asian (16%) races with a minority of other races (American Indian or Alaska native 2.4%; Black or African American 0.8%; other race 1.6%). <u>Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy</u>

Type of special population	Exposure
	In the cabozantinib arm of Study A021602, baseline subject demographics included subjects mostly of White race (85.6%) with a minority of other races (Black or African American 5.6%; Asian 3.6% and other race 5.1%).
Subpopulations carrying relevant genetic polymorphisms	Advanced RCC and HCC in adults At this time there are no known well-defined genetic subsets of RCC or HCC with differing sensitivities to drug treatment. No specific analyses have been conducted for subpopulations carrying genetic polymorphisms.. Pharmacogenetic samples were taken in some patients at baseline in Study XL184-309. However, the results have not been reported in the CSR. Advanced RCC in combination with nivolumab in treatment-naïve adults In the cabozantinib in combination with nivolumab arm of Study CA2099ER, baseline subject demographics for PD-L1+ status based on a 1% cut-off comprised 71.9% (230 subjects) <1% or indeterminate, 25% (80 subjects) ≥1%, and 3.1% (10 subjects) not reported; PD-L1+ status based on a 5% cut-off comprised 80.3% (257 subjects) <5% or indeterminate, 16.6% (53 subjects) ≥5%, and 3.1% (10 subjects) not reported; and PD-L1+ status based on a 10% cut-off comprised 83.8% (268 subjects) <10% or indeterminate, 13.1% (42 subjects) ≥10%, 3.1% (10 subjects) not reported. DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine Pharmacogenetic and biomarker samples were not analysed. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy Pharmacogenetic and biomarker samples were not analysed.
Other: Paediatric patients	The safety and efficacy of cabozantinib in children and adolescents have not been established. Studies in paediatric varied indications have been conducted and are ongoing in the context of the Paediatric Investigation Plan (PIP). A phase I dose finding study (ADVL 1211) conducted in children and adolescents has been completed in various malignant solid tumours. Thirty-nine subjects globally, aged 4 years old or more, with sarcomas, CNS malignant diseases, CNS, neuroblastic tumours, paraganglioma, Wilms tumour, medullary thyroid cancer, RCC, hepatoblastoma or epithelial-myoepithelial carcinoma, were exposed to cabozantinib. The safety profile observed in this study appeared to be in line with the safety profile of cabozantinib as observed in adults. As cabozantinib is an antiangiogenic agent, growth plate evaluation is included in the paediatric ongoing or planned paediatric studies. Few adverse events (AST and ALT increased, lymphocyte count decreased, neutrophil count decreased, lipase increased, hair colour changed, skin hypopigmentation) seemed to occur with an increased frequency based on indirect comparison of ADVL1211 study with all adults safety data and these events are closely monitored in ongoing paediatric studies included in the PIP. Advanced RCC in adults The safety and efficacy of cabozantinib in children and adolescents have not yet been established. While cancers that originate in the kidney do occur in children (e.g. neuroblastoma and Wilms' tumour), their histology, genetics, and treatment are vastly different from those of RCC. The indication of RCC falls under a class waiver for a Paediatric Investigation Plan (covered by the condition of treatment of kidney and renal pelvis carcinoma). HCC in adults who have previously been treated with sorafenib The safety and efficacy of cabozantinib in children and adolescents have not yet been established. However, HCC is a very rare entity in children and

Type of special population	Exposure
	represents a different biologic disease compared to HCC in adults [**Error! Reference source not found.**]. DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine The safety and efficacy of cabozantinib in children and adolescents have not been established. Although rare, paediatric thyroid carcinoma is one of the most common carcinomas in children. Children and adolescents tend to present with more advanced disease and have a higher risk of recurrence than adults with thyroid carcinoma [**Error! Reference source not found.**]. This may be due to a high rate of gene fusions in the paediatric population. Oncogenic gene fusions occur with a higher frequency in paediatric thyroid carcinoma, with 50–60% of paediatric thyroid cancers harbouring a fusion compared with 15% in the adult population [**Error! Reference source not found.**]. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy The safety and efficacy of cabozantinib in children and adolescents have not yet been established. Similar to the adult patient population, NETs have the potential to affect any organ system in the paediatric age group. Neuroendocrine tumours account for a small percentage of paediatric tumours; however, their diagnosis and prevention can be challenging due to their indolent course and vague symptoms [**Error! Reference source not found.**].
Elderly	Advanced RCC, HCC and DTC in adults Cabozantinib did not appear to have a notably different safety profile in the elderly compared with younger patients. No specific dose adjustments for the use of cabozantinib in older people (≥65 years) is recommended (SmPC Section 4.2). Based on population PK data, there was no impact of age on exposure to cabozantinib. No specific requirements for laboratory tests in the elderly population are noted. The lack of PK information in patients with severe renal impairment or severe hepatic impairment regardless of age is noted in Section 5.2 of the SmPC. In addition to their anticancer therapy, patients with RCC usually take multiple medications. The use of these medications is reflected in the populations studied in clinical trials with cabozantinib. The effect of concomitant medication use in the elderly population has not been specifically studied, but no safety trends have been identified in this population. Advanced RCC in adults following prior VEGF-targeted therapy Among the 331 subjects exposed to cabozantinib in the RCC Study XL184-308, 197 (59.5%) were <65 years old, 107 (32.3%) were 65 to 74 years old, and 27 (8.2%) were ≥75 years old (of whom one subject was ≥85 years old). The median age of the 331 subjects exposed to cabozantinib was 62 years; this age is representative of the general RCC population. In the cabozantinib arm of the RCC Study XL184-308, 66 of 197 (33.5%) subjects <65 years old, 47 of 107 (43.9%) subjects 65 to 74 years old, and 14 of 26 (53.8%) subjects ≥75 years old experienced at least one SAE that was not related to disease progression. No SAEs were reported in the subject ≥85 years old. While a slight increase in SAE rate was noted with increasing age, the increase was observed in both the cabozantinib and everolimus treatment arms and was consistent with published data for RCC [89]. The

Type of special population	Exposure
	relatively low total number of subjects in the age group of ≥75 years (n=27) confounds the safety assessment for this age group. Advanced RCC in treatment-naïve adults with intermediate or poor-risk Among the 78 subjects exposed to cabozantinib in the RCC Study A031203, 44 (56%) were <65 years old, 27 (35%) were 65 to 74 years old and seven (9%) were 75 to <85 years old. The median age of the 78 subjects exposed to cabozantinib was 63 years; this age is representative of the general RCC population. The incidence of AEs or ETMs reported in cabozantinib-treated subjects in Study A031203 was generally similar between the age groups, with the exception of the following AEs with a higher incidence in subjects in the older age groups (65 to 74 years; 75 to 84 years) than in subjects <65 years old: AST increased, ALT increased, hypocalcaemia and ETMs of QT prolongation. Related AEs occurring more frequently in older subjects included the PTs of AST increased, ALT increased and hypocalcaemia. It should be noted, however, that comparison of age-related differences in incidence of AEs or ETMs is limited due to the relatively small number of subjects in the older age groups (65 to 74 years, 27 subjects; 75 to 84 years, seven subjects). Advanced RCC in combination with nivolumab in treatment-naïve adults Among the 320 subjects exposed to cabozantinib in combination with nivolumab arm in the RCC Study CA2099ER, 189 (59.1%) were <65 years old, 102 (31.9%) were 65 to 74 years old, and 27 (8.4%) were ≥75 to 84 years old and 2 (0.6%) were ≥85 years old. The median age of the 320 subjects exposed to cabozantinib in combination with nivolumab was 62 years; this age is representative of the general RCC population. The incidence of ETM AEs reported in cabozantinib in combination with nivolumab treated subjects in Study CA2099ER was generally similar between the age groups; 143 of 189 (75.7%) subjects <65 years old, 85 of 102 (83.3%) subjects 65 to 74 years old, 20 of 27 (74.1%) subjects ≥75 to 84 years old and 2 of 2 (100%) subjects ≥85 years old. The incidences of haemorrhage (all grades), hypertension, proteinuria and QT prolongation were higher in subjects in the older age groups (≥75 to 84 years old and ≥85 years old). Abscess, fistula and GI perforation were not reported in the two older age groups. Meanwhile osteonecrosis and PPES were reported more frequently in the two younger age groups (<65 years old and 65 to 74 years old). For ETM SAEs in Study CA2099ER the numbers were too small to determine any notable age-related differences between the different age groups; 20 of 189 (6.3%) ETM SAEs for subjects <65 years old, 16 of 102 (5.0%) ETM SAEs for subjects 65 to 74 years old, 7 of 27 (2.2%) ETM SAEs for subjects ≥75 to 84 years old, and no ETM SAEs in subjects ≥85 years old. HCC in adults who have previously been treated with sorafenib Among the 467 subjects exposed to cabozantinib in the HCC Study XL184-309, 239 (51%) were <65 years old, 156 (33%) were 65 to 74 years old and 72 (15%) were ≥75 years old (of whom five subjects were ≥85 years old). The median age of the 467 subjects exposed to cabozantinib was 64.0 years; this age is representative of the general HCC population. No notable age-related differences in AEs or ETMs were observed for cabozantinib-treated subjects in Study XL184-309. DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine

Type of special population	Exposure
	Among the 125 subjects exposed to cabozantinib in Study XL184-311, 62 (50%) were <65 years old, 48 (38%) were 65 to 74 years old, 14 (11%) were 75 to <85 years old and 1 (0.8%) was ≥85 years old. The median age of the 125 subjects exposed to cabozantinib was 65 years. No notable age-related differences in AEs or ETMs were observed for cabozantinib-treated subjects in Study XL184-311. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy Among the 195 subjects exposed to cabozantinib in Study A021602, 99 (50.8%) were <65 years old, 76 (39%) were 65 to 74 years old, 19 (9.7%) were 75 to <85 years old and 1 (0.5%) was ≥85 years old. In the epNET cohort, the median age of subjects in cabozantinib arm was 66.0 years and in the pNET cohort, the median age of the subjects was 60.0 years in the cabozantinib arm. No notable age-related differences in AEs or ETMs were observed for subjects in cabozantinib arm in Study A021602.

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ATE=arterial thromboembolic events; AUC=area under the plasma drug concentration time curve; AUC_{0-t}=AUC from 0 hours to a specific postdose time, which is the last sampling time point unless otherwise specified; AUC_{0-inf}=AUC from 0 hours to infinity; CDKN1B=cyclin-dependent kinase inhibitor 1B; C_{max}=maximum plasma concentration; CHF=congestive heart failure; CI=confidence interval; CNS=central nervous system; CSR=clinical study report; DAXX=death domain associated protein; ECOG=Eastern Cooperative Oncology Group; epNET=extra-pancreatic neuroendocrine tumour; ETM=event to monitor; GI=gastrointestinal; HCC=hepatocellular carcinoma; LS=least-squares; KPS=karnofsky performance status; MEN1=multiple endocrine neoplasia type 1; NET=neuroendocrine tumour; PD-L1=programmed death-ligand 1; PIP=Paediatric Investigation Plan; PK=pharmacokinetic(s); pNET=pancreatic neuroendocrine tumour; PPES=palmar-plantar erythrodysesthesia syndrome; PS=performance status; PT=preferred term; RCC=renal cell carcinoma; SAE=serious adverse event; SmPC=summary of product characteristics; ULN=upper limit of normal; VEGF=vascular endothelial growth factor; VTE=venous and mixed/unspecified thrombotic events.

Part II: Module SV – Post-authorisation Experience

The marketing authorisation for cabozantinib capsules (Cometriq) was transferred to Ipsen on 03 October 2016, and post-authorisation experience is provided in a separate RMP.

In the United States (US), Exelixis is the MAH and is responsible for distribution of Cometriq and Cabometyx. Takeda is the Cabometyx MAH in Japan. Ipsen Pharma is the Cometriq and Cabometyx MAH outside of the US and Japan.

Exelixis maintains the Global Safety Database for cabozantinib. Signal detection and management activities are performed by Exelixis on all data generated from the use of cabozantinib in the two formulations and in all indications. Pharmacovigilance agreements are in place between the different parties involved, mainly Exelixis, and Ipsen who is the MAH for all indications of cabozantinib in the EU.

SV.1 Post-authorisation Exposure

Cabometyx (tablet formulation) is authorised in the EU as first-line monotherapy in adult patients with intermediate or poor-risk RCC and also in adults with advanced RCC following prior VEGF-targeted therapy, in combination with nivolumab for the first-line treatment of adult patients with advanced RCC, as monotherapy in adults with HCC who have been previously treated with sorafenib, and as monotherapy in adults with locally advanced or metastatic DTC, refractory or not eligible to RAI who have progressed during or after prior systemic therapy. Cabometyx has been approved in the US as monotherapy and in combination with nivolumab for the treatment of patients with advanced RCC, and as monotherapy in patients with HCC who have been previously treated with sorafenib and in adult and paediatric patients 12 years of age and older with locally advanced or metastatic DTC that has progressed following prior VEGFR-targeted therapy and who are RAI-refractory or ineligible. Cabometyx

is authorised in Japan as monotherapy and in combination with nivolumab for patients with curatively unresectable or metastatic RCC, and for patients with unresectable HCC that has progressed after cancer chemotherapy. Cabometyx is also authorised for advanced RCC and/or HCC (one or both indications may be authorised) in more than 50 countries worldwide. Cabometyx is supplied as 20-, 40-, and 60-mg film-coated tablets. The recommended daily dose of Cabometyx is 60 mg orally for RCC monotherapy, HCC, DTC and 40 mg orally for advanced RCC in combination with nivolumab. It is also made available in some countries by Ipsen via Managed Patient Access Programmes (managed access programme (MAP); global access programme, (GAP)).

SV.1.1. Method Used to Calculate Exposure

Estimates of cumulative patient exposure to cabozantinib in the marketed setting (i.e. Cabometyx), including access programmes, are based on product market data available.

Information provided is as of the DLP for the global PSUR for Cabometyx of 28 November 2023.

Commercial Cabometyx exposure was calculated as follows:

- In the US, the number of patients receiving commercial Cabometyx was obtained from 10 specialty pharmacies in the US and was based on individual patient prescriptions as submitted to these 10 specialty pharmacies. The number also includes a patient estimate for product shipments to group oncology providers.
- In Japan, the number of patients receiving commercial Cabometyx was based on the cumulative or interval number of sold commercial Cabometyx units (tabs) and adjusted for the median dose (26.02 mg) and median duration (27 weeks) in the Cabozantinib-2001 study. Cabometyx was launched in Japan on 22 May 2020; therefore, the exposure in Japan may be overestimated at this time.
- Outside of the US and Japan, the number of patients receiving commercial Cabometyx was based on the cumulative or interval number of sold commercial Cabometyx units shipped by Ipsen and adjusted for average exposure duration (seven months). It should be noted that some patients received free commercial product as part of an access programme (ie, MAP_RCC or GAP). Cumulative or interval access programme exposure was based on the number of free Cabometyx units shipped by Ipsen and adjusted for average exposure duration (seven months). Patients enrolled in Ipsen-sponsored NISs receive commercial product and are included in the estimated exposure to Cabometyx in the marketed setting.

SV.1.2. Exposure

Cumulative worldwide Cabometyx exposure (through 28 November 2023) in the marketed setting and MAPs is provided in Table 30. The cumulative patient exposure to Cabometyx in the marketed setting is 172,467 (including 61,817 patients in the EU, 66,469 patients in the US, 13,921 patients in Japan and 30,260 patients in the rest of the world (ROW)). In addition, cumulatively 2548 patients outside of the US and Japan received Cabometyx as part of MAP and GAP programmes (663 patients in the EU and 1885 patients in the ROW).

Table 30 Estimated Worldwide Commercial Patient Exposure for Cabometyx as of 28 November 2023 by Region

By country	
All indications	
	Persons (cumulative exposure through 28 November 2023)
Marketed	
EU	61,817

By country	
All indications	
	Persons (cumulative exposure through 28 November 2023)
US	66,469
Japan	13,921
ROW [a]	30,260
Total	**172,467**
MAP/GAP	
EU	663
US	0
Japan	0
ROW [a]	1885
Total	**2548**
Total exposure (marketed and MAP/GAP)	**175,015**

EU=European Union; GAP=global access programme; MAP=market access programme; RCC=renal cell carcinoma; ROW=Rest of world (outside of US, EU and Japan); US=United States.

a The following countries contributed to ROW (i.e., outside of the US, EU, and Japan) estimates of exposure to cabozantinib in the commercial setting: Australia, Brazil, Canada, Colombia, Egypt, French Polynesia, Hong Kong, Israel, Jordan, Kuwait, Lebanon, Mexico, Malaysia, New Zealand, New Caledonia, Panama, Russian Federation, Saudi Arabia, Singapore, South Korea, Serbia, Switzerland, Taiwan, Thailand, Turkey, Ukraine, United Arab Emirates and United Kingdom.

Patterns of Cabometyx use can be explored through prescribing information obtained by the Specialty Pharmacies that dispense Cabometyx in the US. This prescribing information may include the condition for which Cabometyx is prescribed but may also include other medical conditions present in the patient.

The prescribing information obtained for patients who were dispensed Cabometyx by the Specialty Pharmacies showed that 79.6% had an underlying kidney or hepatocellular cancer; other malignancies were also reported including thyroid cancer, prostate cancer, bone cancer, brain cancer, lung cancer, colorectal cancer, bladder cancer and breast cancer (Table 31).

Information on patient indication from the postmarketing setting outside of the US is not available.

Table 31 Patterns of Cabometyx Use for Indications Reported in the Marketed Setting in the United States through 28 November 2023

Reported Indication	
	Number of Patients
Renal cancer	26,802
Hepatocellular carcinoma	2568
Thyroid cancer	650
Prostate cancer	337
Lung cancer	706
Bone cancer	803
Brain cancer	97
Colorectal cancer	94
Breast cancer	42
Bladder cancer	27
Other cancers	1355
Unknown cancer	3428

Part II: Module SVI – Additional EU Requirements for the Safety Specification

SVI.1. Potential for Misuse for Illegal Purposes

Cabozantinib does not have the potential for central nervous system (CNS) effects such as euphoria, dependence, sedation and mood change that would make it attractive for misuse for illegal purposes. As a class, vascular endothelial growth factor-tyrosine kinase inhibitors (VEGF-TKIs) are not associated with psychoactive effects or dependence.

Part II: Module SVII – Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

The safety concerns presented in the first approved EU-RMP for Cabometyx (Version 1.2) are provided in Table 32.

Table 32 Summary of Safety Concerns from the First Approved RMP

Important identified risks	• Gastrointestinal perforation • Gastrointestinal and nongastrointestinal fistula • Thromboembolic events • Haemorrhage (Grade ≥3) • Wound complications • Hypertension • Reversible posterior leukoencephalopathy syndrome (RPLS) • Diarrhoea • Palmar-plantar erythrodysaesthesia syndrome (PPES) • Hypothyroidism • Osteonecrosis • Proteinuria
Important potential risks	• QT prolongation • Renal failure • Hepatotoxicity • Fertility impairment • Embryotoxicity • Medication error
Missing information	• Use in paediatric population • Use in pregnant or lactating women • Use in patients with cardiac impairment • Use in patients with severe hepatic impairment • Use in patients with severe renal impairment • Carcinogenicity

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The risks not considered important for inclusion in the list of safety concerns in the RMP are summarised in Table 33.

Table 33 Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Reason for risk(s) not being considered important	Justification [a]
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated).	Anaemia, arthralgia, blood ALP increased, thrombocytopenia, decreased appetite, hypocalcaemia, hypomagnesaemia, hypokalaemia, hypoalbuminaemia, dysgeusia, headache, dizziness, dysphonia, dyspnoea, cough, nausea, vomiting, stomatitis, constipation, abdominal pain, dyspepsia, rash, pain in extremity, fatigue, mucosal inflammation, asthenia, peripheral oedema and weight decreased are very common ADRs of cabozantinib treatment and are included in Section 4.8 of the SmPC.

Reason for risk(s) not being considered important	Justification [a]
	Upper respiratory tract infection, decreased appetite, dysgeusia, dizziness, headache, dysphonia, dyspnoea, cough, nausea, constipation, stomatitis, vomiting, abdominal pain, dyspepsia, rash, pruritus, arthralgia, muscle spasm, musculoskeletal pain, proteinuria, fatigue, oedema, pyrexia, increased alkaline phosphatase, increased total bilirubin, hypocalcaemia, increased creatinine, hypoglycaemia, hyperglycaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hypermagnesaemia, hyponatraemia, hypernatraemia, increased lipase, increased amylase, hypophosphataemia, lymphopenia, leucopenia, thrombocytopenia, anaemia, neutropenia, hypercalcaemia, and weight decreased are very common ADRs of cabozantinib in combination with nivolumab treatment and included in Section 4.8 of the SmPC. Abscess, allergic rhinitis, flatulence, neutropenia, lymphopenia, dehydration, hypophosphataemia, hyponatraemia, hypotension, hyperkalaemia, hyperbilirubinaemia, hyperglycaemia, hypoglycaemia, peripheral neuropathy (including sensory), tinnitus, gastroesophageal reflux disease, haemorrhoids, oral pain, dry mouth, dysphagia, pruritus, alopecia, dry skin, dermatitis acneiform, hair colour change, hyperkeratosis, muscle spasms, proteinuria, GGT increased, blood creatinine increased, amylase increased, lipase increased, blood cholesterol increased and blood triglycerides increased are common ADRs and glossodynia is a uncommon ADR of cabozantinib treatment and are included in Section 4.8 of the SmPC. Eosinophilia, dehydration, peripheral neuropathy, tinnitus, dry eye, blurred vision, tachycardia, epistaxis, pleural effusion, dry mouth, gastritis, oral pain, haemorrhoids, dry skin, alopecia, erythema, hair colour change, arthritis, pain, chest pain, blood cholesterol increased, and hypertriglyceridaemia are common ADRs of cabozantinib in combination with nivolumab treatment and included in Section 4.8 of the SmPC. Infusion related hypersensitivity reaction, glossodynia, psoriasis, urticaria, and myopathy are uncommon ADRs of cabozantinib in combination with nivolumab treatment and included in Section 4.8 of the SmPC. Fertility impairment is considered to have minimal clinical impact on patients (in relation to the severity of the indication treated). Medication error with cabozantinib monotherapy is considered to have minimal clinical impact on patients (in relation to the severity of the indications treated). (SmPC Section 4.2).
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated.	Convulsion, cerebrovascular accident, acute myocardial infarction, and hepatitis cholestatic are uncommon ADRs and pancreatitis is a common ADR of cabozantinib treatment and are included in Section 4.8 of the SmPC. Aneurysm and artery dissections are ADRs of cabozantinib treatment that occur at an unknown frequency and are included in Section 4.8 of the SmPC. Hypertensive crisis will be described in Section 4.4 in the proposed SmPC, occurs at an uncommon frequency and is included in Section 4.8 of the SmPC. Pneumonia, hypersensitivity (including anaphylactic reaction), adrenal insufficiency, atrial fibrillation, pneumonitis, colitis, renal failure and acute kidney injury are common ADRs; hypophysitis, thyroiditis, myocarditis, encephalitis autoimmune, Guillain-Barré syndrome, myasthenic syndrome, uveitis, pancreatitis, and nephritis are uncommon ADRs of cabozantinib in combination with nivolumab treatment and included in Section 4.8 of the SmPC.

Reason for risk(s) not being considered important	Justification [a]
Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely, through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised)	Hypertension, diarrhoea, hypothyroidism and PPES are very common ADRs, and hepatic encephalopathy is a common ADR, of cabozantinib treatment, and included in Section 4.8 of the SmPC. Hypertension, diarrhoea, hypothyroidism, hyperthyroidism, and PPES are very common ADRs of cabozantinib in combination with nivolumab treatment and included in Section 4.8 of the SmPC. Monitoring and treatment fall under standard of care. Medication errors; in Study CA2099ER the recommended cabozantinib dose is 40 mg daily for advanced RCC in treatment-naïve adults in combination with nivolumab. This differs from the recommended cabozantinib dose of 60 mg daily as monotherapy for advanced RCC in treatment-naïve adults with intermediate or poor-risk and in adults following prior VEGF-targeted therapy, and for the treatment of HCC in adults who have previously been treated with sorafenib. There is comprehensive guidance in Section 4.2 of the SmPC concerning the recommended posology for each indication. Furthermore, Cabometyx is available as 20 mg, 40 mg and 60 mg film-coated tablets and therefore it is expected the 40 mg film-coated tablets would be prescribed for treatment-naïve patients with advanced RCC for use in combination with nivolumab in clinical practice. Medication errors involving cabozantinib in combination with nivolumab will be followed up during postmarketing use to monitor whether the recommended dose of 40 mg Cabometyx is being used.
Known risks that do not impact the risk-benefit profile	Not applicable
Other reasons for considering the risks not important	QT prolongation; no medically meaningful QT prolongation was observed in RCC and HCC and no cases of Torsades de Pointes have been associated with the use of cabozantinib since its early development.

ADR=adverse drug reaction; ALP=alkaline phosphatase; EU=European Union; GGT=gamma-glutamyl transpeptidase; HCC=hepatocellular carcinoma; PPES=palmar-plantar erythrodysaesthesia syndrome; RCC=renal cell carcinoma; RMP=risk management plan; SmPC=summary of product characteristics; VEGF=vascular endothelial growth factor.

a very common ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1000 to <1/100; unknown (cannot be estimated from the available data).

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

The risks included in the safety concerns as important identified risks, important potential risks or missing information are discussed in this section.

Important Identified Risks:

The identified risks considered important for inclusion as a safety concern in the RMP are presented in Table 34. The important identified risks are considered the same for all indications.

Table 34 Important Identified Risks

Important identified risk	Risk-benefit impact
Gastrointestinal perforation	<u>Advanced RCC monotherapy:</u> The incidence of GI perforation was low in the cabozantinib arm of Study XL184-308 (three subjects (0.9%)). No events in the cabozantinib arm were life-threatening or fatal. The incidence of GI perforation was low in the cabozantinib arm of Study A031203 (two events). Both events of GI perforation in the cabozantinib arm were Grade 4, serious and treatment related. One of these subjects experienced a Grade 4 AE of jejunal perforation due to jejunal mass eroding adjacent bowel as reported in the clinical database; however, follow-up reporting indicates that the investigator later reassessed the cause of death as jejunal perforation (Grade 5 AE related to study treatment). <u>Advanced RCC in combination with nivolumab in treatment-naïve adults:</u>

Important identified risk	Risk-benefit impact
	The incidence of GI perforation was low in the cabozantinib and nivolumab arm of Study CA2099ER (four subjects (1.3%)). All four events of GI perforation in the cabozantinib and nivolumab arm were serious and of ≥Grade 3 severity. Two of the subjects with treatment related AEs recovered. For the other two subjects the outcome was fatal, including Grade 5 intestinal perforation (not considered treatment related) and Grade 4 intestinal perforation in a subject who died 51 days after the last dose of nivolumab and 46 days after the last dose of cabozantinib. The event was considered by the investigator to be related to study drug toxicity. HCC in adults who have previously been treated with sorafenib: The incidence of GI perforation was low in the cabozantinib arm of Study XL184-309 (four subjects (0.9%)). Although all four subjects experienced SAEs, no events were fatal. DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine: The incidence of GI perforation was low in the cabozantinib arm of Study XL184-311 (one subject [0.8%]) The event occurred 97 days after the first dose of cabozantinib and resolved on Day 105. The event was considered Grade 4, treatment related and led to study drug discontinuation. Events as described can have debilitating, disabling or fatal outcomes and therefore GI perforation is an important identified risk for cabozantinib. Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): Overall incidence of GI perforation was 0.7% (95% CI: 0.2, 1.7) in CASSIOPE study. The incidence of GI perforation in second-line therapy group was 0.6% (2 subjects) and in third and later line therapy group was 0.9% (3 subjects). Five subjects (0.7%) experienced serious TEAEs of which 2 events were assessed as treatment related; all the events reported were non-fatal. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): The incidence of GI perforation was low in the cabozantinib arm of the Study A021602 (one subject (0.5%)). The serious, Grade 3 event of spontaneous bacterial peritonitis was considered treatment related. Further details of the risk are provided in Table 36.
Gastrointestinal and nongastrointestinal fistula	Advanced RCC monotherapy: The incidence of fistulae in the cabozantinib arm of Study XL184-308 was 1.2%. No events were life-threatening or fatal. No events of fistula were reported for the cabozantinib arm of Study A031203. Advanced RCC in combination with nivolumab in treatment-naïve adults: The incidence of fistulae in the cabozantinib and nivolumab arm of Study CA2099ER was 0.9% (three subjects), with one of the events assessed as related to treatment. Two of the AEs were serious but none of the three AEs were of ≥ Grade 3 severity. HCC in adults who have previously been treated with sorafenib: The incidence of fistulae in the cabozantinib arm of Study XL184-309 was 1.3% (six subjects), with three SAEs reported. One subject experienced a Grade 5 AE of oesophagobronchial fistula, which was assessed as related to cabozantinib.

Important identified risk	Risk-benefit impact
	DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine: No events of fistulae in the cabozantinib arm of Study XL184-311 were reported. Events as described can have debilitating, disabling or fatal outcomes and therefore GI and nonGI fistula is an important identified risk for cabozantinib. Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 [CASSIOPE]): Overall incidence of Gastrointestinal and nongastrointestinal fistula was 0.6% (95% CI: 0.2, 1.5) in CASSIOPE study. The incidence of Gastrointestinal and nongastrointestinal fistula was similar when cabozantinib was used as second-line (2 subjects (0.6%)) or third and later line therapy (2 subjects (0.6%)). Two subjects (0.3%) experienced serious TEAEs one in each treatment line group of which 1 event in the second-line therapy group was assessed as treatment related. None of the events were fatal. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): The incidence of fistulae in the cabozantinib arm of Study A021602 was 1.0% (two subjects). Both the AEs (i.e. anal fistula and biliary fistula) were non-serious, and treatment related. None of the two AEs were of ≥ Grade 3 severity. Further details of the risk are provided in Table 37.
Thromboembolic events	Advanced RCC monotherapy: While the incidence of all grades, all causality events of VTE events was higher in the cabozantinib treatment arm of Study XL184-308 compared to that seen with other VEGF pathway inhibitors, the incidence of Grade 3/4 events was similar to that seen with other VEGF pathway inhibitors. The incidence of ATEs was low in in the cabozantinib arm of Study XL184-308 (three subjects (0.9%)). In Study A031203, "thromboembolic event" was generally reported as the nonspecific PT of embolism, and therefore not captured in the formal summaries of VTEs and ATEs. Nine subjects reported a PT of embolism. Though no subjects reported an ATE, one subject with a reported event of embolism was found to have experienced stroke, thrombosis of the axillary artery and thrombosis of the left internal carotid artery. Another of the subjects with embolism also reported a VTE of superior vena cava syndrome. Of the nine subjects with embolism, five were determined to have a pulmonary embolism. Further review of the uncoded AEs and data in the cabozantinib Global Safety Database identified two more subjects with pulmonary embolism (seven total). Including data from all sources, 11 subjects had a VTE. Advanced RCC in combination with nivolumab in treatment-naïve adults: The incidence of ATEs was 2.2% in the cabozantinib and nivolumab treatment arm of Study CA2099ER. Five SAEs were reported in subjects in the cabozantinib in combination with nivolumab arm. Three of the ATEs were of Grade 3 severity including myocardial infarction (0.6%) (not considered treatment related) and ischaemic stroke (0.3%) (treatment related). All subjects who experienced ATEs recovered. In the cabozantinib and nivolumab treatment arm of Study CA2099ER the incidence of VTEs was 11.3%. A total of 17 SAEs (5.3%) were reported in subjects treated with cabozantinib and nivolumab. The majority of SAEs were resolved/resolved with sequelae (76.5%) or

Important identified risk	Risk-benefit impact
	resolving (11.8%). The most frequently reported VTE was pulmonary embolism with 20 AEs (6.3%), of which 17 (5.3%) were of ≥Grade 3 severity and 9 (2.8%) of these severe AEs were considered treatment related. None of the VTEs had a fatal outcome. HCC in adults who have previously been treated with sorafenib: The incidences of ATEs and VTEs were 2.6% and 3.9%, respectively, in the cabozantinib arm of Study XL184-309. Three additional subjects experienced the following ATEs that were not captured as part of the ETM of arterial thrombotic events: intestinal ischaemia, ischaemic hepatitis and peripheral ischaemia. Ten subjects (2.1%) experienced Grade 3 to 4 ATEs (inclusive of two events of intestinal ischaemia and ischaemic hepatitis that were not captured as part of the ETM of arterial thrombotic events). Three subjects in the cabozantinib arm had Grade 5 arterial thrombotic AEs of ischaemic hepatitis, ischaemic stroke and cerebrovascular accident. Grade 5 venous and mixed/unspecified thrombotic AEs of portal vein thrombosis and pulmonary embolism were each experienced by one subject in the cabozantinib arm; these Grade 5 events were assessed as related to study treatment. There were 11 serious arterial thrombotic AEs and 11 serious venous and mixed/unspecified thrombotic AEs. DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine: The incidences of ATEs and VTEs were 0.8% and 9.6%, respectively, in the cabozantinib arm of Study XL184-311 compared to 0 in the placebo arm. One subject experienced an aortic thrombosis (Grade 1) at Day 113, which was assessed as not related to cabozantinib and resolved on Day 117. Of the 12 subjects that experienced venous and mixed/unspecified thrombotic events, 4 subjects (3.2%) had Grade 3 to 4 events (pulmonary embolism [n=3], assessed as related [n=2] and not related [n=1] to cabozantinib) and deep vein thrombosis [n=1, assessed as related to cabozantinib]) and 1 subject had a Grade 5 event (pulmonary embolism) considered not related to cabozantinib. Thromboembolic events can have debilitating, disabling or fatal outcomes and therefore thromboembolic events is an important identified risk for cabozantinib. Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): Overall incidence of thromboembolic events was 7.1% (95% CI: 5.3, 9.3) in CASSIOPE study. The incidence of Thromboembolic events in third and later line therapy was 7.9% (27 subjects) and in second-line therapy was 6.3% (21 subjects). Overall, 31 TEAEs reported in the second-line (15 events) and third/ later line (16 events) group were serious of which 6 events were fatal (1 event in second-line group and 5 events in third and later line group). A total of 19 events reported in 17 subjects were assessed as treatment related in the second-line (11 events) and third/ later line (8 events) groups. Of the 17 subjects, 10 subjects had AEs of pulmonary embolism, 3 subjects had AEs of deep vein thrombosis and 1 subject each had AEs of acute myocardial infarction, disseminated intravascular coagulation, pelvic venous thrombosis, peripheral embolism, thrombosis of any grade. Of the 10 subjects with pulmonary embolism 6 subjects reported Grade 3-4 events and 2 subjects reported Grade 5 events; 2 subjects reported Grade 3-4 deep vein thrombosis and 1 subject reported Grade 3-4 acute myocardial infarction. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602):

Important identified risk	Risk-benefit impact
	The incidences of ATEs and VTEs were 1.5% and 8.7%, respectively, in the cabozantinib arm of Study A021602. Three ATEs of acute myocardial infarction, coronary artery occlusion, and myocardial infarction were of Grade 4 severity and one ATE of embolism arterial was of Grade 3 severity. The ATE of coronary artery occlusion was not considered related to cabozantinib and the remaining all other ATEs were assessed as related to cabozantinib. Of the 17 subjects that experienced VTEs, three subjects (1.5%) had Grade 4 events (pulmonary embolism [n=2], and cerebrovascular accident [n=1]; all these events were assessed as related to cabozantinib) and eight subjects had a Grade 3 event (embolism [n=4], embolism venous [n=1], and pulmonary embolism [n=4]; all these events were assessed as related to cabozantinib). None of the ATEs and VTEs had a fatal outcome. Further details of the risk are provided in Table 38.
Haemorrhage (Grade ≥3)	Advanced RCC monotherapy: In Study XL184-308, the incidence of higher grade (≥Grade 3) haemorrhages was low in cabozantinib-treated subjects (seven subjects (2.1%)). Two subjects had a Grade 5 event (one postprocedural (iatrogenic) haemorrhage and one extradural haematoma which occurred 31 days after the last dose); both were assessed as unrelated to cabozantinib. In Study A031203, the incidence of higher grade haemorrhages was low (5.1%). Two subjects had SAEs of haemorrhage, both assessed as unrelated to cabozantinib. Advanced RCC in combination with nivolumab in treatment-naïve adults: The incidence of ≥Grade 3 haemorrhage was 1.6% in the cabozantinib and nivolumab treatment arm of Study CA2099ER. Three SAEs of Grade ≥3 haemorrhages were reported. Two SAEs were reported as resolved and 1 had a fatal outcome in which the subject had a Grade 5 haemorrhagic AE of upper gastrointestinal haemorrhage manifested with hematemesis and melena but was not considered related to treatment. HCC in adults who have previously been treated with sorafenib: The incidence of ≥Grade 3 haemorrhage was 7.3% in the cabozantinib arm of Study XL184-309. Five subjects (1%) experienced Grade 5 haemorrhagic AEs: one of these experienced a treatment related AE of upper gastrointestinal haemorrhage. There were 31 SAEs. DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine: The incidence of ≥Grade 3 haemorrhage was 2.4 % (n=3) in the cabozantinib arm of Study XL184-311 and considered not related to study drug. In 2 subjects, Grade 3 events were haemoptysis and haematoma with muscle haemorrhage. Arterial haemorrhage was reported as a Grade 5 event and not related to cabozantinib. These events can have debilitating, disabling or fatal outcomes and therefore haemorrhage (Grade ≥3) is an important identified risk for cabozantinib. Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): Overall incidence of haemorrhage (Grade ≥3) events was 2.5% (95% CI: 1.5, 4.0) in CASSIOPE study. The incidence of Grade ≥3 haemorrhage events in third and later line therapy group was 2.0% (7 subjects) and in second-line therapy group was 3.0% (10 subjects). Overall, 12 TEAEs reported in the second-line (9 events) and third/ later

Important identified risk	Risk-benefit impact
	line (3 events) group were serious of which 3 events were fatal (2 events in second-line group and 1 event in third and later line). A total of 6 events reported in 6 subjects were assessed as treatment related in the second-line (4 events) and third/ later line (2 events) groups. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): The incidence of ≥Grade 3 haemorrhage was 2.1 % (n=4) in the cabozantinib arm of Study A021602. In three subjects, Grade 3 events were haemorrhoidal haemorrhage, oesophageal haemorrhage and rectal haemorrhage. Oesophageal haemorrhage and rectal haemorrhage were considered related and haemorrhoidal haemorrhage was considered as not related to cabozantinib treatment. A Grade 5 event of gastrointestinal haemorrhage was also reported. The investigator assessed gastrointestinal haemorrhage as serious and possibly related to cabozantinib and possibly related to the underlying carcinoid tumour of the lung, and probably related to heparin therapy. Further details of the risk are provided in Table 39.
Wound complications	Advanced RCC monotherapy: The incidence of wound complications was low for the cabozantinib treatment arm of Study XL184-308 (eight subjects (2.4%)). Wound complications were primarily postsurgical events, and all but one AE were low grade (≤Grade 2). The Grade 3 AE (impaired healing) occurred in the context of PPES; the event was non-serious and resolved within 2 weeks of onset. No coded events of wound complications were reported for the cabozantinib arm of Study A031203. One cabozantinib-treated subject reported a related Grade 2, non-serious AE with verbatim terms related to wound complications. Advanced RCC in combination with nivolumab in treatment-naïve adults: The incidence of wound complications was 2.8% (nine subjects) in the cabozantinib and nivolumab arm of Study CA2099ER. None of the AEs were serious and only 3 AEs were considered related to treatment. One subject experienced a Grade 3 AE of wound; all other wound complications had a severity of ≤Grade 2. HCC in adults who have previously been treated with sorafenib: The incidence of wound complications was low for the cabozantinib treatment arm of Study XL184-309 (four subjects (0.9%)). One subject experienced a Grade 3 SAE of wound sepsis; all other wound complications were reported as non-serious and had a severity of ≤Grade 2. DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine: The incidence of wound complications was low for the cabozantinib treatment arm of Study XL184-311 (two subjects (1.6%)). Wound dehiscence and wound infection were reported as non-serious Grade 3 events not related to study drug. These events can have debilitating, disabling or fatal outcomes and therefore wound complications is an important identified risk for cabozantinib. Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): Overall incidence of wound complications events was 1.2% (95% CI: 0.5, 2.3) in CASSIOPE study. The incidence of wound complications events was similar when cabozantinib was used as second-line

Important identified risk	Risk-benefit impact
	(4 subjects (1.2%)) and third/ later line therapy (4 subjects (1.2%)). Two TEAEs reported in the second-line group were serious. None of the events were fatal. A total of 3 events reported in 3 subjects were assessed as treatment related in the second-line (1 events) and third/ later line (2 events) groups. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): The incidence of wound complications was 3.1% (six subjects) in the cabozantinib arm of Study A021602. One subject experienced a Grade 3 AE of wound infection (serious, related) and treatment with cabozantinib was discontinued in response to the event. All other wound complications had a severity of Grade 1. Further details of the risk are provided in Table 40.
Posterior reversible encephalopathy syndrome (PRES)[a]	Globally in interventional clinical trials, the event of PRES was reported in 3 subjects up to the DLP of this RMP. Advanced RCC monotherapy: None of the 331 cabozantinib-treated subjects in Study XL184-308 experienced PRES. [b] No events of PRES were reported for the cabozantinib arm of Study A031203. Advanced RCC in combination with nivolumab in treatment-naïve adults: None of the 320 cabozantinib in combination with nivolumab treated subjects in Study CA2099ER experienced PRES. HCC in adults who have previously been treated with sorafenib: None of the 467 cabozantinib-treated subjects in Study XL184-309 experienced PRES. DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine[c]: Among the 125 cabozantinib-treated subjects in study XL 184-311, 1 subject with pre-existing hypertension experienced Grade 4 event of hypertension (Blood pressure [BP] 201/112 mmHg) on Day 55 which was associated with neurological symptoms confirmed as being PRES but coded as such only after the study initial DLP. The patient's antihypertensive treatment was adapted. Study treatment had been initially interrupted when BP increased and was then discontinued. The patient was said to have recovered from PRES symptoms a week later. These events can have debilitating, disabling or fatal outcomes and PRES is therefore an important identified risk for cabozantinib. Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): Overall incidence of PRES events was 0.3% (95% CI: 0.0, 1.1) in CASSIOPE study. The incidence of PRES events was similar when cabozantinib was used as second-line (1 subject (0.3%)) and third/ later line therapy (1 subject (0.3%)) of which, 1 event reported in the third and later line group was serious. None of the events were fatal. One event reported in 1 subject in third and later line group was assessed as treatment related. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): The incidence of PRES was low for the cabozantinib treatment arm of Study A021602 (one subject (0.5%)). One event of PRES was reported, the event was assessed as serious, Grade 3 event and related to study

Important identified risk	Risk-benefit impact
	drug. Treatment with cabozantinib was discontinued in response to the event of PRES. Further details of the risk are provided in Table 41.
Osteonecrosis	Advanced RCC monotherapy: Two subjects (0.6%) in the cabozantinib arm of Study XL184-308 experienced ONJ. The cabozantinib-treated subject who had a Grade 3 AE of ONJ had a Grade 2 event at baseline and received denosumab on study; the other subject with a Grade 2 ONJ had a prior history of ONJ which resolved before enrolling in the study. No events of osteonecrosis were reported for the cabozantinib arm of Study A031203. Advanced RCC in combination with nivolumab in treatment-naïve adults: In Study CA2099ER 18 subjects (5.6%) in the cabozantinib in combination with nivolumab arm experienced osteonecrosis (identified using the osteonecrosis SMQ) including 2 subjects (0.6%) who developed ONJ. None of the AEs were serious. The AEs of ONJ were of Grade 2 and Grade 3 severity. HCC in adults who have previously been treated with sorafenib: None of the 467 cabozantinib-treated subjects in Study XL184-309 experienced ONJ. DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine [d]: In Study XL184-311, 3 subjects (2.4%) in the cabozantinib arm had an event included in the ETM list of Osteonecrosis, all considered non serious and not related to cabozantinib . Among them was 1 case (0.8%) of ONJ Grade 3.These events can have debilitating, disabling or disfiguring outcomes and ONJ is therefore an important identified risk for cabozantinib. Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): Overall incidence of Osteonecrosis events was 2.8% (95% CI: 1.7, 4.3) in CASSIOPE study. The incidence of Osteonecrosis events in second-line therapy group was 1.8% (6 subjects) and in third and later line therapy group was 3.8% (13 subjects). One event reported in the third and later line group was serious. None of the events reported were fatal. A total of 10 events reported in 8 subjects were assessed as treatment related in the second-line (2 events) and third/ later line (8 events) groups. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): No subjects in Study A021602 developed ONJ. Six subjects (3.1%) in the cabozantinib arm had an event included in the ETM list of osteonecrosis. None of these AEs were serious. One Grade 3 event of tooth infection was reported which was not considered treatment related. The remaining TEAEs of tooth abscess (n=1) and tooth infection (n=5) were of Grade 2 severity. Two Grade 2 AEs of tooth infection were considered treatment related, remaining all the Grade 2 AEs were assessed as not related to the cabozantinib. Further details of the risk are provided in Table 42.

AE=adverse event; ATE=arterial thromboembolic event; BP=blood pressure; CI=confidence interval; CTCAE=Common Terminology Criteria for Adverse Events; DLP=data lock point; DTC=differentiated thyroid carcinoma; ETM=event to monitor; GI=gastrointestinal; HCC=hepatocellular carcinoma; MedDRA=Medical Dictionary for Regulatory Activities; MTC=medullary thyroid cancer; ONJ=osteonecrosis of the jaw; PRES=posterior reversible encephalopathy syndrome; PT=preferred term; RCC=renal cell carcinoma; RMP=risk management plan; SAE=serious adverse event;

Important identified risk	Risk-benefit impact

SMQ=standardised MedDRA query; TEAE=treatment-emergent adverse events; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor; VEGFR=vascular endothelial growth factor receptor; VTE=venous thromboembolic event.

a Posterior reversible encephalopathy syndrome (PRES) (previously presented in the RMP as reversible posterior leukoencephalopathy syndrome (RPLS)).

b After the 22 May 2015 cut-off, one unconfirmed case of PRES was reported by a nonstudy physician via the postmarketing process for a subject who was enrolled in Study XL184-308. The report was not contemporaneous with the event (made >1 year afterwards) and there was inconsistent information in the report regarding the date of the event relative to study treatment. The subject also had confounding factors including receipt of a prior VEGF-TKI and radiation for brain metastases. There is no evidence of imaging supporting the diagnosis of PRES, and the event was not confirmed by the study investigator. In addition, one MTC subject (0.46%) developed PRES in MTC Study XL184-301.

c Per CTCAE v5, there are no events of PRES with severity > Grade 3 in Study XL184-311.

Source for Study A021602: Incidence of TEAEs by ETM, PT and Severity (sorted by alphabetic order), with CI - Safety Population, A021602 study, RMP Analyses (DLP 24 August 2023).

Important Potential Risks:

The potential risks considered important for inclusion as a safety concern in the RMP are presented in Table 35.

Table 35 Important Potential Risks

Important potential risk	Risk-benefit impact
Renal failure	<u>Advanced RCC monotherapy:</u> Nineteen (5.7%) subjects in the cabozantinib arm in Study XL184-308 met laboratory screening criteria for renal failure. A subsequent medical review of these subjects confirmed that none had drug-induced renal toxicity. In addition to the laboratory analysis for renal failure, SAEs using the renal failure and impairment HLT were examined. One subject (0.3%) in the cabozantinib treatment arm, also identified by laboratory screening approach described above, experienced a serious event of renal failure, which was ascribed to contrast agent by the investigator. In addition, two non-serious Grade 1 events of renal failure acute were reported. In Study A031203, a total of five (6.4%) [a][b] cabozantinib-treated subjects had ≥Grade 3 AE PTs, while two (2.6%) cabozantinib-treated subjects had Grade 1 to 2 AE PTs [c]. One subject had a Grade 5 AE of acute renal failure, which was assessed as related to cabozantinib. This subject had elevated creatinine at screening and died of acute renal failure following dehydration and the subject refusing dialysis. <u>Advanced RCC in combination with nivolumab in treatment-naïve adults:</u> Twenty-two (6.9%) subjects in the cabozantinib in combination with nivolumab arm in Study CA2099ER experienced renal failure AEs; 4.4% (14 subjects) had treatment related renal failure AEs. There were 3 SAEs (0.9%) in the cabozantinib in combination with nivolumab arm and of these 2 SAEs were reported as resolved (66.7%) and 1 SAE as resolving (33.3%). The majority of AEs were of Grade 1 and Grade 2 severity. The Grade 3 AEs included renal failure (0.3%) and acute kidney injury (0.6%). <u>HCC in adults who have previously been treated with sorafenib:</u> Eleven subjects (2.4%) in the cabozantinib arm of Study XL183309 experienced renal failure-related AEs (four Grade 3 and one Grade 4). A Grade 5 event of prerenal failure was also reported and there were six renal failure-related SAEs. <u>DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine:</u> Selected AEs grouped as renal failure were reported for 3 subjects (2.4%) in the cabozantinib only arm and none in the placebo arm. In the cabozantinib only arm, acute kidney injury and renal impairment were reported as Grade 3

Important potential risk	Risk-benefit impact
	SAEs in 1 subject (0.8%) each; renal failure was reported as a Grade 4 SAE in 1 subject (0.8%). All events resolved while study drug continued. These events can have debilitating, disabling or fatal outcomes and therefore, renal failure is an important potential risk for cabozantinib. <u>Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)):</u> Overall incidence of renal failure events was 2.1% (95% CI: 1.1, 3.4) in CASSIOPE study. Fourteen subjects (2.1%) from CASSIOPE study had experienced renal failure of which 6 events reported in 6 subjects were serious. The incidence of events of renal failure in second-line therapy group was 2.4% (8 subjects) and in third and later line therapy group was 1.7% (6 subjects). Overall, 3 events reported were fatal (1 event in second-line therapy group and 2 events in third and later-line therapy group). A total of 6 events reported in 6 subjects were assessed as treatment related in the second-line (4 events) and third/ later line (2 events) groups. <u>Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602):</u> Overall incidence of renal failure was 1.0% (95% CI: 0.12, 3.66) in Study A021602. Two subjects (1.0%) experienced serious TEAEs of acute kidney injury (Grade 3) one of which was assessed as treatment related. Further details of the risk are provided in Table 43.
Hepatotoxicity	<u>Advanced RCC monotherapy:</u> Elevations of liver enzymes are frequent in cabozantinib-treated subjects in Studies XL184-308 and A031203. However, these abnormalities are readily monitorable and there was no evidence of drug-induced liver injury with cabozantinib treatment. One cabozantinib-treated subject in Study XL184-308 developed a Grade 4 event of cholestatic hepatitis; the case was confounded by the use of concomitant ciprofloxacin and acetaminophen with an additional potential cause of autoimmune-mediated hepatitis following receipt of nivolumab prior to study entry. <u>Advanced RCC in combination with nivolumab in treatment-naïve adults:</u> In Study CA2099ER ALT increased AEs and AST increased AEs were experienced by 28.1% (24.7% treatment related AEs) and 25.3% (23.4% treatment related AEs) of cabozantinib in combination with nivolumab treated subjects respectively. Grade 3 severity AEs included 5.3% ALT increased AEs and 3.4% AST increased AEs. The majority of AEs were non-serious with only 0.6% SAEs of ALT increased and 0.3% SAE of AST increased. Twenty-nine (9.1%) subjects experienced hepatotoxicity AEs; 8.1% (26 subjects) were treatment related hepatotoxicity AEs. There were 5 SAEs (1.6%) in the cabozantinib in combination with nivolumab arm, all reported as resolved (80%) or resolved with sequelae (20%) with the use of corticosteroids. There were 13 (4.1%) Grade 3 AEs including the PTs hepatotoxicity (2.2%), hepatitis (0.9%), autoimmune hepatitis (0.6%) and hepatocellular injury (0.3%) and 1 (0.3%) Grade 4 AE of hepatotoxicity. Four subjects in the cabozantinib in combination with nivolumab arm met Hy's Law criteria of concurrent ALT or AST > 3× ULN with total bilirubin > 2×ULN elevation based on lab results within 30 days of last dose. These 4 subjects also reported concurrent ALT/AST and total bilirubin increases as AEs, of which 3 subjects had hepatotoxicity reported as an AE. All these 4 cases resolved with the use of corticosteroids. While patients treated with cabozantinib in combination with nivolumab have an increased risk of hepatotoxicity compared to cabozantinib monotherapy, these events were found to be manageable with patient monitoring, use of corticosteroids as treatment and dose modifications of cabozantinib and nivolumab. <u>HCC in adults who have previously been treated with sorafenib:</u> Elevations of liver enzymes are frequent in cabozantinib-treated subjects in Study XL184-309. Based on laboratory data, there was an increase in ALT in

Important potential risk	Risk-benefit impact
	73% (any grade) and 12% (Grade 3 to 4) of subjects, and an increase in AST in 73% (any grade) and 24% (Grade 3 to 4) of subjects treated with cabozantinib. All grade AEs of ALT increased and AST increased were experienced by 17% and 22%, respectively, of cabozantinib-treated subjects in Study XL184-309. Grade 3 or 4 AEs of ALT increased and AST increased were experienced by 5% and 12%, respectively, of subjects. One SAE of ALT increased and three SAEs of AST increased were reported. There were no confirmed cases of drug-induced liver injury with cabozantinib treatment. DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine (if radioactive iodine is an appropriate treatment): There were no ≥ Grade 3 events of hepatotoxicity. No subjects in the study met Hy's Law screening criteria for potential DILI. These events can have debilitating, disabling or fatal outcomes and therefore, hepatotoxicity is an important potential risk for cabozantinib. Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): Overall incidence of Hepatotoxicity (Grade ≥3) was 1.2% (95% CI: 0.5, 2.3) in CASSIOPE study. The incidence of Hepatotoxicity in third and later line therapy was 1.5% (5 subjects) and in second therapy group was 0.9% (3 subjects). Overall, 3 events reported were serious (1 event in second-line group and 2 events in third and later line group). One event reported in second-line group was fatal. A total of 5 events reported in 5 subjects were assessed as treatment related in the second-line (2 events) and third/ later line (3 events) groups. Of the 5 subjects, 3 subjects reported Hepatotoxicity and 1 subject each reported Hepatic failure and Hepatitis cholestatic of Grade 3-4. There were no Grade 5 events reported. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Ten (5.1%) subjects in cabozantinib arm in Study A021602 experienced hepatotoxicity AEs. The majority of AEs were of Grade 3 severity. The Grade 3 AEs included ascites (1.5%), hepatic encephalopathy (0.5%), hepatic failure (0.5%), portal hypertension (0.5%) and spontaneous bacterial peritonitis (0.5%). Grade 4 and Grade 5 events of hepatic failure (one each) were also reported which were assessed as not related to the cabozantinib treatment. Two AEs of ascites were of Grade 2 severity. The AEs of ALT increased and AST increased were experienced by 66% and 72% of subjects, respectively, in cabozantinib arm. Grade 3 AEs of AST increased was experienced by 3.1% and Grade 4 AEs of ALT increased was experienced by 0.5% of the subjects. No Grade 3 AEs were reported for ALT increased. The higher incidence of ALT increased and AST increased in Study A021602 may be because these adverse events are considered expected and their presence/absence should be solicited, per the study protocol. Further details of the risk are provided in Table 44.
Embryotoxicity	These events could be lethal to a human embryo or produce serious congenital abnormalities. In advanced cancer populations, only a small number of female patients are expected to be of child-bearing potential, though a higher number of male patients would be of reproductive potential. 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. Embryotoxicity is therefore an important potential risk for cabozantinib. No events relevant to embryotoxicity were reported from CASSIOPE study. In Study A021602, overall incidence of embryotoxicity was 0.5% (95% CI: 0.01, 2.82) . One subject experienced serious TEAE of atrial septal defect (Grade 3) which was assessed as treatment related. There was no explanation

Important potential risk	Risk-benefit impact
	offered as to how study drug might induce an anatomic lesion in the chambers of the heart. No similar events have been reported in the literature. Previous myocardial infarction and history of poor wound healing offer alternative explanations for or may have contributed to atrial septal defect. Further details of the risk are provided in Table 45.
Carcinogenicity	The risk of carcinogenicity was identified based on nonclinical data. In a 2-year rat carcinogenicity study, administration of cabozantinib resulted in benign and malignant pheochromocytoma in males and females at doses equivalent to doses less than the 60 mg human dose in RCC and HCC patients. Advanced RCC monotherapy: Four subjects (1.2%) in the cabozantinib arm of Study XL184-308 experienced second primary malignancies that were not related to RCC: one subject each experienced AEs of adenocarcinoma, adenocarcinoma of colon, basal cell carcinoma and chronic lymphocytic leukaemia. Three events were SAEs. No subjects in the cabozantinib arm of Study A031203 experienced second primary malignancies. Advanced RCC in combination with nivolumab in treatment-naïve adults: Six subjects (1.9%) in the cabozantinib in combination with nivolumab arm of Study CA2099ER experienced second primary malignancies that were not related to RCC. The following second primary malignancies included basal cell carcinoma (2), squamous cell carcinoma (2), bladder neoplasm (1), and keratoacanthoma (1). None of these events were assessed as related to treatment. Three events were SAEs, all reported as resolved. HCC in adults who have previously been treated with sorafenib: Four subjects (0.9%) in the cabozantinib arm of Study XL184-309 experienced second primary malignancies that were not related to HCC: two subjects experienced AEs of squamous cell carcinoma assessed as not related to cabozantinib, one subject experienced a new onset second primary malignancy of acute lymphocytic leukaemia assessed as not related and one subject with a prior history of breast cancer experienced a new onset second primary malignancy of intraductal proliferative breast lesion assessed as not related. Two events were SAEs. DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine (if radioactive iodine is an appropriate treatment): The overall incidence of malignancies grouped under the system organ class (SOC) "neoplasms benign, malignant and unspecified was 4.0% in the cabozantinib only arm and 6.5% in the placebo arm. All of the reported AEs in both arms were related to DTC including metastases to various organs. No preferred terms were suggestive of secondary malignancies. These events can have debilitating, disabling or fatal outcomes and therefore carcinogenicity is an important potential risk for cabozantinib. Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): The overall incidence of malignancies was 3.5% (95% CI: 2.3, 5.2) in CASSIOPE study. The incidence of malignancies were similar when cabozantinib was used as second-line (12 subjects (3.6%)) and third/ later line therapy (12 subjects (3.5%)). Overall, 19 events reported were serious of which 6 events were fatal (2 events in second-line group and 4 events third/later line group). Two events reported in 2 subjects in third and later line group were assessed as treatment related. Of the 19 events, 14 events were related to disease progression/underlying tumour. The following serious TEAE preferred terms were reported in one subject each: Gallbladder neoplasm, invasive ductal breast carcinoma, lung neoplasm, malignant neuroendocrine carcinoma of the skin and lyphangiosis carcinomatosa. These were assessed as not related to cabozantinib. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602):

Important potential risk	Risk-benefit impact
	No subjects in the cabozantinib arm of Study A021602 experienced primary or secondary malignancies. Further details of the risk are provided in Table 46.

ADR=adverse drug reaction; AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CI=confidence interval; DILI=drug-induced liver injury; DLP=data lock point; DTC=differentiated thyroid carcinoma; ETM=event to monitor; HCC=hepatocellular carcinoma; HLT=high level term; PT=preferred term; RCC=renal cell carcinoma; RMP=risk management plan; SAE=serious adverse event; SOC=system organ class; TEAE=treatment-emergent adverse event; ULN=upper limit of normal; VEGF=Vascular endothelial growth factor.

a comprises four subjects with AEs of acute renal failure and one subject with an AE of chronic renal failure, all of which were serious.

b in addition, there was a Grade 3 SAE of 'acute renal failure' not related to study treatment reported in the cabozantinib arm identified from other sources.

c comprises one subject with a Grade 1 AE of acute renal failure and one subject with a Grade 2 AE of chronic renal failure.

Source for Study A021602: Incidence of TEAEs by ETM, PT and Severity (sorted by alphabetic order), with CI - Safety Population, A021602 study, RMP Analyses (DLP 24 August 2023).

Missing information:

There are no risks considered important for inclusion as missing information for this RMP.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Summaries of the characterisation of the important identified risks are provided in Table 36 to Table 42. The important identified risks are considered the same for all indications. The important identified risks of Gastrointestinal and nongastrointestinal fistula, posterior reversible encephalopathy syndrome (PRES) and osteonecrosis have not been observed for HCC. Posterior reversible encephalopathy syndrome has not been observed for the RCC first-line indication either as cabozantinib monotherapy or in combination with nivolumab. Summaries of the characterisation of the important potential risks are provided in Table 43 to Table 46. For Studies A031203 and A021602, data pertaining to the outcomes of the serious adverse events (SAEs) were not available. The cumulative incidence is available for monotherapy studies (i.e. XL184-308, A031203, XL184-309, XL184-311 and A021602) only.

Table 36 Important Identified Risk – Gastrointestinal Perforation

Identified risk	Gastrointestinal perforation
Potential mechanisms:	Vascular endothelial growth factor plays a role in maintaining mucosal homeostasis and mucosal epithelialisation after mucosal damage. In mice inhibition of VEGF signalling caused regression of capillaries of intestinal villi which could contribute to perforation in the presence of inflammation [**Error! Reference source not found.**]. GI perforations could be the result of tumour necrosis in some cases when tumour has invaded or encased the GI tract.
Evidence source(s) and strength of evidence:	The risk of GI perforation was identified based on data from cabozantinib clinical studies. Additional data confirming the risk were from postmarketing use of cabozantinib. Gastrointestinal perforation has been reported in Studies XL184-308, A031203, CA2099ER, XL184-309, XL184-311, A021602 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.

Identified risk	Gastrointestinal perforation
Characterisation of the risk: Frequency	Cumulatively in clinical trials conducted in HCC, RCC, DTC, and NET the incidence of GI perforation is 1.3%. Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Incidence 0.9% (95% CI: 0.1, 2.6) Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): Incidence 2.6% (95% CI: 0.3, 8.9) Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): Incidence 1.3% (95% CI: 0.3, 3.2) HCC in adults who have previously been treated with sorafenib (Study XL184-309): Incidence 0.9% (95% CI: 0.2, 2.2)[a] DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): Incidence 0.8% (95% CI: 0.02, 4.38) Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): Incidence 0.7% (95% CI: 0.2, 1.7) Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Incidence 0.5% (95% CI: 0.01, 2.82)
Characterisation of the risk: Seriousness/outcomes	Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Serious: 3 events Resolved: 66.7% Resolved with sequelae: 33.3% Not resolved: 0% Fatal: 0% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): Serious: 2 subjects Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): Serious: 4 events Resolved: 50% Resolved with sequelae: 0% Not resolved: 0% Fatal: 50% HCC in adults who have previously been treated with sorafenib (Study XL184-309): Serious: 6 events Resolved: 67% Resolved with sequelae: 17% Not resolved: 17% Fatal: 0% DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): Serious: 1 subject Resolved: 100% Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): Total TEAEs: 5 Serious TEAEs: 5 (5/5-100%) Resolved TEAEs: 4 (4/5-80%)

Identified risk	Gastrointestinal perforation
	Resolved with sequelae TEAE: 1 (1/5-20%) Not resolved: 0 Fatal: 0 Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Total TEAE: 1 Serious TEAE: 1 (1/1-100%) Fatal: 0
Characterisation of the risk: Severity and nature of risk	Cumulatively in clinical trials in RCC, HCC and DTC, severe cases included 0.5% Grade 4 and 1 fatal case of jejunal perforation (0.1%). Considering both clinical trials and postmarketing experience, GI perforations in both large and small intestine.as well as gastric perforation have been observed. They usually occur after several months of cabozantinib treatment (average time to onset in DTC XL184-311 :13.8 weeks) and often led to treatment discontinuation. Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): 3 of 331 (0.9%) subjects: Incidence (by highest grade reported): Grade 1: 0.3% Grade 2: 0% Grade 3: 0.6% Grade 4: 0% Grade 5: 0% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): 2 of 78 (2.6%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0% Grade 4: 2.6%[b] Grade 5: 0% Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): 4 of 320 (1.3%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0.3% Grade 4: 0.6% Grade 5: 0.3% HCC in adults who have previously been treated with sorafenib (Study XL184-309): 4 of 467 (0.9%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0.4% Grade 4: 0.4% Grade 5: 0% DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): 1 of 125 (0.8%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0%

Identified risk	Gastrointestinal perforation
	Grade 3: 0.8% Grade 4: 0% Grade 5: 0% Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): 5 of 679 (0.7%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0.4% Grade 4: 0.3% Grade 5: 0% Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): 1 of 195 (0.5%) subjects: Grade 1: 0% Grade 2: 0% Grade 3: 0.5% Grade 4: 0% Grade 5: 0%
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 GI 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.
Preventability:	While certain risk factors have been identified that may help reduce the incidence of GI perforation, there are no data to suggest that avoiding use in such at risk patients will eliminate the potential for events of GI perforation to occur.
Impact on the risk-benefit balance of the product:	Events as described, including intra-abdominal and pelvic abscess that are linked pathophysiologically to GI perforations, can have debilitating, disabling or fatal outcomes. The risk minimisation measures discussed in Part V are thought to satisfactorily minimise the risk of GI perforation.
Public health impact:	Gastrointestinal perforations may be serious or fatal events and can lead to hospitalisation and often require surgical repair. Advanced RCC monotherapy in adults The incidence of GI perforation was low in the cabozantinib treatment arm (three subjects (0.9%)) of Study XL184-308. No events in the cabozantinib arm were life-threatening or fatal. The incidence of GI perforation in subjects exposed to cabozantinib (0.9%) in Study XL184-308 is consistent with the published overall incidence in cancer patients (1.3%) [**Error! Reference source not found.**] and comparable to the risk seen with other VEGF pathway inhibitors [**Error! Reference source not found.**, **Error! Reference source not found.**,**Error! Reference source not found.**]. The incidence of GI perforation was low in the cabozantinib treatment arm (two subjects (2.6%)) of Study A031203. Both events were Grade 4, serious and treatment related. Given that the RCC patient population is limited, the observed frequency for GI perforation is ≤2.6% and the incidence of SAEs of GI perforation is 0.15% in the postmarketing setting for Cabometyx, the impact on public health is expected to be small. Advanced RCC in combination with nivolumab in treatment-naïve adults The incidence of GI perforation was low in the cabozantinib and nivolumab treatment arm (four subjects (1.3%)) of Study CA2099ER. All four of the events

Identified risk	Gastrointestinal perforation
	of GI perforation in the cabozantinib and nivolumab arm were serious and of ≥Grade 3 severity. Two of the subjects with treatment related AEs recovered. For the other two subjects the outcome was fatal, including Grade 5 intestinal perforation (not considered treatment related) and Grade 4 intestinal perforation in a subject who died 51 days after the last dose of nivolumab and 46 days after the last dose of cabozantinib. The event was considered by the investigator to be related to study drug toxicity. Given that the RCC population is limited, the observed frequency for GI perforation for cabozantinib in combination with nivolumab is 1.3% in Study CA2099ER and the incidence of SAEs of GI perforation is 0.15% in the postmarketing setting for Cabometyx, the impact on public health is expected to be small. HCC in adults who have previously been treated with sorafenib The incidence of GI perforation was low in the cabozantinib treatment arm (four subjects (0.9%)) of Study XL184-309. No events were fatal. The incidence of GI perforation in subjects with HCC exposed to cabozantinib in Study XL184-309 is comparable to that seen with sorafenib in HCC [**Error! Reference source not found.**]. Given that the HCC population is limited, the observed frequency for GI perforation is 0.9% in Study XL184-309. Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311) The incidence of GI perforation was low (one subject (0.8%)) The event occurred 97 days after the first dose of cabozantinib and resolved on Day 105. The event was considered Grade 4, treatment related and led to study drug discontinuation. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602) The incidence of GI perforation was low in the cabozantinib arm of the Study A021602 (one subject (0.5%)). The reported event was spontaneous bacterial peritonitis which was considered serious, Grade 3 and treatment related. The reporting rate of SAEs of GI perforation in the postmarketing setting for Cabometyx was 0.15% (DLP of previous PSUR (i.e. 28 November 2022)). No significant data has been received for GI perforation from Study A021602, hence, the impact on public health is expected to be small.
MedDRA PTs:	MedDRA terms can be found in Annex 7.

AE=adverse event; CI=confidence interval; DLP=data lock point; DTC=differentiated thyroid carcinoma; ETM=event to monitor; EU=European Union; GI=gastrointestinal; HCC=hepatocellular carcinoma; MedDRA=Medical Dictionary for Regulatory Activities; NET=neuroendocrine tumour; PASS=post-authorisation-authorisation safety study; PSUR=periodic safety update report; PT=preferred term; RCC=renal cell carcinoma; RMP=risk management plan; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor.

a the subject who experienced large intestine perforation and duodenal perforation also experienced a Grade 3 SAE of gallbladder perforation not related to study treatment, which was not captured under the ETM of gastrointestinal perforation (Subject [redacted]).

b one of these subjects experienced a Grade 4 AE of jejunal perforation due to jejunal mass eroding adjacent bowel as reported in the clinical database; however, follow-up reporting indicates that the investigator later reassessed the cause of death as jejunal perforation (Grade 5 AE related to study treatment).

Source for Study A021602: Incidence of TEAEs by ETM, PT and Severity (sorted by alphabetic order), with CI - Safety Population, A021602 study, RMP Analyses (DLP 24 August 2023).

Table 37 Important Identified Risk – Gastrointestinal and Nongastrointestinal Fistula

Identified risk	**Gastrointestinal and nongastrointestinal fistula**
Potential mechanisms:	Fistula formation may also be related to VEGF inhibition with impaired healing of epithelial barrier disruptions. The inhibition of neovascularisation and re-epithelialisation may be implicated in poor healing and subsequent fistula formation [**Error! Reference source not found.**]. GI perforations (see above) or mucosal inflammation could also lead to fistulae formation. Necrosis of infiltrating tumour could also potentially lead to fistulae formation.
Evidence source(s) and strength of evidence:	The risk of fistula was identified based on data 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 A021602, 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.
Characterisation of the risk: Frequency	Cumulatively in clinical trials conducted in HCC, RCC, DTC and NET, the incidence of fistula is 1.4%. Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Incidence 1.2% (95% CI: 0.3, 3.0) Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): No subjects in Study A031203 developed GI and nonGI fistula. Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): Incidence 0.9% (95% CI: 0.2, 2.7) HCC in adults who have previously been treated with sorafenib (Study XL184-309): Incidence 1.3% (95% CI: 0.5, 2.8) Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): None Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): Incidence: 0.6% (95% CI: 0.2, 1.5) Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Incidence 1.0% (95% CI: 0.12, 3.66)
Characterisation of the risk: Seriousness/outcomes	Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Serious: 4 events Resolved: 100% Resolved with sequelae: 0% Not resolved: 0% Fatal: 0% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): Serious: 0 subjects Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): Serious: 2 events Resolved: 100% Resolved with sequelae: 0% Not resolved: 0% Fatal: 0% HCC in adults who have previously been treated with sorafenib: (Study XL184-309): Serious: 3 events Resolved: 33% Resolved with sequelae: 0% Not resolved: 33%

Identified risk	Gastrointestinal and nongastrointestinal fistula
	Fatal: 33% Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): Total TEAEs: 4 Serious TEAEs: 2 (2/4-50%) Resolved TEAEs: 4 (4/4-100%) Resolved with sequelae: 0 Not resolved: 0 Fatal: 0 Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Total TEAEs: 2 Serious TEAEs: 0 Fatal: 0
Characterisation of the risk: Severity and nature of risk	Cumulatively in clinical trials on RCC, HCC and DTC, severe cases included one fatal case (0.1%) of oesophagobronchial fistula. Cases of serious fistula and fatal acquired tracheo-oesophageal fistula have been described in an investigator sponsored study conducted in salivary gland cancer and occurred in a zone previously exposed to high dose radiotherapy. Considering both clinical trials and postmarketing experience, anal fistula are the most commonly reported fistulae. Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): 4 of 331 subjects (1.2%) Incidence (by highest grade reported): Grade 1: 0.3% Grade 2: 0.6% Grade 3: 0.3% Grade 4: 0% Grade 5: 0% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): 0 of 78 subjects (0%) Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0% Grade 4: 0% Grade 5: 0% Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): 3 of 320 subjects (0.9%) Incidence (by highest grade reported): Grade 1: 0.6% Grade 2: 0.3% Grade 3: 0% Grade 4: 0% Grade 5: 0% HCC in adults who have previously been treated with sorafenib: (Study XL184-309): 6 of 467 subjects (1.3%) Incidence (by highest grade reported) Grade 1: 0.2% Grade 2: 0.4% Grade 3: 0.4% Grade 4: 0% Grade 5: 0.2% Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)):

Identified risk	**Gastrointestinal and nongastrointestinal fistula**
	4 of 679 (0.6%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0.3% Grade 3: 0.3% Grade 4: 0% Grade 5: 0% Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): 2 of 195 (1.0%) subjects: Incidence (by highest grade reported): Grade 1: 0.5% Grade 2: 0.5% Grade 3: 0% Grade 4: 0% Grade 5: 0%
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 nonGI fistulae include infiltration of viscera by tumour (spread of tumour into the abdomen), radiation therapy and incomplete healing after surgery.
Preventability:	There are no data to suggest that avoiding use in such at risk patients will eliminate the potential for events of fistula to occur.
Impact on the risk-benefit balance of the product:	Events as described, including intra-abdominal and pelvic abscess that are linked pathophysiologically to fistulas, can have debilitating, disabling or fatal outcomes.
Public health impact:	Fistulae may lead to hospitalisation and may result in long-term morbidity. They can lead to secondary and chronic infections and can be fatal. Advanced RCC in adults The incidence of fistulae in the cabozantinib arm of Study XL184-308 was 1.2%, while no subjects in Study A031203 developed fistula. No events in Study XL184-308 were life-threatening or fatal. This is comparable to the risk seen with other VEGF-TKIs in RCC [**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**]. Given that the RCC patient population is limited, the observed frequency for fistulae is ≤1.2% and the incidence of SAEs of fistulae is 0.07% in the postmarketing setting for Cabometyx, the impact on public health is expected to be small. Advanced RCC in combination with nivolumab in treatment-naïve adults The incidence of fistulae was low in the cabozantinib and nivolumab treatment arm (three subjects (0.9%)) of Study CA2099ER with one of the events assessed as related to treatment. Two of the three events of fistulae in the cabozantinib and nivolumab arm were serious. None of the AEs were of ≥Grade 3 severity. Given that the RCC population is limited, the observed frequency for fistulae for cabozantinib in combination with nivolumab is 0.9% in Study CA2099ER and the incidence of SAEs of fistulae is 0.07% in the postmarketing setting for Cabometyx, the impact on public health is expected to be small. HCC in adults who have previously been treated with sorafenib The incidence of fistulae in the cabozantinib arm of Study XL184-309 was 1.3%. One subject experienced a Grade 5 AE of oesophagobronchial fistula, which was assessed as related to study treatment, while two subjects experienced Grade 3 AEs of anal fistula. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602)

Identified risk	Gastrointestinal and nongastrointestinal fistula
	The incidence of fistulae in the cabozantinib arm of Study A021602 was 1.0% (two subjects). Both the AEs (i.e. anal fistula and biliary fistula) were non-serious, and treatment related. None of the two AEs were of ≥ Grade 3 severity. The reporting rate of SAEs of fistulae in the postmarketing setting for Cabometyx was 0.07% (DLP of previous PSUR (i.e. 28 November 2022)). No significant data has been received for GI perforation from Study A021602, hence, the impact on public health is expected to be small.
MedDRA PTs:	MedDRA terms can be found in Annex 7.

AE=adverse event; CI=confidence interval; DLP=data lock point; ETM=event to monitor; DTC=differentiated thyroid carcinoma; GI=gastrointestinal; HCC=hepatocellular carcinoma; MedDRA=Medical Dictionary for Regulatory Activities; NET=neuroendocrine tumour; PASS=post-authorisation safety study; PSUR=periodic safety update report; PT=preferred term; RCC=renal cell carcinoma; RMP=risk management plan; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor.

Source for Study A021602 Incidence of TEAEs by ETM, PT and Severity (sorted by alphabetic order), with CI - Safety Population, A021602 study, RMP Analyses (DLP 24 August 2023).

Table 38 Important Identified Risk – Thromboembolic Events

Identified risk	Thromboembolic events
Potential mechanisms:	Inhibition of VEGF pathways could diminish the regenerative capacity of endothelial cells leading to defects that could expose platelets and clotting factors to procoagulant phospholipids in the intercellular matrix. Inhibition of endothelial derived nitric oxide formation and PGI2 may also predispose to thromboembolic events [**Error! Reference source not found.**]. Blockade of VEGF pathways may also lead to diminished secretion of inhibitors of clotting and thrombus formation [**Error! Reference source not found.**]. Treatment with VEGF TKIs may cause the release of procoagulants from the tumour into the blood stream or increase the expression of pro-inflammatory cytokines leading to in situ thrombus formation [**Error! Reference source not found.**].
Evidence source(s) and strength of evidence:	The risk of thromboembolic events was identified based on data 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 were reported in Studies XL184-308, A031203, CA2099ER,XL184-309 and A021602. 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 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.
Characterisation of the risk: Frequency	Cumulatively in clinical trials conducted in HCC, RCC, DTC and NET, the incidence of venous and mixed thromboembolic events was 7.7%. Pulmonary embolism was reported with a frequency of 2.7%, embolism with a frequency of 1.5% and deep vein thrombosis with a frequency of 1.3%. Cumulatively in clinical trials conducted in HCC, RCC, DTC and NET, the incidence of ATEs was 1.4%. Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Arterial thromboembolic events: Incidence 0.9% (95% CI: 0.1, 2.6) Venous thromboembolic events: Incidence 7.3% (95% CI: 4.7, 10.6 Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): In Study A031203, “thromboembolic event” was generally reported as the nonspecific PT of embolism, and therefore not captured in the formal summaries of VTEs and ATEs. Nine subjects reported a PT of embolism.

Identified risk	Thromboembolic events
	Though no subjects reported an ATE, one subject with a reported event of embolism was found to have experienced stroke, thrombosis of the axillary artery and thrombosis of the left internal carotid artery. Another of the subjects with embolism also reported a VTE of superior vena cava syndrome. Of the nine subjects with embolism, five were determined to have a pulmonary embolism. Further review of the uncoded AEs and data in the cabozantinib Global Safety Database identified two more subjects with pulmonary embolism (seven total). Including data from all sources, 11 subjects had a VTE of any grade. Arterial thromboembolic events: Incidence: 0%[a]. Venous and mixed/unspecified thrombotic events: Incidence 1.3% (95% CI: 0.0, 6.9)[b] Embolism: Incidence 11.5%[c],[d] Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): Arterial thrombotic events: Incidence 2.2% (95% CI: 0.9, 4.5) Venous and mixed/unspecified thrombotic events: Incidence 11.3% (95% CI: 8.0, 15.2) HCC in adults who have previously been treated with sorafenib (Study XL184-309): Arterial thrombotic events: Incidence 2.6% (95% CI: 1.3, 4.5) [a] Venous and mixed/unspecified thrombotic events: Incidence 3.9% (95% CI: 2.3, 6.0) Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): Arterial thrombotic events: One case of aortic thrombosis Grade 1(incidence 0.8% (0.02-4.38) as well as 2 cases of myocardial infarction (0.2%) including a Grade 4 were reported. Venous and mixed/unspecified thrombotic events: Incidence 9.6% (5.06 - 16.17). Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): Incidence: 7.1% (95% CI: 5.3, 9.3) Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Arterial thrombotic events: Incidence 1.5% (95% CI: 0.32, 4.43) Venous and mixed/unspecified thrombotic events: Incidence 8.7% (95% CI: 5.16, 13.59)
Characterisation of the risk: Seriousness/outcomes	Cumulatively in clinical trials in RCC, HCC and DTC, severe cases included four fatal cases (0.4%) linked to pulmonary embolism, portal vein thrombosis or cerebrovascular accident. In Study XL184-311, median time to onset of venous or arterial thrombosis was 8.8 weeks. Considering both clinical trials and postmarketing experience, pulmonary embolism, thrombosis including deep venous thrombosis and cerebrovascular accident are the most commonly reported thromboembolic venous or arterial events respectively. Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): **Arterial thromboembolic events:** Serious: 2 events Resolved: 50% Resolved with sequelae: 0% Not resolved: 50% Fatal: 0% **Venous thromboembolic events:** Serious: 11 events Resolved: 18.2% Resolved with sequelae: 18.2% Not resolved: 63.6%

Identified risk	Thromboembolic events
	Fatal: 0% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): **Arterial thromboembolic events:** Serious: 0 subjects[a] **Venous thromboembolic events:** Serious: 0 subjects **Embolism:** Serious: 7 subjects[d] Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): **Arterial thrombotic events:** Serious: 5 events Resolved: 100% Resolved with sequelae: 0% Resolving: 0% Not resolved: 0% Fatal: 0% **Venous and mixed/unspecified thrombotic events:** Serious: 17 events Resolved: 64.7% Resolved with sequelae: 11.8% Resolving: 11.8% Not resolved: 5.9% Fatal: 0% HCC in adults who have previously been treated with sorafenib (Study XL184-309): **Arterial thrombotic events:** Serious: 11 events Resolved: 36% Resolved with sequelae: 18% Not resolved: 18% Fatal: 27% **Venous and mixed/unspecified thrombotic events:** Serious: 11 events Resolved: 45% Resolved with sequelae: 0% Not resolved: 36% Fatal: 18% Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): **Arterial thrombotic events:** Serious: 0 events **Venous and mixed/unspecified thrombotic events:** Serious: 5 events Resolved: 40% Resolved with sequelae: 0% Not resolved: 40% Fatal: 20% Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): Total TEAEs: 55 Serious TEAEs: 31 (31/55-56%) Resolved TEAEs: 21 (21/55-38%) Resolving TEAEs: 4 (4/55-7%) Resolved with sequelae TEAE: 1 (1/55-2%) Not resolved TEAEs: 21 (21/55-38%) Fatal TEAEs: 6 (6/55-11%)

Identified risk	Thromboembolic events
	Unknown TEAEs: 2 (2/55-3.6%) Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): **Arterial thrombotic events:** Total TEAEs: 4 Serious TEAEs: 4 (4/4-100%) Fatal: 0 **Venous and mixed/unspecified thrombotic events:** Total TEAEs: 20 Serious TEAEs: 11 (11/20-55%) Fatal: 0
Characterisation of the risk: Severity and nature of risk	Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): **Arterial thromboembolic events:** 3 of 331 (0.9%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 1% Grade 4: 0% Grade 5: 0% **Venous thromboembolic events:** 24 of 331 (7.3%) subjects: Incidence (by highest grade reported): Grade 1: 1% Grade 2: 3% Grade 3: 3% Grade 4: 0.3% Grade 5: 0% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): **Arterial thromboembolic events:** 0 of 78 (0%) subjects: Incidence (by highest grade reported)[a]: Grade 1: 0% Grade 2: 0% Grade 3: 0% Grade 4: 0% Grade 5: 0% **Venous and mixed/unspecified thrombotic events:** 1 of 78 (1.3%) subjects. Incidence (by highest grade reported)[b]: Grade 1: 0% Grade 2: 0% Grade 3: 1.3% Grade 4: 0% Grade 5: 0% **Embolism:** 9 of 78 (11.5%) subjects. Incidence (by highest grade reported)[c][d]: Grade 1: 0% Grade 2: 3.8% Grade 3: 5.1%[d] Grade 4: 2.6% Grade 5: 0% Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): **Arterial thrombotic events:** 7 of 320 (2.2%) subjects. Incidence (by highest grade reported): Grade 1: 0.3% Grade 2: 0.9% Grade 3: 0.9%

Identified risk	Thromboembolic events
	Grade 4: 0.0% Grade 5: 0.0% **Venous and mixed/unspecified thrombotic events:** 36 of 320 (11.3%) subjects. Incidence (by highest grade reported): Grade 1: 1.6% Grade 2: 2.5% Grade 3: 5.6% Grade 4: 1.6% Grade 5: 0.0% HCC in adults who have previously been treated with sorafenib (Study XL184-309): **Arterial thrombotic events:** 12 of 467 (2.6%) [a] subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0.2% Grade 3: 1.1% Grade 4: 0.6% Grade 5: 0.6% **Venous and mixed/unspecified thrombotic events:** 18 of 467 (3.9%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0.6% Grade 3: 2.6% Grade 4: 0.2% Grade 5: 0.4% Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): **Arterial thrombotic events:** 1 of 125 (0.8%) Grade 1: 0.8% Grade 2: 0% Grade 3: 0% Grade 4: 0% Grade 5: 0% **Venous and mixed/unspecified thrombotic events:** 12 of 125 (9.6%) subjects: Incidence (by highest grade reported): Grade 1: 0.8 % Grade 2: 4.8% Grade 3: 3.2% Grade 4: 0% Grade 5: 0.8 % Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): 48 of 679 (7.1%) subjects: Incidence (by highest grade reported): Grade 1: 0.7 % Grade 2: 3.7% Grade 3: 2.1% Grade 4: 0.4% Grade 5: 0.9 % Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): **Arterial thrombotic events:** 3 of 195 (1.5%) subjects Grade 1: 0% Grade 2: 0% Grade 3: 0.5%

Identified risk	Thromboembolic events
	Grade 4: 1.0% Grade 5: 0% **Venous and mixed/unspecified thrombotic events:** 17 of 195 (8.7%) subjects: Incidence (by highest grade reported): Grade 1: 0.5% Grade 2: 3.6% Grade 3: 4.1% Grade 4: 1.5% Grade 5: 0%
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).
Preventability:	Risk factors have been identified that may help reduce the incidence of thrombotic events; there are no data to suggest that avoiding use in such at risk patients will eliminate the potential for thrombotic events to occur. Medical management and the use of anticoagulants are proven to be useful in the mitigation of the thrombotic risk in cancer patients and in those patients at risk.
Impact on the risk-benefit balance of the product:	Events as described can have debilitating, disabling or fatal outcomes.
Public health impact:	Arterial thrombotic events, particularly myocardial infarctions and stroke can be fatal or lead to long-term morbidity and disability. Venous thrombotic events such as pulmonary emboli can also be fatal. Treatment of venous thrombosis and pulmonary emboli with anticoagulants can lead to haemorrhage. Advanced RCC monotherapy in adults The incidence of ATEs was low in the cabozantinib arm (0.9%) of Study XL184-308 and one subject in Study A031203 developed ATEs. The observed incidence of ATEs in subjects exposed to cabozantinib (≤0.9%) in Studies XL184-308 and A031203 is consistent with the published overall incidence of ATEs in RCC patients [**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**,**Error! Reference source not found.**]. Given that the RCC patient population is limited, the observed frequency for ATEs is low in Studies XL184-308 and A031203 and the incidence of ATEs is 0.19% in the postmarketing setting for Cabometyx, the impact on public health is expected to be small. While the incidence of all grade all causality events of VTE events was higher (7.3%) in the cabozantinib treatment arm of Study XL184-308 compared to that seen with other VEGF pathway inhibitors, the incidence of G3/4 events (3.6%) is similar to that seen with other VEGF pathway inhibitors [**Error! Reference source not found.**,**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**]. In Study A031203, one subject in the cabozantinib arm experienced a VTE (a Grade 3 non-serious event of superior vena cava syndrome). The incidence

Identified risk	Thromboembolic events
	of all grade all causality events of embolism was 11.5% in the cabozantinib arm (7.7% ≥Grade 3). Two subjects had Grade 4 events of pulmonary embolism, which were both assessed as treatment-related. Given that the RCC patient population is limited, the observed frequency for VTEs is 7.3% (Grades 1 to 4) in Study XL184-308 and 1.3% (1.3% Grade 3) in Study A031203 and the incidence of VTEs is 0.76% in the postmarketing setting for Cabometyx, the impact on public health is expected to be small. <u>Advanced RCC in combination with nivolumab in treatment-naïve adults</u> The incidence of ATEs was low in the cabozantinib and nivolumab treatment arm (seven subjects (2.2%)) of Study CA2099ER. Five SAEs were reported in the cabozantinib and nivolumab arm. Three of the ATEs were of Grade 3 severity including myocardial infarction (0.6%) and ischaemic stroke (0.3%). Given that the RCC patient population is limited, the observed frequency for ATEs is low in Study CA2099ER and the incidence of ATEs is 0.19% in the postmarketing setting for Cabometyx, the impact on public health is expected to be small. In the cabozantinib and nivolumab treatment arm of Study CA2099ER the incidence of VTEs was 11.3% (36 subjects). A total of 17 SAEs (5.3%) were reported in subjects treated with cabozantinib and nivolumab. The most frequently reported VTE was pulmonary embolism 20 AEs (6.3%), of which 17 (5.3%) ≥Grade 3 severity and 9 (2.8%) of these severe AEs were considered treatment related. Given that the RCC population is limited, the observed frequency for VTEs is 11.3% (5.6% Grade 3 and 1.6% Grade 4) in Study CA2099ER and the incidence of VTEs is 0.76% in the postmarketing setting for Cabometyx, the impact on public health is expected to be small. <u>HCC in adults who have previously been treated with sorafenib</u> The incidence of ATEs was 2.6% [a] in the cabozantinib arm of Study XL184-309. Given that the HCC patient population is limited, the observed frequency for ATEs is 2.6% in Study XL184-309 and the incidence of ATEs is 0.19% in the postmarketing setting for Cabometyx, the impact on public health is expected to be small. The incidence of VTEs was 3.9% in the cabozantinib arm of Study XL184-309. Given that the HCC patient population is limited, the observed frequency for VTEs is 3.9% in Study XL184-309. <u>Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311)</u> The incidences of ATEs and VTEs were 0.8% and 9.6%, respectively, in the cabozantinib arm of Study XL184-311 compared to 0 in the placebo arm. One subject experienced an aortic thrombosis (Grade 1) at Day 113, which resolved on Day 117. Of the 12 subjects that experienced venous and mixed/unspecified thrombotic events, 4 subjects (3.2%) had Grade 3 to 4 events (pulmonary embolism [n=3] and deep vein thrombosis [n=1]) and 1 subject had a Grade 5 event (pulmonary embolism). <u>Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602)</u> The incidences of ATEs and VTEs were 1.5% and 8.7%, respectively, in the cabozantinib arm of Study A021602. Three ATEs of acute myocardial infarction, coronary artery occlusion, and myocardial infarction were of Grade 4 severity and one ATE of embolism arterial was of Grade 3 severity. The ATE of coronary artery occlusion was not considered related to cabozantinib and the remaining all other ATEs were assessed as related to cabozantinib. Of the 17 subjects that experienced VTEs, three subjects (1.5%) had Grade 4 events (pulmonary embolism [n=2], and cerebrovascular accident [n=1], all these events were assessed as related to cabozantinib) and eight subjects had a Grade 3 event (embolism [n=4], embolism venous [n=1], and pulmonary embolism [n=4], all these events were assessed as related to cabozantinib). None of the ATEs and VTEs had a fatal outcome.

Identified risk	Thromboembolic events
	The reporting rate of ATEs and VTEs in the postmarketing setting for Cabometyx was 0.19% and 0.76%, respectively (DLP of previous PSUR (i.e. 28 November 2022)). No significant data has been received for thromboembolic events from Study A021602, hence, the impact on public health is expected to be small.
MedDRA PTs:	MedDRA terms can be found in Annex 7.

AE=adverse event; ATE=arterial thromboembolic event; CI=confidence interval; CTCAE=Common Terminology Criteria for Adverse Events; DLP=data lock point; DTC=differentiated thyroid carcinoma; ETM=event to monitor; HCC=hepatocellular carcinoma; MedDRA=Medical Dictionary for Regulatory Activities; NET=neuroendocrine tumour; PASS=post-authorisation safety study; PGI2=prostaglandin I2; PSUR=periodic safety update report; PT=preferred term; RCC=renal cell carcinoma; RMP=risk management plan; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor; VTE=venous thromboembolic event.

a three additional subjects experienced the following events that were not captured as part of the ETM of ATEs: Grade 4 intestinal ischaemia, Grade 5 ischaemic hepatitis and Grade 4 peripheral ischaemia.

b the nonspecific PT of embolism was reported in the clinical database for one subject. According to the cabozantinib Global Safety Database the subject experienced ATEs of stroke, thrombosis of the axillary artery, and thrombosis of the left internal carotid artery (seriousness and CTCAE grades unknown). The subject also experienced a concurrent venous thrombotic event of pulmonary embolism (see below).

c the nonspecific PT of embolism was reported in the clinical database for one subject. According to the cabozantinib Global Safety Database, the subject had an unspecified event described as thrombosis of the left internal jugular vein caused by compression of a large supraclavicular lymph node; this subject also had a Grade 3 event of superior vena cava syndrome (reported in this row).

d nonspecific PT of embolism was reported in the clinical database for a total of nine subjects (including the two in footnotes [b] and [c]), pulmonary embolism was identified for five of these subjects.

e in addition, two cabozantinib subjects with Grade 3 pulmonary embolism (one serious, one non-serious) were identified from other sources.

Source for Study A021602: Incidence of TEAEs by ETM, PT and Severity (sorted by alphabetic order), with CI - Safety Population, A021602 study, RMP Analyses (DLP 24 August 2023).

Table 39 Important Identified Risk – Haemorrhage (Grade ≥3)

Identified risk	Haemorrhage (Grade ≥3)
Potential mechanisms	Endothelial and perivascular cells are directly involved in coagulation homeostasis. Blockade of VEGF pathways in these cells could lead to diminished repair of endothelial cells leading to loss of integrity of vasculature. Inhibition of tissue repair due to decreased secretion of Tissue Factor may also play a role [**Error! Reference source not found.**]. Necrosis of tumour tissue that has invaded blood vessels could also lead to haemorrhage [**Error! Reference source not found.**].
Evidence source(s) and strength of evidence	The risk of haemorrhage (of 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, XL184-311 and A021602. A similar risk was observed with other VEGF TKIs 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.

Identified risk	**Haemorrhage (Grade ≥3)**
Characterisation of the risk: Frequency	Cumulatively in clinical trials conducted in HCC, RCC, DTC and NET, the incidence of haemorrhage all grades were 21.2% , the most frequently reported event was epistaxis (5.6%) that were mainly Grade 1-2. Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Incidence: 2.1% (95% CI: 0.8, 4.3) Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): Incidence: 5.1% Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): Incidence: 1.6% (95% CI: 0.5, 3.6) HCC in adults who have previously been treated with sorafenib (Study XL184-309): Incidence: 7.3% (95% CI: 5.1, 10.0) Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): Incidence: 2.5% (95% CI: 1.5, 4.0) Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Incidence: 2.1% (95% CI: 0.56, 5.17)
Characterisation of the risk: Seriousness/outcomes	Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Serious: 8 events Resolved: 37.5% Resolved with sequelae: 12.5% Not resolved: 25.0% Fatal: 25.0% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): Serious: 2 subjects Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): Serious: 3 events Resolved: 66.7% Resolved with sequelae: 0% Resolving: 0% Not resolved: 0% Fatal: 33.3% HCC in adults who have previously been treated with sorafenib (Study XL184-309): Serious: 31 events Resolved: 68% Resolved with sequelae: 3% Not resolved: 6% Resolving: 3% Fatal: 19% Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): Serious: 3 events Resolved: 66.7% Resolved with sequelae: 0% Not resolved: 0% Resolving: 0% Fatal: 33.3% Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): Total TEAEs: 19 Serious TEAEs: 12 (12/19-63%) Resolved TEAEs: 14 (14/19-74%) Resolved with sequelae: 0 Not resolved TEAEs: 2 (2/19-11%)

Identified risk	Haemorrhage (Grade ≥3)
	Fatal TEAEs: 3 (3/19-16%) Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Total TEAEs: 4 Serious TEAEs: 4 (4/4-100%) Fatal TEAE: 1 (1/4-25%)
Characterisation of the risk: Severity and nature of risk	Cumulatively in clinical trials on RCC, HCC,DTC and A021602, severe cases of haemorrhages included 9 fatal cases mainly associated with gastrointestinal, cerebral or tumour haemorrhage. In Study XL184-311 median time to onset of haemorrhage Grade 3 was 14 weeks. Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): 7 of 331 (2.1%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 1.2% Grade 4: 0.3% Grade 5: 0.6% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): 4 of 78 (5.1%) subjects: Incidence (by highest grade reported): Grade 1: NA Grade 2: NA Grade 3: 3.8% Grade 4: 1.3% Grade 5: 0% Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): 5 of 320 (1.6%) subjects Incidence (by highest grade reported): Grade 1: NA Grade 2: NA Grade 3: 0.6% Grade 4: 0.6% Grade 5: 0.3% HCC in adults who have previously been treated with sorafenib (Study XL184-309): 34 of 467 (7.3%) subjects Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 6% Grade 4: 0.4% Grade 5: 1% Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): 3 of 125 (2.4%) subjects Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 1.6% Grade 4: 0% Grade 5: 0.8 % Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): 17 of 679 (2.5%) subjects Incidence (by highest grade reported): Grade 1: 0%

Identified risk	Haemorrhage (Grade ≥3)
	Grade 2: 0% Grade 3: 1.9% Grade 4: 0.1% Grade 5: 0.4 % Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): 4 of 195 (2.1%) subjects Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 1.5% Grade 4: 0% Grade 5: 0.5 %
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.
Preventability:	Patients who may develop severe (Grade ≥3) haemorrhage following the exposure to cabozantinib cannot be identified prospectively. While certain risk factors have been identified that may help reduce the incidence of haemorrhage, there are no data to suggest that avoiding use in such at risk patients will eliminate the potential for events of haemorrhage to occur. Because of the risk of thrombotic events in patients with RCC or HCC and the association of thrombosis with therapy with inhibitors of the VEGF pathway, some patients treated with cabozantinib will require anticoagulation, which could increase the risk of haemorrhage.
Impact on the risk-benefit balance of the product:	Events as described can have debilitating, disabling or fatal outcomes.
Public health impact:	Haemorrhage may require transfusions with their attendant risks. Bleeding may be sudden and/or uncontrollable, leading to death. In the setting of thrombotic events, clinical judgement will be required to balance the opposing risks of thrombosis and haemorrhage and the need for cabozantinib therapy. Advanced RCC monotherapy in adults In Study XL184-308, the incidence of high-grade (≥Grade 3) haemorrhages was low (seven cabozantinib subjects (2.1%)). Two subjects had a Grade 5 event (one postprocedural (iatrogenic) haemorrhage and one extradural haematoma which occurred 31 days after last dose); both were assessed as unrelated to cabozantinib. The observed incidence of 2.1% in Study XL184-308 is similar to that seen with other VEGF pathway inhibitors [**Error! Reference source not found.**,**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**]. In Study A031203, the incidence of high-grade (≥Grade 3) haemorrhages was low (four cabozantinib-treated subjects (5.1%)). Two subjects had an SAE (one Grade 3 gastric haemorrhage and one Grade 4 haemorrhage intracranial; both were assessed as unrelated to cabozantinib). Given that the RCC patient population is limited and the observed frequency for haemorrhage is low in both studies, with an all grade serious event reporting rate of 0.23% in the postmarketing setting for Cabometyx, the impact on public health is expected to be small. Advanced RCC in combination with nivolumab in treatment-naïve adults The incidence of high grade (≥Grade 3) haemorrhages was low in the cabozantinib and nivolumab treatment arm (five subjects (1.6%)) of Study CA2099ER. Three SAEs of Grade ≥3 haemorrhages were reported, 2 were reported as resolved and 1

Identified risk	Haemorrhage (Grade ≥3)
	had a fatal outcome. One subject had a Grade 5 haemorrhagic AE of upper gastrointestinal haemorrhage manifested with hematemesis and melena but was not considered related to treatment. Given that the RCC patient population is limited and the observed frequency for Grade ≥3 haemorrhages is 1.6% in Study CA2099ER, with an all grade serious event reporting rate of 0.23% in the postmarketing setting for Cabometyx, the impact on public health is expected to be small. HCC in adults who have previously been treated with sorafenib In Study XL184-309, the incidence of high-grade (≥Grade 3) haemorrhages was 7.3%. Five subjects (1%) had Grade 5 haemorrhagic AEs: one subject with a treatment related AE of upper gastrointestinal haemorrhage and four subjects with AEs of intracranial tumour haemorrhage, oesophageal varices haemorrhage, oesophageal varices haemorrhage and tumour haemorrhage that were not considered related to cabozantinib. The observed incidence of 7.3% in Study XL183309 is lower than that seen with sorafenib in patients with HCC [**Error! Reference source not found.**]. Given that the HCC patient population is limited and the observed frequency for Grade ≥3 haemorrhage is 7.3% in Study XL184-309. Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311) The incidence of ≥Grade 3 haemorrhage was Grade 3-4 events 2.4 % (n=3) in the cabozantinib arm of Study XL184-311. Grade 3-4 events were reported (haemoptysis and haematoma with muscle haemorrhage). In 1 subject who had presented with aortic thrombosis Grade 1 on Day 113, an event of arterial haemorrhage from right carotid artery was reported on Day 117 leading to death (Grade 5). It was assessed as not related (consequence of soft tissue tumour lesions infiltrating blood vessels in the neck area). Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602) The incidence of ≥Grade 3 haemorrhage was 2.1 % (n=4) in the cabozantinib arm of Study A021602. In three subjects, Grade 3 events were haemorrhoidal haemorrhage, oesophageal haemorrhage and rectal haemorrhage. Oesophageal haemorrhage and rectal haemorrhage were considered related and haemorrhoidal haemorrhage was considered as not related to cabozantinib treatment. A Grade 5 event of gastrointestinal haemorrhage was also reported. The investigator assessed gastrointestinal haemorrhage as serious and possibly related to cabozantinib and possibly related to the underlying carcinoid tumour of the lung, and probably related to heparin therapy. The reporting rate of all grade serious events of haemorrhage in the postmarketing setting for Cabometyx was 0.23% (DLP of previous PSUR (i.e. 28 November 2022)). Given the observed frequency of haemorrhage in Study A021602 (2.1%)the impact on public health is expected to be small.
MedDRA PTs:	MedDRA terms can be found in Annex 7.

AE=adverse event; CI=confidence interval; DLP=data lock point; DTC=differentiated thyroid carcinoma; ETM=event to monitor; HCC=hepatocellular carcinoma; MedDRA=Medical Dictionary for Regulatory Activities; NA=not applicable; NET=neuroendocrine tumour; PSUR=periodic safety update report; PT=preferred term; RCC=renal cell carcinoma; RMP=risk management plan; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor.

Source for Study A021602: Incidence of TEAEs by ETM, PT and Severity (sorted by alphabetic order), with CI - Safety Population, A021602 study, RMP Analyses (DLP 24 August 2023).

Table 40 Important Identified Risk – Wound Complications

Identified risk	Wound complications
Potential mechanisms:	Inhibitors of VEGF pathways may cause inadequate wound healing due to impairment of revascularisation required for tissue repair. Inhibition of re-epithelialisation and inhibition of VEGF secreted by platelets may also be involved [**Error! Reference source not found.**, **Error! Reference source not found.**].
Evidence source(s) and strength of evidence:	The risk of wound complications was identified based on data from cabozantinib clinical studies. Additional data confirming the risk were from postmarketing use of

Identified risk	Wound complications
	cabozantinib. Wound complications were reported in Studies XL184-308, CA2099ER, XL184-309,XL184-311 and A021602 confirmed by wound complications 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.
Characterisation of the risk: Frequency	Cumulatively in clinical trials conducted in HCC, RCC, DTC and NET, the incidence of wound complications all grades were 2.9%, with a majority of Grade 1-2 and 1 Grade 4 (0.1%). Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Incidence: 2.4% (95% CI: 1.0, 4.7) Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): Incidence: 0%[a]. Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): Incidence 2.8% (95% CI: 1.3, 5.3) HCC in adults who have previously been treated with sorafenib (Study XL184-309): Incidence: 0.9% (95% CI: 0.2, 2.2) Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): Incidence 1.6 % (95% CI: 0.19 - 5.66) Advanced RCC following prior VEGF-targeted therapy (PASS F-FR-60000-001 (CASSIOPE)): Incidence: 1.2% (95% CI: 0.5, 2.3) Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Incidence: 3.1% (95% CI: 1.14, 6.58)
Characterisation of the risk: Seriousness/outcomes	Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Serious: 1 event Resolved: 100% Resolved with sequelae: 0% Not resolved: 0% Fatal: 0% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): Serious: 0 subjects Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): Serious: 0 events Resolved: 0% Resolved with sequelae: 0% Resolving: 0% Not resolved: 0% Fatal: 0% HCC in adults who have previously been treated with sorafenib (Study XL184-309): Serious: 1 event Resolved: 100% Resolved with sequelae: 0% Not resolved: 0% Fatal: 0% Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): Serious: 0 events Resolved: 0% Resolved with sequelae: 0% Not resolved: 0% Fatal: 0%

Identified risk	Wound complications
	Advanced RCC following prior VEGF-targeted therapy (PASS Study F-FR-60000-001 (CASSIOPE)): Total TEAEs: 9 Serious TEAEs: 2 (2/9-22%) Resolved TEAEs: 6 (6/9-67%) Resolved with sequelae: 0 Not resolved TEAEs: 3 (3/9-33%) Fatal: 0 Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Total TEAEs: 6 Serious TEAE: 1 (1/6-17%) Fatal: 0
Characterisation of the risk: Severity and nature of risk	Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): 8 of 331 (2.4%) subjects: Incidence (by highest grade reported): Grade 1: 0.9% Grade 2: 1.2% Grade 3: 0.3% Grade 4: 0% Grade 5: 0% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): 0 of 78 (0%) subjects[a]: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0% Grade 4: 0% Grade 5: 0% Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): 9 of 320 (2.8%) subjects: Incidence (by highest grade reported): Grade 1: 1.6% Grade 2: 0.9% Grade 3: 0.3% Grade 4: 0% Grade 5: 0% HCC in adults who have previously been treated with sorafenib (Study XL184-309): 4 of 467 (0.9%) subjects: Incidence (by highest grade reported): Grade 1: 0.4% Grade 2: 0.2% Grade 3: 0.2% Grade 4: 0% Grade 5: 0% Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): 2 of 125 (1.6%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 1.6% Grade 4: 0% Grade 5: 0% Advanced RCC following prior VEGF-targeted therapy (PASS Study F-FR-60000-001 (CASSIOPE)):

Identified risk	Wound complications
	8 of 679 (1.2%) subjects: Incidence (by highest grade reported): Grade 1: 0.6% Grade 2: 0.3% Grade 3: 0.3% Grade 4: 0% Grade 5: 0% Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): 6 of 195 (3.1%) subjects: Incidence (by highest grade reported): Grade 1: 2.6% Grade 2: 0% Grade 3: 0.5% Grade 4: 0% Grade 5: 0%
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 (buildup of fluid in the abdomen), uraemia (blood in the urea), diabetes, and hypertension (high blood pressure).
Preventability:	While it may be possible to prevent wound healing complications by avoiding treatment in patients with any wound, this is not practical in a cancer patient population that is subject to surgery and other invasive medical procedures.
Impact on the risk-benefit balance of the product:	Events as described can have debilitating, disabling or fatal outcomes.
Public health impact:	Poor wound healing can result in infectious complications. Gastrointestinal perforations and fistula formation could occur after major surgery. Poorly healed wounds may require additional surgical repair and prolonged hospitalisations. Advanced RCC in adults The incidence of wound complications was low for the cabozantinib treatment arm of Study XL184-308 (eight subjects (2.4%)). Wound complications were primarily postsurgical events, and all but one AE were low grade (≤ Grade 2). The Grade 3 AE (impaired healing) occurred in the context of PPES; the event was non-serious and resolved within 2 weeks of onset. One subject in Study A031203 developed a Grade 2 related non-serious AE with verbatim terms related to wound complications. Given that the RCC patient population is limited, the observed frequency for wound complication is low in both studies with an all grade reporting rate of 0.32% in the postmarketing setting for Cabometyx, the impact on public health is expected to be small. Advanced RCC in combination with nivolumab in treatment-naïve adults The incidence of wound complications was low in the cabozantinib and nivolumab treatment arm (nine subjects (2.8%)) of Study CA2099ER. None of the events of wound complications in the cabozantinib and nivolumab arm were serious. One of the events was Grade 3; all other wound complications had a severity of ≤Grade 2. Given that the RCC population is limited, the observed frequency for wound complications for cabozantinib in combination with nivolumab is 2.8% in Study CA2099ER with an all grade reporting rate of 0.32% in the postmarketing setting for Cabometyx, the impact on public health is expected to be small. HCC in adults who have previously been treated with sorafenib The incidence of wound complications was low for the cabozantinib treatment arm of Study XL184-309 (four subjects (0.9%)). One subject experienced a Grade 3 SAE of wound sepsis; all other wound complications were reported as non-serious and had a severity of ≤Grade 2.

Identified risk	Wound complications
	Given that the HCC patient population is limited and the observed frequency for wound complications is 0.9% in Study XL184-309. Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311) DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine (if radioactive iodine is an appropriate treatment). The incidence of wound complications was low for the cabozantinib treatment arm of Study XL184-311 (two subjects (1.6%)). Wound dehiscence and wound infection were reported as non-serious Grade 3 events not related to study drug. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602) The incidence of wound complications was 3.1% (six subjects) in the cabozantinib arm of Study A021602. One subject experienced a Grade 3 AE of wound infection (serious, related) and treatment with cabozantinib was discontinued in response to the event. All other wound complications had a severity of Grade 1. Wound complications of all grade reporting rate were 0.32% in the postmarketing setting for Cabometyx (DLP of previous PSUR (i.e. 28 November 2022)). No significant data has been received for wound complications from Study A021602, hence, the impact on public health is expected to be small.
MedDRA PTs:	MedDRA terms can be found in Annex 7.

AE=adverse event; CI=confidence interval; DLP=data lock point; DTC=differentiated thyroid carcinoma; ETM=event to monitor; HCC=hepatocellular carcinoma; MedDRA=Medical Dictionary for Regulatory Activities; NET=neuroendocrine tumour; PPES=palmar-plantar erythrodysaesthesia syndrome; PSUR=periodic safety update report; PT=preferred term; RCC=renal cell carcinoma; RMP=risk management plan; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor.

a there were no coded events of wound complications regardless of causality of any grade reported for the cabozantinib arm. However, one subject had reported a related non-serious AE with verbatim terms related to wound complications (Grade 2).

Source for Study A021602: Incidence of TEAEs by ETM, PT and Severity (sorted by alphabetic order), with CI - Safety Population, A021602 study, RMP Analyses (DLP 24 August 2023).

Table 41 Important Identified Risk – Posterior reversible encephalopathy syndrome (PRES)

Identified risk	Posterior reversible encephalopathy syndrome (PRES)[a]
Potential mechanisms:	PRES is usually associated with acute hypertensive encephalopathy of various aetiologies or use of certain medications such as immunosuppressive drugs. PRES has been reported in patients receiving agents targeting the VEGF pathway (sunitinib, sorafenib, pazopanib, axitinib, bevacizumab). Several mechanisms for inhibitors of the VEGF pathway have been proposed. These include impaired regulation of cerebral blood flow, a breakdown of the blood-brain barrier, and endothelial [**Error! Reference source not found.**, **Error! Reference source not found.**]. A mechanism for PRES associated with cabozantinib has not been identified. Hypertension is described as a very common ADR associated with cabozantinib.
Evidence source(s) and strength of evidence:	The risk of PRES (a neurologic condition with fits, headaches, confusion, or finding it difficult to concentrate) was identified based on data from cabozantinib clinical studies using the cabozantinib capsule but not in Studies XL184-308, A031203, CA2099ER or XL184-309 using the cabozantinib tablet. One case was reported in Study XL184-311 with cabozantinib tablet in the context of a Grade 4 hypertension and one case reported in the cabozantinib arm of Study A021602. Additional data confirming 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.

Identified risk	Posterior reversible encephalopathy syndrome (PRES)[a]
Characterisation of the risk: Frequency	Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Incidence: No subjects in Study XL184-308 developed PRES. [b] Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): Incidence: No subjects in Study A031203 developed PRES. Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): Incidence: No subjects in Study CA2099ER developed PRES. HCC in adults who have previously been treated with sorafenib (Study XL184-309): Incidence: No subjects in Study XL184-309 developed PRES. Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): Incidence: One subject in Study XL184-311 developed PRES. This subject had pre-existing hypertension and experienced a Grade 4 event of hypertension (BP 201/112 mmHg) on Day 55 which was associated with neurological symptoms confirmed as being PRES but coded as such only after the study initial DLP. The patient's antihypertensive treatment was adapted. Study treatment had been initially interrupted, when BP increased and was then discontinued. The patient was said to have recovered from PRES symptoms a week later. Advanced RCC following prior VEGF-targeted therapy (PASS Study F-FR-60000-001 (CASSIOPE)): Incidence: 0.3% (95% CI: 0.0, 1.1) Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Incidence: 0.5% (95% CI: 0.01, 2.82)

Identified risk	Posterior reversible encephalopathy syndrome (PRES)[a]
Characterisation of the risk: Seriousness/outcomes	Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Serious: 0 events Resolved: 0% Resolved with sequelae: 0% Not resolved: 0% Fatal: 0% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): Serious: 0 subjects Advanced RCC in treatment-naïve adults in combination with treatment-naïve nivolumab (Study CA2099ER): Serious: 0 events Resolved: 0% Resolved with sequelae: 0% Resolving: 0% Not resolved: 0% Fatal: 0% HCC in adults who have previously been treated with sorafenib (Study XL184-309): Serious: 0 events Resolved: 0% Resolved with sequelae: 0% Not resolved: 0% Fatal: 0% Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): The one PRES confirmed case was not yet coded as such in the database at the time of initial DLP (see above) Advanced RCC following prior VEGF-targeted therapy (PASS Study F-FR-60000-001 (CASSIOPE)): Total TEAEs: 2 Serious TEAEs: 1 (1/2-50%) Resolved TEAE: 1 (1/2-50%) Resolved with sequelae TEAE: 0 Not resolved TEAE: 1 (1/2-50%) Fatal: 0 Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Total TEAE: 1 Serious TEAE: 1 (1/1-100%) Fatal: 0
Characterisation of the risk: Severity and nature of risk	Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): 0 of 331 (0%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0% Grade 4: 0% Grade 5: 0% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): 0 of 78 (0%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0% Grade 4: 0% Grade 5: 0%

Identified risk	Posterior reversible encephalopathy syndrome (PRES)[a]
	Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): 0 of 320 (0%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0% Grade 4: 0% Grade 5: 0% HCC in adults who have previously been treated with sorafenib (Study XL184-309): 0 of 467 (0%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0% Grade 4: 0% Grade 5: 0% Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): One PRES confirmed case was not yet coded as such in the database at the time of the initial DLP (see above) Advanced RCC following prior VEGF-targeted therapy (PASS Study F-FR-60000-001 (CASSIOPE)): 2 of 679 (0.3%) subjects Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0.1% Grade 3: 0% Grade 4: 0.1% Grade 5: 0% Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): 1 of 195 (0.5%) subjects Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0.5% Grade 4: 0% Grade 5: 0%
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 and hypertension is a frequent adverse drug reaction of cabozantinib.
Preventability:	Posterior reversible encephalopathy syndrome is an infrequent syndrome. The appropriate early and regular monitoring of blood pressure increase could prevent aggravation of hypertension and hypertensive crisis which increases the risk for PRES. Guidance in the proposed SmPC includes adaptation of antihypertensive drugs, interruption of cabozantinib and dose reduction when blood pressure stabilises. In the case of hypertensive crisis or severe hypertension that cannot be controlled with antihypertensive therapy, cabozantinib treatment should be discontinued.
Impact on the risk-benefit balance of the product:	Events as described can have debilitating, disabling or fatal outcomes.
Public health impact:	Posterior reversible encephalopathy syndrome is usually reversible if the offending agent is discontinued; however, sequelae from seizures and severe hypertension such as cerebral oedema or haemorrhage may be permanent. Posterior reversible encephalopathy syndrome can also be fatal.

Identified risk	Posterior reversible encephalopathy syndrome (PRES)[a]
	Advanced RCC monotherapy in adults None of the 409 cabozantinib-treated subjects in Studies XL184-308 and A031203 experienced PRES. The incidence and reporting rate of PRES in cabozantinib-treated patients during the clinical development of cabozantinib is similar to that seen with other VEGF pathway inhibitors in RCC [**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**,**Error! Reference source not found.**]. In the postmarketing setting PRES is an uncommon event. Given that the RCC patient population is limited, no events of PRES were observed in Studies XL184-308 and A031203 and the postmarketing reporting rate for PRES is 0.02% for patients exposed to Cabometyx, the impact on public health is expected to be small. Advanced RCC in combination with nivolumab in treatment-naïve adults None of the 320 cabozantinib in combination with nivolumab treated subjects in Study CA2099ER experienced PRES. In the postmarketing setting PRES is an uncommon event. Given that the RCC patient population is limited, no event of PRES was observed in Study CA2099ER and the postmarketing reporting rate for PRES is 0.02% for patients exposed to Cabometyx, the impact on public health is expected to be small. HCC in adults who have previously been treated with sorafenib None of the 467 cabozantinib-treated subjects in Study XL184-309 experienced PRES. The incidence of PRES was comparable to that seen with sorafenib in patients with HCC [**Error! Reference source not found.**]. In the postmarketing setting PRES is an uncommon event. Given that the HCC patient population is limited, no event of PRES was observed in Study XL184-309. Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311) Incidence: The one PRES confirmed case was not yet coded as such in the database at the time of initial DLP (see above). Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602) The incidence of PRES was low for the cabozantinib treatment arm of Study A021602 (one subject (0.5%)). One event of PRES was reported, the event was assessed as serious, Grade 3 event and related to study drug. Treatment with cabozantinib was discontinued in response to the event of PRES. The postmarketing reporting rate for PRES is 0.02% for patients exposed to Cabometyx (DLP of previous PSUR (i.e. 28 November 2022)). Given the low observed frequency for PRES in Study A021602 (i.e. 0.5%), the impact on public health is expected to be small.
MedDRA PTs:	MedDRA terms can be found in Annex 7.

ADR=adverse drug reaction; BP=blood pressure; CI=confidence interval; DLP=data lock point; DTC=differentiated thyroid carcinoma; ETM=event to monitor; HCC=hepatocellular carcinoma; MedDRA=Medical Dictionary for Regulatory Activities; MTC=medullary thyroid cancer; PRES=posterior reversible encephalopathy syndrome; PSUR=periodic safety update report; PT=preferred term; RCC=renal cell carcinoma; RMP=risk management plan; RPLS=reversible posterior leukoencephalopathy syndrome; SMQ=Standardised MedDRA Query; TEAE=treatment-emergent adverse event; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor; VEGFR=vascular endothelial growth factor receptor.

a Posterior reversible encephalopathy syndrome (PRES) (previously presented in the RMP as reversible posterior leukoencephalopathy syndrome (RPLS)

b After the 22 May 2015 cut-off, one unconfirmed case of PRES was reported by a nonstudy physician via the postmarketing process for a subject who was enrolled in Study XL184-308. The report was not contemporaneous with the event (made >1 year afterwards) and there was inconsistent information in the report regarding the date of the event relative to study treatment. The subject also had confounding factors including receipt of a prior VEGF-TKI and radiation for brain metastases. There is no evidence of imaging supporting the diagnosis of PRES, and the event was not confirmed by the study investigator. In addition, one MTC subject (0.46%) developed PRES in MTC Study XL184-301.

Source for Study A021602: Incidence of TEAEs by ETM, PT and Severity (sorted by alphabetic order), with CI - Safety Population, A021602 study, RMP Analyses (DLP 24 August 2023).

Table 42 Important Identified Risk – Osteonecrosis

Identified risk	**Osteonecrosis**
Potential mechanisms:	The potential mechanism of osteonecrosis is not well understood. Potential mechanisms have been proposed and include suppression of bone turnover, immune dysfunction, and suppressed angiogenesis [**Error! Reference source not found.**].
Evidence source(s) and strength of evidence:	The risk of osteonecrosis was identified based on data 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. Osteonecrosis of the jaw (ONJ) was not seen in Studies A031203 or XL184-309 and A021602. Six subjects (3.1%) in the cabozantinib arm of the Study A021602 had an event included in the ETM list of osteonecrosis such as tooth abscess and tooth infection. Osteonecrosis of the jaw can have debilitating, disabling or disfiguring outcomes and osteonecrosis is therefore an important identified risk for cabozantinib.
Characterisation of the risk: Frequency	Cumulatively in clinical trials conducted in HCC, RCC, DTC and NET, the incidence of osteonecrosis was 3.6%. Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Incidence ONJ: 0.6% (95% CI: 0.0, 2.1) Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): Incidence osteonecrosis: No subjects in Study A031203 developed osteonecrosis. Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): Incidence osteonecrosis: 5.6% (95% CI: 3.4, 8.7) Incidence ONJ: 0.6% (95% CI: 0.1, 2.2) HCC in adults who have previously been treated with sorafenib: (Study XL184-309): Incidence ONJ: No subjects in Study XL184-309 developed ONJ. Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): Incidence osteonecrosis: 2.4% (95% CI: 0.50 - 6.85) Incidence ONJ: 0.8% (95% CI: 0.02 - 4.38) Advanced RCC following prior VEGF-targeted therapy (PASS Study F-FR-60000-001 (CASSIOPE)): Incidence: 2.8% (95% CI: 1.7, 4.3) Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Incidence ONJ: No subjects in Study A021602 developed ONJ. Incidence osteonecrosis: 3.1% (95% CI: 1.14, 6.58)
Characterisation of the risk: Seriousness/outcomes	Cumulatively in clinical trials conducted in RCC, HCC, DTC and NET, incidence of events retrieved by the ETM of osteonecrosis was 3.6% including 5 cases (0.5%) of osteonecrosis of the jaw including 0.4% Grade 3-4. Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): ONJ: Serious: 1 event Resolved: 0% Resolved with sequelae: 0% Not resolved: 100% Fatal: 0% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): Osteonecrosis: Serious: 0 subjects Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): Osteonecrosis: Serious: 0 events Resolved: 0%

Identified risk	Osteonecrosis
	Resolved with sequelae: 0% Resolving: 0% Not resolved: 0% Fatal: 0% ONJ: Serious: 0 events Resolved: 0% Resolved with sequelae: 0% Resolving: 0% Not resolved: 0% Fatal: 0% HCC in adults who have previously been treated with sorafenib (Study XL184-309): ONJ: Serious: 0 events Resolved: 0% Resolved with sequelae: 0% Not resolved: 0% Fatal: 0% Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): ONJ: Serious: 1 event (Note: This SAE of osteonecrosis of the jaw was considered as not related to cabozantinib but more likely due to recurrent gingivitis and recent start of Xgeva treatment for bone metastasis). Resolved: 100% Resolved with sequelae: 0% Not resolved: 0% Fatal: 0% Advanced RCC following prior VEGF-targeted therapy (PASS Study F-FR-60000-001 (CASSIOPE)): Total TEAEs: 21 Serious TEAE: 1 (1/21-5%) Resolved TEAEs: 18 (18/21-86%) Resolved with sequelae: 0 Not resolved TEAEs: 3 (3/21-14%) Fatal: 0 Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): ONJ: Serious: 0 Fatal: 0 Osteonecrosis: Total TEAEs: 7 Serious TEAEs: 0 Fatal: 0
Characterisation of the risk: Severity and nature of risk	Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): ONJ: 2 of 331 (0.6%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0.3% Grade 3: 0.3% Grade 4: 0% Grade 5: 0% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): Osteonecrosis: 0 of 78 (0%) subjects:

Identified risk	Osteonecrosis
	Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0% Grade 4: 0% Grade 5: 0% Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): Osteonecrosis: 18 of 320 (5.6%) subjects: Incidence (by highest grade reported): Grade 1: 1.6% Grade 2: 3.4% Grade 3: 0.6% Grade 4: 0% Grade 5: 0% ONJ: 2 of 320 (0.6%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0.3% Grade 3: 0.3% Grade 4: 0% Grade 5: 0% HCC in adults who have previously been treated with sorafenib (Study XL184-309): ONJ: 0 of 467 (0%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0% Grade 4: 0% Grade 5: 0% Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): ONJ: 1 of 125 (0%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0.8% Grade 4: 0% Grade 5: 0% Advanced RCC following prior VEGF-targeted therapy (PASS Study F-FR-60000-001 (CASSIOPE)): 19 of 679 (2.8%) subjects: Incidence (by highest grade reported): Grade 1: 1.0% Grade 2: 1.5% Grade 3: 0.4% Grade 4: 0% Grade 5: 0% Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): ONJ: 0 of 195 (0%) subjects: Incidence (by highest grade reported): Grade 1: 0%

Identified risk	**Osteonecrosis**
	Grade 2: 0% Grade 3: 0% Grade 4: 0% Grade 5: 0% Osteonecrosis 6 of 195 (3.1%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 2.6% Grade 3: 0.5% Grade 4: 0% Grade 5: 0%
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.
Preventability:	While certain risk factors and dosing guidelines (e.g. dose interruption for invasive dental procedures) have been identified and certain measures for oral hygiene have been proposed [**Error! Reference source not found.**] that may help reduce the incidence of osteonecrosis, there are no data to suggest that avoiding use in such at risk patients will eliminate the potential for events of osteonecrosis to occur.
Impact on the risk-benefit balance of the product:	Events as described can have debilitating, disabling or disfiguring outcomes.
Public health impact:	Advanced RCC monotherapy in adults Two subjects (0.6%) in the cabozantinib arm of Study XL184-308 experienced ONJ. The cabozantinib-treated subject who had a Grade 3 AE of ONJ had a Grade 2 event at baseline and received denosumab on study; the other subject with a Grade 2 ONJ had a prior history of ONJ which resolved before enrolling in the study. No subjects in Study A031203 developed osteonecrosis. Given that the RCC patient population is limited, the observed frequency for ONJ is <1% in both studies with a reporting rate for osteonecrosis of 0.18% in the postmarketing setting for Cabometyx, the impact on public health is expected to be small. Advanced RCC in combination with nivolumab in treatment-naïve adults In Study CA2099ER 18 subjects (5.6%) in the cabozantinib in combination with nivolumab arm experienced osteonecrosis (identified using the osteonecrosis SMQ) including 2 subjects (0.6%) who developed ONJ. None of the AEs were serious. The AEs of ONJ were of Grade 2 and Grade 3 severity but only one of these AEs (0.3%) was considered treatment related. Given that the RCC patient population is limited, the observed frequencies for osteonecrosis and ONJ are 5.6% and 0.6% respectively in Study CA2099ER, and with a reporting rate for osteonecrosis of 0.18% in the postmarketing setting for Cabometyx, the impact on public health is expected to be small. HCC in adults who have previously been treated with sorafenib None of the 467 cabozantinib-treated subjects in Study XL184-309 experienced ONJ. Given that the HCC patient population is limited, no event of ONJ was observed in Study XL184-309. Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311) In Study XL184-311, among the 3 cases retrieved in the ETM terms for osteonecrosis, one subject experienced osteonecrosis of the jaw, which was considered serious, Grade 3 and not related to study drug.

Identified risk	Osteonecrosis
	Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602) No subjects in Study A021602 developed ONJ. Six subjects (3.1%) in the cabozantinib arm had an event included in the ETM list of osteonecrosis. None of these AEs were serious. One Grade 3 event of tooth infection was reported which was not considered treatment related. The remaining TEAEs of tooth abscess (n=1) and tooth infection (n=5) were of Grade 2 severity. Two Grade 2 AEs of tooth infection were considered treatment related, remaining all the Grade 2 AEs were assessed as not related to the cabozantinib. The postmarketing reporting rate for osteonecrosis is 0.18% for patients exposed to Cabometyx (DLP of previous PSUR (i.e. 28 November 2022)). No significant data has been received for Osteonecrosis from Study A021602, hence the impact on public health is expected to be small.
MedDRA PTs:	MedDRA terms can be found in Annex 7.

AE=adverse event; CI=confidence interval; DLP=data lock point; DTC=differentiated thyroid carcinoma; ETM= events to monitor; HCC=hepatocellular carcinoma; MedDRA=Medical Dictionary for Regulatory Activities; NET=neuroendocrine tumour; ONJ=osteonecrosis of the jaw; PSUR=Periodic Safety Update Report; PT=preferred term; RCC=renal cell carcinoma; RMP=risk management plan; SAE=serious adverse event; TEAE=treatment-emergent adverse event; VEGF=vascular endothelial growth factor.

Source for Study A021602: Incidence of TEAEs by ETM, PT and Severity (sorted by alphabetic order), with CI - Safety Population, A021602 study, RMP Analyses (DLP 24 August 2023).

Table 43 Important Potential Risk – Renal Failure

Potential risk	Renal failure
Potential mechanisms:	Vascular endothelial growth factor -inhibiting agents, diabetes, hypertension, and urinary tract infections can cause dysfunction of endothelial cells in the kidney and damage to renal cell capillaries. Dehydration and anaemia can affect kidney function through inadequate blood supply to renal cells and renal tissues.
Evidence source(s) and strength of evidence:	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, XL184-309 and A021602. 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.
Characterisation of the risk: Frequency	Cumulatively in clinical trials on RCC, HCC and DTC, the incidence of renal failure was 1.1% including 1 fatal case (0.1%) of prerenal failure. Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Incidence: 0.3% (95% CI: >0.0, 1.7) Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): Incidence: 9.0% Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): Incidence: 6.9% (95% CI: 4.4, 10.2) HCC in adults who have previously been treated with sorafenib (Study XL184-309): Incidence: 2.4% (95% CI: 1.2, 4.2) Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): Incidence: 2.4% (95% CI: 0.50 - 6.85) Advanced RCC following prior VEGF-targeted therapy (PASS Study F-FR-60000-001 (CASSIOPE)): Incidence: 2.1% (95% CI: 1.1, 3.4) Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Incidence: 1.0% (95% CI: 0.12, 3.66)
Characterisation of the risk:	Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Serious: 1 event

Potential risk	Renal failure
Seriousness/outcomes	Resolved: 0% Resolved with sequelae: 0% Not resolved: 100% Fatal: 0% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): Serious: 5 events Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): Serious: 3 events Resolved: 66.7% Resolved with sequelae: 0% Resolving: 33.3% Not resolved: 0% Fatal: 0% HCC in adults who have previously been treated with sorafenib (Study XL184-309): Serious: 6 events Resolved: 67% Resolved with sequelae: 0% Not resolved: 17% Fatal: 17% Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): Serious: 3 events Resolved: 100% Resolved with sequelae: 0% Not resolved: 0% Fatal: 0% Advanced RCC following prior VEGF-targeted therapy (PASS Study F-FR-60000-001 (CASSIOPE)): Total TEAEs: 15 Serious TEAEs: 6 (6/15-40%) Resolved TEAEs: 6 (6/15-40%) Resolved with sequelae: 0 Not resolved TEAEs: 6 (6/15-40%) Fatal TEAEs: 3 (3/15-20%) Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Total TEAEs: 2 Serious TEAEs: 2 (2/2-100%) Fatal: 0
Characterisation of the risk: Severity and nature of risk	Cumulatively in clinical trials conducted in RCC, HCC,DTC and A021602, severe cases of renal failure, including 2 cases of Grade 4, 2 cases of Grade 3 and 1 fatal case, were observed. Dehydration, diarrhoea and vomiting known ADRs for cabozantinib were triggering factors in several of the clinical trial cases. Proteinuria is a frequently reported ADR in both clinical trials and postmarketing setting but no reports of nephrotic syndrome have been reported in clinical trials conducted in RCC, HCC or DTC, and it has been rarely reported in the postmarketing setting. Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): 1 of 331 (0.3%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0.3% Grade 4: 0% Grade 5: 0% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203):

Potential risk	Renal failure
	Renal failure (≥Grade 3) 5 of 78 (6.4%) subjects [a]: Incidence (by highest grade reported) [b]: Grade 3: 3.8% Grade 4: 1.3% Grade 5: 1.3% Renal failure (Grades 1-2) 2 of 78 (2.6%) subjects [c]: Incidence (by highest grade reported): Grade 1: 1.3% Grade 2: 1.3% Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): 22 of 320 (6.9%) subjects: Incidence (by highest grade reported): Grade 1: 3.8% Grade 2: 2.2% Grade 3: 0.9% Grade 4: 0% Grade 5: 0% HCC in adults who have previously been treated with sorafenib (Study XL184-309): 11 of 467 (2.4%) subjects: Incidence (by highest grade reported): Grade 1: 0.4% Grade 2: 0.6% Grade 3: 0.9% Grade 4: 0.2% Grade 5: 0.2% Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): 3 of 125 (2.4%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 1.6% Grade 4: 0.8% Grade 5: 0.8% Advanced RCC following prior VEGF-targeted therapy (PASS Study F-FR-60000-001 (CASSIOPE)): 14 of 679 (2.1%) subjects: Incidence (by highest grade reported): Grade 1: 0.7% Grade 2: 0.3% Grade 3: 0.6% Grade 4: 0% Grade 5: 0.4% Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): 2 of 195 (1.0%) subjects: Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 1.0% Grade 4: 0% Grade 5: 0%
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.

Potential risk	**Renal failure**
Preventability:	While renal failure may not be completely preventable, certain precautions can be taken, such as monitoring and treatment of dehydration, vomiting, and diarrhoea. Monitor for proteinuria and treat hypertension and diabetes as appropriate.
Impact on the risk-benefit balance of the product:	Events as described can have debilitating, disabling or fatal outcomes.
Public health impact:	Advanced RCC monotherapy in adults Nineteen (5.7%) subjects in the cabozantinib arm in Study XL184-308 met laboratory screening criteria for renal failure. A subsequent medical review of these subjects confirmed that none had drug-induced renal toxicity. In addition to the laboratory analysis for renal failure, SAEs using the renal failure and impairment HLT were examined. One subject (0.3%) in the cabozantinib treatment arm also identified by laboratory screening approach described above experienced a serious event of renal failure, which was ascribed to contrast agent by the investigator. In addition, two non-serious Grade 1 events of renal failure acute were reported. A total of five (6.4%) subjects in the cabozantinib arm of Study A031203 had ≥Grade 3 PTs for renal failure. One subject had a Grade 5 AE of acute renal failure, which was assessed as related to cabozantinib. This subject had elevated creatinine at screening and died of acute renal failure following dehydration and the subject refusing dialysis. There was one Grade 3 AE of renal failure chronic in the cabozantinib arm, which was serious and assessed as related to cabozantinib. The observed incidence of renal failure is similar to that seen with other VEGF pathway inhibitors in RCC [**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**,**Error! Reference source not found.**]. Given that the RCC patient population is limited, the observed frequency for renal failure is low in Studies XL184-308 and A031203 and the reporting rate for serious events in the HLT of Renal failure and impairment and SMQ of Acute renal failure in the Cabometyx postmarketing setting is 0.52%, the impact on public health is expected to be small. Advanced RCC in combination with nivolumab in treatment-naïve adults Twenty-two (6.9%) subjects in the cabozantinib in combination with nivolumab arm in Study CA2099ER experienced renal failure AEs; 4.4% (14 subjects) experienced treatment related renal failure AEs. There were 3 SAEs (0.9%) in the cabozantinib in combination with nivolumab arm. Grade 3 AEs included renal failure (0.3%) and acute kidney injury (0.6%). Given that the RCC patient population is limited, the observed frequency for renal failure is low in Study CA2099ER and the reporting rate for serious events in the HLT of Renal failure and impairment and SMQ of Acute renal failure in the Cabometyx postmarketing setting is 0.52%, the impact on public health is expected to be small. HCC in adults who have previously been treated with sorafenib Thirteen (2.8%) subjects in the cabozantinib arm of Study XL184-309 met the laboratory screening criteria for renal failure. Cases meeting renal dysfunction screening criteria were reviewed and there was no excess occurrence of nephrotoxicity in the cabozantinib arm relative to placebo. Eleven subjects (2.4%) in the cabozantinib arm of Study XL183309 experienced renal failure AEs (four Grade 3 and one Grade 4). A Grade 5 event of prerenal failure was also reported. The observed incidence of renal failure is comparable to that seen with sorafenib in subjects with HCC [**Error! Reference source not found.**]. Given that the HCC population is limited, the observed frequency for renal failure is 2.4%. Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311) Selected AEs grouped as renal failure were reported for 3 subjects (2.4%) in the cabozantinib only arm and none in the placebo arm. In the cabozantinib only arm, acute kidney injury and renal impairment were reported as Grade 3 SAEs in 1 subject (0.8%) each; renal failure was reported as a Grade 4 SAE in 1 subject (0.8%). All events resolved while study drug continued. Moreover, all subjects were screened for possible treatment -emergent renal toxicity using serum creatinine, and estimated glomerular filtration rate (eGFR) thresholds and identified subjects were then

Potential risk	Renal failure
	evaluated by the sponsor in blinded fashion. Of the 2 subjects in the cabozantinib arm who met qualifying criteria , none were determined to have cabozantinib-induced renal toxicity. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602) Overall incidence of renal failure was 1.0% (95% CI: 0.12, 3.66) in Study A021602. Two subjects (1.0%) experienced serious, Grade 3 AEs of acute kidney injury, one of which was assessed as treatment related. The reporting rate for serious events in the HLT of Renal failure and impairment and SMQ of Acute renal failure in the Cabometyx postmarketing setting was 0.52% (DLP of previous PSUR (i.e. 28 November 2022)). Given the low observed frequency of renal failure from Study A021602, the impact on public health is expected to be small.
MedDRA PTs:	MedDRA terms can be found in Annex 7.

AE=adverse event; ADR=adverse drug reaction; CI=confidence interval; DLP=data lock point; DTC=differentiated thyroid carcinoma; eGFR= estimated glomerular filtration rate; ETM=event to monitor; G=Grade; HCC=hepatocellular carcinoma; HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities; PSUR=periodic safety update report; PT=preferred term; RCC=renal cell carcinoma; RMP=risk management plan; SAE=serious adverse event; SMQ=Standardised MedDRA query; TEAE=treatment-emergent adverse event; VEGF=vascular endothelial growth factor.

a comprises four subjects with AEs of acute renal failure and one subject with an AE of chronic renal failure, all of which were serious.

b in addition, there was a Grade 3 SAE of 'acute renal failure' not related to study treatment reported in the cabozantinib arm identified from other sources.

c comprises one subject with a Grade 1 AE of acute renal failure and one subject with a Grade 2 AE of chronic renal failure.

Source for Study A021602: Incidence of TEAEs by ETM, PT and Severity (sorted by alphabetic order), with CI - Safety Population, A021602 study, RMP Analyses (DLP 24 August 2023).

Table 44 Important Potential Risk – Hepatotoxicity

Potential risk	Hepatotoxicity
Potential mechanisms:	As far as the TKIs are concerned, a class effect based on inhibition of a specific tyrosine kinase is unlikely because pharmacologically diverse TKIs are known to be hepatotoxic. Neither is there any evidence that hepatotoxicity of these drugs may be related to a particular chemical class. Pazopanib-induced hepatotoxicity has been associated with the HFE (haemochromatosis gene) mutation on chromosome 6, but the pathophysiologic explanation for this association is not known. It is known that pazopanib and sorafenib/sunitinib undergo metabolism largely via CYP enzymes, but a definitive role for hepatic CYP modulation in the development of pazopanib hepatotoxicity has not been demonstrated. Other hypotheses have been inconclusive, including association with metabolism through CYP2D6 and, like acetaminophen, the activation of c-Jun kinase. However, activation or inhibition of other signal transduction pathways may also play a role [**Error! Reference source not found.**].
Evidence source(s) and strength of evidence:	The risk of hepatotoxicity was identified from cabozantinib clinical studies. Additional data confirming the risk were from postmarketing use of cabozantinib. Elevations of liver enzymes were frequently reported however mainly with low grade severity in cabozantinib-treated patients in Studies XL184-308, A031203, XL184-309, XL184-311 and A021602. 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.

Potential risk	Hepatotoxicity
	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.
Characterisation of the risk: Frequency	Cumulatively in clinical trials conducted in RCC, HCC, and DTC, incidence of ALT and AST increased were 21% and 24 % respectively, mainly of grades 1-2, including 0.2% and 0.6% of Grade 4 respectively. The incidence of events gathered under the ETM of hepatotoxicity was 14% including 5.4 % fatal cases mainly related to underlying hepatocellular carcinoma disease. Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Incidence: 0.3% (95% CI: >0.0,1.7) [a] Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): ALT increased [b] Incidence: 55% AST increased [b] Incidence: 60% Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): ALT increased: Incidence: 28.1% (95% CI: 23.3, 33.4) AST increased: Incidence: 25.3% (95% CI: 20.6, 30.4) Hepatotoxicity Incidence: 9.1% (95% CI: 6.2, 12.8) HCC in adults who have previously been treated with sorafenib (Study XL184-309): ALT increased: Incidence 17% (95% CI: 13.8, 20.9) Based on laboratory data, there was an increase in ALT in 73% (any grade) and 12% (Grade 3 to 4) of subjects treated with cabozantinib. AST increased: Incidence 22% (95% CI: 18.8, 26.6) Based on laboratory data, there was an increase in AST in 73% (any grade) and 24% (Grade 3 to 4) of subjects treated with cabozantinib. Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): Based on laboratory data, all grades of ALT increased, and AST increased were reported in 24% and 23% respectively. Only 1 cabozantinib subject experienced a Grade 3 ALT increase. Based on the hepatotoxicity ETM, 2 cases were reported (incidence of 1.6%), 1 non-serious case of Grade 1 hepatitis (transaminases increased) assessed as related and 1 serious case of Grade 2 ascites. Advanced RCC following prior VEGF-targeted therapy (PASS Study F-FR-60000-001 (CASSIOPE)): Incidence 1.2% (95% CI: 0.5, 2.3) Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Hepatotoxicity Incidence 5.1% (95% CI: 2.49, 9.23) ALT increased (solicited AEs) 66% AST increased (solicited AEs) 72%
Characterisation of the risk: Seriousness/outcomes	Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Serious: 1 event Resolved: 0% Resolved with sequelae: 0% Not resolved: 100% Fatal: 0%

Potential risk	Hepatotoxicity
	Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): ALT increased: Serious: 2 subjects AST increased: Serious: 1 subject Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): ALT increased: Serious: 2 events Resolved: 100% Resolved with sequelae: 0% Resolving: 0% Not resolved: 0% Fatal: 0% AST increased: Serious: 1 event Resolved: 100% Resolved with sequelae: 0% Resolving: 0% Not resolved: 0% Fatal: 0% Hepatotoxicity Serious: 5 events Resolved: 80% Resolved with sequelae: 20% Resolving: 0% Not resolved: 0% Fatal: 0% HCC in adults who have previously been treated with sorafenib (Study XL184 309): ALT increased: Serious: 1 event Resolved: 100% Resolved with sequelae: 0% Not resolved: 0% Fatal: 0% AST increased: Serious: 3 events Resolved: 67% Resolved with sequelae: 0% Not resolved: 0% Fatal: 0% Unknown: 33% Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): ALT increased: Serious: 0 event Resolved: 0% Resolved with sequelae: 0% Not resolved: 0% Fatal: 0% AST increased: Serious: 0 event Resolved: 0% Resolved with sequelae: 0% Not resolved: 0% Fatal: 0%

Potential risk	Hepatotoxicity
	There was no case of potential DILI based on laboratory data screening subjects for possible treatment -emergent hepatic toxicity. One serious case of ascites Grade 2 was reported 35 days after study drug interruption and was considered as related to the treated disease (diagnosis of peritoneal carcinosis and carcinomatous lymphangitis). Advanced RCC following prior VEGF-targeted therapy (PASS Study F-FR-60000-001 (CASSIOPE)): Total TEAEs: 8 Serious TEAEs:3 (3/8-38%) Resolved TEAE: 1 (1/8-12%) Resolving TEAE: 1 (1/8-12%) Resolved with sequelae TEAE: 0 Not resolved TEAEs: 5 (5/8-63%) Fatal TEAE: 1 (1/8-12%) Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Hepatotoxicity Total TEAEs: 11 Serious TEAEs: 6 (6/11-55%) Fatal TEAE: 1 (1/11-9%) ALT increased Serious TEAE: 0% Fatal TEAE: 0% AST increased Serious TEAE: 1.6% Fatal TEAE: 0%
Characterisation of the risk: Severity and nature of risk	Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Incidence: 1 of 331 (0.3%) subjects (1 case of hepatitis cholestatic) [a] Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0% Grade 4: 0.3% Grade 5: 0% ALT increased [c] Incidence: 53 of 331 (16%) subjects Incidence (by highest grade reported) Grade 1/2:14% Grade 3:2.1% Grade 4: 0.3% Grade 5: 0% AST increased [c] Incidence: 58 of 331 (18%) subjects Incidence (by highest grade reported) Grade 1/2: 16% Grade 3:1.8% Grade 4: 0% Grade 5: 0% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): ALT increased: Incidence: 43 of 78 (55%) subjects, Incidence (by highest grade reported): Grade 1: 42% Grade 2: 7.7% Grade 3: 3.8% Grade 4: 1.3% Grade 5: 0% AST increased:

Potential risk	Hepatotoxicity
	Incidence: 47 of 78 (60%) subjects, Incidence (by highest grade reported): Grade 1: 53% Grade 2: 5.1% Grade 3: 1.3% Grade 4: 1.3% Grade 5: 0% Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): ALT increased: Incidence: 90 of 320 (28.1%) subjects, Incidence (by highest grade reported): Grade 1: 16.3% Grade 2: 6.6% Grade 3: 5.3% Grade 4: 0% Grade 5: 0% AST increased: Incidence: 81 of 320 (25.3%) subjects, Incidence (by highest grade reported): Grade 1: 17.5% Grade 2: 4.4% Grade 3: 3.4% Grade 4: 0% Grade 5: 0% Hepatotoxicity Incidence: 29 of 320 (9.1%) subjects, Incidence (by highest grade reported): Grade 1: 1.3% Grade 2: 3.4% Grade 3: 4.1% Grade 4: 0.3% Grade 5: 0% HCC in adults who have previously been treated with sorafenib (Study XL184-309): ALT increased: Incidence: 80 of 467 (17%) subjects, Incidence (by highest grade reported): Grade 1: 7% Grade 2: 5% Grade 3: 5% Grade 4: 0% Grade 5: 0% AST increased: Incidence: 105 of 467 (22%) subjects Incidence (by highest grade reported): Grade 1: 5% Grade 2: 6% Grade 3: 11% Grade 4: 0.9% Grade 5: 0% Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): ALT increased: Incidence 30 of 125 (24%) subjects Incidence (by highest grade reported): Grade 1: 19% Grade 2: 4% Grade 3: 0.8 %

Potential risk	Hepatotoxicity
	Grade 4: 0% Grade 5: 0% AST increased: Incidence 29 of 125 (23%) subjects Incidence (by highest grade reported): Grade 1: 21% Grade 2: 2.4% Grade 3: 0% Grade 4: 0% Grade 5: 0% Advanced RCC following prior VEGF-targeted therapy (PASS Study F-FR-60000-001 (CASSIOPE)): 8 of 679 (1.2%) subjects, Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 1.0% Grade 4: 0% Grade 5: 0.1% Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Hepatotoxicity 10 of 195 (5.1%) subjects, Incidence (by highest grade reported): Grade 1: 0% Grade 2: 1.0% Grade 3: 3.1% Grade 4: 0.5% Grade 5: 0.5% ALT increased: Grade 1: 56% Grade 2: 9.2% Grade 3: 0.5% Grade 4: 0.5% Grade 5: 0% AST increased: Grade 1: 57% Grade 2: 12.3% Grade 3: 3.1% Grade 4: 0% Grade 5: 0%
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.
Preventability:	While hepatotoxicity may not be completely preventable in the presence of co-morbidities (such as liver metastasis) and concomitant medications (with potential hepatotoxic drug interactions); certain precautions can be taken, such as monitoring liver enzymes and liver function tests and modifying cabozantinib doses whenever indicated.
Impact on the risk-benefit balance of the product:	Events as described can have debilitating, disabling or fatal outcomes.
Public health impact:	Advanced RCC monotherapy in adults Elevations of liver enzymes are frequent in cabozantinib-treated patients. However, these abnormalities are readily monitorable and there was no evidence of drug-induced liver injury with cabozantinib treatment. One cabozantinib-treated subject in

Potential risk	Hepatotoxicity
	Study XL184-308 developed a Grade 4 event of cholestatic hepatitis; the case was confounded by the use of concomitant ciprofloxacin and acetaminophen with an additional potential cause of autoimmune-mediated hepatitis following receipt of nivolumab prior to study entry. The RCC patient population is limited and the observed frequency for hepatotoxicity is 0.3% (a case of hepatitis cholestatic) in Study XL184-308. Despite the frequent occurrences of increased liver enzymes which may be indicative of hepatotoxicity, there were no confirmed cases of drug-induced liver injury in Study A031203. Given that the reporting rate for serious events of hepatotoxicity in the SMQ Drug-induced liver toxicity – severe events only in the Cabometyx postmarketing setting is 0.25%, the impact on public health is expected to be small. <u>Advanced RCC in combination with nivolumab in treatment-naïve adults</u> Elevations of liver enzymes were frequent in cabozantinib in combination with nivolumab treated subjects in Study CA2099ER. All grade AEs of ALT increased and AST increased were experienced by 28.1% and 25.3%, respectively, of cabozantinib in combination with nivolumab treated subjects in Study CA2099ER. Grade 3 AEs of ALT increased and AST increased were experienced by 5.3% and 3.4%, respectively, of subjects. The majority of AEs were non-serious with only 0.6% SAEs of ALT increased and 0.3% SAE of AST increased. Twenty-nine (9.1%) subjects in the cabozantinib in combination with nivolumab arm in Study CA2099ER experienced hepatotoxicity AEs; 8.1% (26 subjects) had treatment related hepatotoxicity AEs. There were 5 SAEs (1.6%) in the cabozantinib in combination with nivolumab arm. There were 13 (4.1%) Grade 3 including the PTs hepatotoxicity (2.2%), hepatitis (0.9%), autoimmune hepatitis (0.6%) and hepatocellular injury (0.3%) and 1 (0.3%) Grade 4 hepatotoxicity AE. Four subjects in the cabozantinib in combination with nivolumab arm met Hy's Law criteria of concurrent ALT or AST > 3X ULN with total bilirubin > 2X ULN elevation based on lab results within 30 days of last dose. These 4 subjects also reported concurrent ALT/AST and total bilirubin increases as AEs, of which 3 subjects had hepatotoxicity reported as an AE. All these 4 cases resolved with the use of corticosteroids. These events were manageable using established AE treatment algorithms and dose modification guidelines for both cabozantinib and nivolumab. In clinical practice dose interruption and use of corticosteroids should be considered if immune-mediated reaction is suspected when cabozantinib is used in combination with nivolumab in RCC and after recovery treatment should be re-initiated with a single medicine or sequentially. Given that the reporting rate for serious events of hepatotoxicity in the SMQ Drug-induced liver toxicity – severe events only in the Cabometyx postmarketing setting is 0.25%, the impact on public health is expected to be small. <u>HCC in adults who have previously been treated with sorafenib (Study XL184-309):</u> Elevations of liver enzymes were frequent in cabozantinib-treated subjects in Study XL184-309. All grade AEs of ALT increased, and AST increased were experienced by 17% and 22%, respectively, of cabozantinib-treated subjects in Study XL184-309. Grade 3 or 4 AEs of ALT increased, and AST increased were experienced by 5% and 12%, respectively, of subjects. Given that the HCC patient population is limited, there were no cases of drug-induced liver injury in Study XL184-309. <u>Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311)</u> Elevations of liver enzymes were frequent in cabozantinib-treated subjects in Study XL184-311. All grade AEs of ALT increased, and ALT increased were experienced by 24% and 23% respectively in cabozantinib-treated subjects. None of these events were reported as SAEs. Apart from 1 Grade 3 event, all were Grade 1-2 These ALT and AST increases led to treatment interruption in 4.8% and 3.2% of subjects respectively. There were no cases of DILI. <u>Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602)</u>

Potential risk	Hepatotoxicity
	Ten (5.1%) subjects in cabozantinib arm in Study A021602 experienced hepatotoxicity AEs. The majority of AEs were of Grade 3 severity. The Grade 3 AEs included ascites (1.5%), hepatic encephalopathy (0.5%), hepatic failure (0.5%), portal hypertension (0.5%) and spontaneous bacterial peritonitis (0.5%). Grade 4 and Grade 5 events of hepatic failure (one each) were also reported which were assessed as not related to the cabozantinib treatment . Two AEs of ascites were of Grade 2 severity. The AEs of ALT increased and AST increased were experienced by 66% and 72% of subjects, respectively, in cabozantinib arm. Grade 3 AEs of AST increased was experienced by 3.1% and Grade 4 AEs of ALT increased was experienced by 0.5% of the subjects. No Grade 3 AEs were reported for ALT increased. The reporting rate for serious events of hepatotoxicity in the SMQ Drug-induced liver toxicity – severe events only in the Cabometyx postmarketing setting is 0.25% (DLP of previous PSUR (i.e. 28 November 2022)). The higher incidence of ALT increased and AST increased in Study A021602 may be because these adverse events are considered expected and their presence/absence should be solicited, per the study protocol. The impact on public health is expected to be small.
MedDRA PTs:	MedDRA terms can be found in Annex 7.

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CI=confidence interval; CYP=cytochrome P450; DILI=drug-induced liver injury; DLP=data lock point; DTC=differentiated thyroid carcinoma; ETM=event to monitor; HCC=hepatocellular carcinoma; HFE=human haemochromatosis; MedDRA=Medical Dictionary for Regulatory Activities; PASS=post-authorisation safety study; PSUR=periodic safety update report; PT=preferred term; RCC=renal cell carcinoma; RMP=risk management plan; SAE=serious adverse event; SMQ=standardised MedDRA query; TEAE=treatment-emergent adverse event; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor.

a one SAE of hepatitis cholestatic.

b solicited AE in Study A031203.

c AEs (any grade) in Study XL184-308

Source for Study A021602 study: Incidence of TEAEs by ETM, PT and Severity (sorted by alphabetic order), with CI - Safety Population, A021602 study, RMP Analyses (DLP 24 August 2023).

Table 45 Important Potential Risk – Embryotoxicity

Potential risk	**Embryotoxicity**
Potential mechanisms:	Angiogenesis plays a key role in embryo–foetal development. As for other anti-angiogenic VEGF inhibitors, cabozantinib administration resulted in embryotoxicity in nonclinical safety studies. Although the mechanism(s) leading to these adverse effects on reproduction and development are unknown, these findings are consistent with a cabozantinib-mediated inhibition of VEGF signalling. Vascular endothelial growth factor plays an important physiologic role in the female reproductive cycle (e.g. mucosal integrity), ovarian corpus luteum angiogenesis, and testicular spermatogenesis [**Error! Reference source not found.**, **Error! Reference source not found.**] and has also been shown to play an essential function on the growth and survival of neonatal mice [**Error! Reference source not found.**].
Evidence source(s) and strength of evidence:	The risk of embryotoxicity was identified based on nonclinical data. No cases of pregnancy or pregnancy in partner have been described for cabozantinib during post-marketing experience through to 28 November 2023. 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.
Characterisation of the risk: Frequency	No events relevant to embryotoxicity were reported from CASSIOPE study. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Incidence: 0.5% (95% CI: 0.01, 2.82)
Characterisation of the risk: Seriousness/outcomes	Limited clinical data exist on events related to embryotoxicity. However, preclinical data suggest that serious effects on a foetus could result from the mother receiving cabozantinib therapy. No events relevant to embryotoxicity were reported from CASSIOPE study. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Total TEAE: 1 Serious TEAE: 1 (1/1-100%) Fatal: 0
Characterisation of the risk: Severity and nature of risk	Possibility of serious life-threatening event in the foetus. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): 1 of 195 (0.5%) subjects Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0.5% Grade 4: 0% Grade 5: 0%
Risk factors and risk groups:	The ‘at risk’ group for experiencing cabozantinib related embryotoxicity comprises female patients of child-bearing 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.
Preventability:	Embryotoxicity can be prevented through use of effective methods of contraception 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 another method, such as a barrier method, should also be used.

Potential risk	**Embryotoxicity**
Impact on the risk-benefit balance of the product:	Could be lethal to a human embryo or produce serious congenital abnormalities.
Public health impact:	Advanced RCC in adults In Studies XL184-308 and A031203, the median ages of female subjects exposed to cabozantinib were 60 years and 63 years, respectively. Only a small number of female patients are expected to be of child-bearing potential, though a higher number of male patients would be of reproductive potential. No cases of pregnancy were reported from the Cabometyx postmarketing experience as of 28 November 2023. The impact to public health is expected to be minimal. Advanced RCC in combination with nivolumab in treatment-naïve adults In Study CA2099ER, the median age of female subjects exposed to cabozantinib in combination with nivolumab was 66 years. In this study no pregnancies of female subjects were reported and there were no pregnancies in female partners of male subjects exposed to cabozantinib. No cases of pregnancy were reported from the Cabometyx postmarketing experience as of 28 November 2023. The impact to public health is expected to be minimal. HCC in adults who have previously been treated with sorafenib In Study XL184-309, no pregnancies of female subjects were reported and there were no pregnancies in female partners of male subjects exposed to cabozantinib. Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): In Study XL184-311, no pregnancies of female subjects were reported and there were no pregnancies in female partners of male subjects exposed to cabozantinib. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602) In Study A021602, no pregnancies of female subjects were reported and there were no pregnancies in female partners of male subjects exposed to cabozantinib. Overall incidence of embryotoxicity was 0.5% (95% CI: 0.01, 2.82) in Study A021602. One subject experienced Grade 3 AE of atrial septal defect (Grade 3) which was assessed as treatment related. There was no explanation offered as to how study drug might induce an anatomic lesion in the chambers of the heart. No similar events have been reported in the literature. Previous myocardial infarction and history of poor wound healing offer alternative explanations for or may have contributed to atrial septal defect. No cases of pregnancy were reported from the Cabometyx postmarketing experience as of 28 November 2023. The impact to public health is expected to be minimal.
MedDRA PTs:	MedDRA terms can be found in Annex 7.

AE=adverse event; CI=confidence interval; DLP=data lock point; DTC=differentiated thyroid carcinoma; ETM=event to monitor; HCC=hepatocellular carcinoma; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; RCC=renal cell carcinoma; RMP=risk management plan; TEAE=treatment-emergent adverse event; VEGF=vascular endothelial growth factor.

Source for Study A021602: Incidence of TEAEs by ETM, PT and Severity (sorted by alphabetic order), with CI - Safety Population, A021602 study, RMP Analyses (DLP 24 August 2023).

Table 46 Important Potential Risk – Carcinogenicity

Potential risk	**Carcinogenicity**
Potential mechanisms:	The carcinogenic potential of cabozantinib has been evaluated in mice and rats. Cabozantinib was not carcinogenic in a 26-week mouse study. In a 2-year rat carcinogenicity study, administration of cabozantinib resulted in benign and malignant pheochromocytoma in males and females at doses equivalent to doses less than the 60 mg human dose in RCC and HCC patients. However, there is no evidence this translates to an increased risk in humans. In male rats, pheochromocytomas are frequently found when the following conditions are involved: hypoxia, uncoupling of oxidative phosphorylation, disturbance in calcium homeostasis or disturbance of the hypothalamic endocrine axis. Compounds that interfere with these pathways may also produce pheochromocytomas. Several points of attack have been identified, including receptor tyrosine kinase [**Error! Reference source not found.**].
Evidence source(s) and strength of evidence:	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 28 November 2023. 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.
Characterisation of the risk: Frequency	Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Incidence: 1.2% (95% CI: 0.3, 3.1) Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): Incidence: No subjects in Study A031203 developed second primary malignancies. Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): Incidence: 1.9% (95% CI: 0.7, 4) HCC in adults who have previously been treated with sorafenib (Study XL184-309): Incidence: 0.9% (95% CI: 0.2, 2.2) Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): Incidence: No subjects were identified to have developed secondary malignancies. Advanced RCC following prior VEGF-targeted therapy (PASS Study F-FR-60000-001 (CASSIOPE)): Incidence: 3.5% (95% CI: 2.3, 5.2) Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Incidence: No subjects were identified to have developed secondary malignancies.
Characterisation of the risk: Seriousness/outcomes	Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): Serious: 3 events Resolved: 33% Resolved with sequelae: 0% Not resolved: 33% Fatal: 0% Not reported: 33% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): Serious: 0 subjects Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): Serious: 3 events Resolved: 100% Resolved with sequelae: 0% Resolving: 0% Not resolved: 0%

Potential risk	Carcinogenicity
	Fatal: 0% HCC in adults who have previously been treated with sorafenib (Study XL184-309): Serious: 2 events Resolved: 0% Resolved with sequelae: 0% Not resolved: 50% Fatal: 50% Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): Serious: 0 subjects Advanced RCC following prior VEGF-targeted therapy (PASS Study F-FR-60000-001 (CASSIOPE)): Total TEAEs: 28 Serious TEAEs: 19 (19/28-68%) Resolved TEAEs: 6 (6/28-21%) Resolving TEAE: 1 (1/28-4%) Resolved with sequelae TEAE: 0 Not resolved TEAEs: 15 (15/28-54%) Fatal TEAEs: 6 (6/28-21%) Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): Serious: 0 subjects
Characterisation of the risk: Severity and nature of risk	Advanced RCC in adults following prior VEGF-targeted therapy (Study XL184-308): 4 of 331 (1.2%) subjects Incidence (by highest grade reported): Grade 1: 0.9% Grade 2: 0.3% Grade 3: 0% Grade 4: 0% Grade 5: 0% Advanced RCC in treatment-naïve adults with intermediate or poor-risk (Study A031203): 0 of 78 (0%) subjects Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0% Grade 4: 0% Grade 5: 0% Advanced RCC in combination with nivolumab in treatment-naïve adults (Study CA2099ER): 6 of 320 (1.9%) subjects Grade 1: 0.3% Grade 2: 1.2% Grade 3: 0.3% Grade 4: 0% Grade 5: 0% HCC in adults who have previously been treated with sorafenib (Study XL184-309): 4 of 467 (0.9%) subjects Incidence (by highest grade reported): Grade 1: 0.2% Grade 2: 0.2% Grade 3: 0% Grade 4: 0.2% Grade 5: 0.2% Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311): 0 of 125 (0%) subjects

Potential risk	Carcinogenicity
	Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0% Grade 4: 0% Grade 5: 0% Advanced RCC following prior VEGF-targeted therapy (PASS Study F-FR-60000-001 (CASSIOPE)): 24 of 679 (3.5%) subjects Incidence (by highest grade reported): Grade 1: 0.4% Grade 2: 0.6% Grade 3: 1.5% Grade 4: 0.4% Grade 5: 0.9% Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602): 0 of 195 (0%) subjects Incidence (by highest grade reported): Grade 1: 0% Grade 2: 0% Grade 3: 0% Grade 4: 0% Grade 5: 0%
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.
Preventability:	None described.
Impact on the risk-benefit balance of the product:	Events as described can have debilitating, disabling or fatal outcomes.
Public health impact:	Advanced RCC monotherapy in adults Four subjects in the cabozantinib arm of Study XL184-308 experienced second primary malignancies that were not related to RCC. The following second primary malignancies were reported in one subject each: adenocarcinoma, adenocarcinoma of the colon, basal cell carcinoma and chronic lymphocytic leukaemia. No subjects in the cabozantinib arm of Study A031203 experienced second primary malignancies. Given that the RCC patient population is limited, 1.2% and 0% of subjects experienced second primary malignancies that were not related to RCC in Studies XL184-308 and A031203, respectively, and the reporting rate from the Cabometyx postmarketing experience is 0.05%, the impact on public health is expected to be minimal. Advanced RCC in combination with nivolumab in treatment-naïve adults Six subjects in the cabozantinib in combination with nivolumab arm of Study CA2099ER experienced second primary malignancies that were not related to RCC. The following second primary malignancies included basal cell carcinoma (2), squamous cell carcinoma (2), bladder neoplasm (1), and keratoacanthoma (1). None of these events were assessed as related to treatment. Given that the RCC patient population is limited, 1.9% of subjects experienced second primary malignancies that were not related to RCC in Study CA2099ER and the reporting rate from the Cabometyx postmarketing experience is 0.05%, the impact on public health is expected to be minimal.

Potential risk	Carcinogenicity
	HCC in adults who have previously been treated with sorafenib Four subjects in the cabozantinib arm of Study XL184-309 experienced second primary malignancies that were not related to HCC. Two subjects experienced AEs of squamous cell carcinoma assessed as not related to cabozantinib: one subject had a medical history of squamous cell carcinoma; one subject experienced squamous cell carcinoma of the larynx, which was assessed as a second primary malignancy, signs of which (dysphonia) predated the first dose of study treatment. Additionally, one subject experienced a new onset secondary malignancy of acute lymphocytic leukaemia and one subject with a prior history of breast cancer experienced a new onset secondary malignancy of intraductal proliferative breast lesion; both of these events were assessed as not related to cabozantinib. Given that the HCC patient population is limited, 0.9% of subjects experienced second primary malignancies that were not related to HCC in Study XL184-309, and the reporting rate from the Cabometyx postmarketing experience is 0.05%, the impact on public health is expected to be minimal. Progressive, locally advanced or metastatic DTC in adults following prior systemic therapy and refractory to radioactive iodine (Study XL184-311) No subjects were identified to have developed secondary malignancies. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy (Study A021602) No subjects were identified to have developed primary or secondary malignancies.
MedDRA PTs:	MedDRA terms can be found in Annex 7.

AE=adverse event; CI=confidence interval; DLP=data lock point; DTC=differentiated thyroid carcinoma; ETM=event to monitor; HCC=hepatocellular carcinoma; MedDRA=Medical Dictionary for Regulatory Activities; PASS=post-authorisation safety study; PT=preferred term; RCC=renal cell carcinoma; RMP=risk management plan; TEAE=treatment-emergent adverse event; VEGF=vascular endothelial growth factor.

Source for Study A021602: Incidence of TEAEs by ETM, PT and Severity (sorted by alphabetic order), with CI - Safety Population, A021602 study, RMP Analyses (DLP 24 August 2023).

SVII.3.2. Presentation of the Missing Information

Not applicable.

Part II: Module SVIII – Summary of the Safety Concerns

Summary of Ongoing Safety Concerns

Important identified and potential risks are summarised in Table 47.

Table 47 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Gastrointestinal perforation • Gastrointestinal and nongastrointestinal fistula • Thromboembolic events • Haemorrhage (Grade ≥3) • Wound complications • Posterior reversible encephalopathy syndrome (PRES) • Osteonecrosis
Important potential risks	• Renal failure • Hepatotoxicity • Embryotoxicity • Carcinogenicity
Missing information	• None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance will be conducted to monitor the safety of Cabometyx and to detect any change in its risk-benefit balance.

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are presented below.

Specific adverse reaction follow-up questionnaires:

Not applicable.

Other forms of routine pharmacovigilance activities for Medication errors:

Patterns of use in the authorised indications for cabozantinib are monitored for medication errors. The reporter of AEs is requested to provide the following additional elements: a) the indication, b) the formulation, and c) the dose; aggregate information is assessed as part of PSUR aggregate reporting. Medication errors involving cabozantinib in combination with nivolumab will be followed up during postmarketing use to monitor whether the recommended dose of 40 mg Cabometyx is being used.

Other Forms of Routine Pharmacovigilance Activities for Hepatotoxicity with Combination Therapy

Postmarketing serious reports of hepatotoxicity with cabozantinib in combination with nivolumab for the treatment of advanced RCC in adults will be evaluated in the PSURs.

III.2 Additional Pharmacovigilance Activities

Not applicable. Following completion and submission of the CASSIOPE Study F-FR-60000-001 ‘Prospective non-interventional study of cabozantinib tablets in adults with advanced RCC following prior VEGF-targeted therapy,’ Clinical Study Report (CSR) (submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) on 24 March 2023) was removed from cabozantinib’s Risk Management Plan.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 48 Summary of Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit-risk)				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit-risk)				
Not applicable				
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
Not applicable				

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no planned or ongoing post-authorisation efficacy studies which are conditions of the marketing authorisation or Specific Obligations for cabozantinib.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

Routine risk minimisation is proposed for the important identified risks. Most identified risks occurred infrequently or have been observed with other drugs that inhibit the VEGF pathway. The infrequent nature of some of the risks would preclude additional risk minimisation activities that would be beneficial to patients.

Routine risk minimisation is also proposed for the important potential risks, as these are risks for populations in which no data or limited data are available. Physician and patient assessment of risk-benefit would be required for use in these settings. The use of standard queries is aimed to identify if there are any additional at risk population subgroups or ways of managing the risks that might warrant future risk minimisation activities.

V.1 Routine Risk Minimisation Measures

Details of the routine risk minimisation measures are provided in Table 49.

Table 49 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Gastrointestinal perforation	**Routine risk communication:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendations for management of suspected ADRs by dose interruption/reduction are included in SmPC Section 4.2. Recommendation for evaluation and monitoring of patients with inflammatory bowel disease, tumour infiltration in the GI tract or complications from prior GI surgery is included in SmPC Section 4.4. Discontinuation of cabozantinib in patients with GI perforation that cannot be adequately managed is recommended in SmPC Section 4.4. What patients need to know or tell their doctor or pharmacist before taking Cabometyx is included in PL Section 2. How to detect signs and symptoms of GI perforation and details for reporting side effects are described in PL Section 4. **Other routine risk minimisation measures beyond the Product Information:** **Legal status:** Restricted medical prescription.

Safety concern	Routine risk minimisation activities
Gastrointestinal and nongastrointestinal fistula	**Routine risk communication:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendations for management of suspected ADRs by dose interruption/reduction are included in SmPC Section 4.2. Recommendation for evaluation and monitoring of patients with inflammatory bowel disease, tumour infiltration in the GI tract or complications from prior GI surgery is included in SmPC Section 4.4. Warning that persistent or recurring diarrhoea while on treatment may be a risk factor for the development of anal fistula is included in SmPC Section 4.4. Discontinuation of cabozantinib in patients with GI fistula that cannot be adequately managed is recommended in SmPC Section 4.4. What patients need to know or tell their doctor or pharmacist before taking Cabometyx is included in PL Section 2. Warning that a painful tear or abnormal connection of the tissues in the body is an common side effect and details for reporting side effects is described in PL Section 4. **Other routine risk minimisation measures beyond the Product Information:** **Legal status:** Restricted medical prescription.
Thromboembolic events	**Routine risk communication:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8[a] PL Section 2 PL Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendations for management of suspected ADRs by dose interruption/reduction are included in SmPC Section 4.2. Recommendation that cabozantinib should be used with caution in patients who at risk for, or have a history of, thromboembolic events is included in SmPC Section 4.4. Discontinuation of cabozantinib in patients who develop acute myocardial infarction, or any other clinically significant thromboembolic complication is recommended in SmPC Section 4.4. What patients need to know or tell their doctor or pharmacist before taking Cabometyx is included in PL Section 2. Warning that blood clots in the veins and lungs is a common side effect and blood clots in arteries is an uncommon side effect and details for reporting side effects is described in PL Section 4. **Other routine risk minimisation measures beyond the Product Information:** **Legal status:** Restricted medical prescription.

Safety concern	Routine risk minimisation activities
Haemorrhage (Grade ≥3)	**Routine risk communication:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendations for management of suspected ADRs by dose interruption/reduction are included in SmPC Section 4.2. Recommendation for evaluation of patients with a history of severe bleeding prior to treatment initiation and warning that cabozantinib should not be administered to patients that have, or are at risk for, severe haemorrhage is included in SmPC Section 4.4. What patients need to know or tell their doctor or pharmacist before taking Cabometyx is included in PL Section 2. How to detect signs and symptoms of bleeding and details for reporting side effects is included in PL Section 4. **Other routine risk minimisation measures beyond the Product Information:** **Legal status:** Restricted medical prescription.
Wound complications	**Routine risk communication:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendations for management of suspected ADRs by dose interruption/reduction is included in SmPC Section 4.2. Recommendation that cabozantinib treatment should be stopped at least 28 days prior to scheduled surgery, including dental surgery or invasive dental procedures, if possible, and that the decision to resume cabozantinib therapy after surgery should be based on clinical judgement of adequate wound healing is included in SmPC Section 4.4. Discontinuation of cabozantinib in patients with wound healing complications requiring medical intervention is recommended in SmPC Section 4.4. What patients need to know or tell their doctor or pharmacist before taking Cabometyx is included in PL Section 2. Warnings to report a wound that does not heal to a doctor immediately and that wound complications are an uncommon side effect included in PL Section 4. **Other routine risk minimisation measures beyond the Product Information:** **Legal status:** Restricted medical prescription.

Safety concern	Routine risk minimisation activities
Posterior reversible encephalopathy syndrome (PRES)	**Routine risk communication:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendations for management of suspected ADRs by dose interruption/reduction is included in SmPC Section 4.2. Recommendations for management of severe hypertensive events, known risk factors of PRES are included in Section 4.4 of the SmPC. Warning that PRES should be considered in any patient presenting with multiple symptoms, including seizures, headache, visual disturbances, confusion or altered mental function and that cabozantinib should be discontinued in patients with PRES is included in SmPC Section 4.4. What patients need to know or tell their doctor or pharmacist before taking Cabometyx is included in PL Section 2. How to detect signs and symptoms of PRES and that PRES is an uncommon side effect is described in PL Section 4. Details for reporting side effects are included in PL Section 4. **Other routine risk minimisation measures beyond the Product Information:** **Legal status:** Restricted medical prescription.
Osteonecrosis	**Routine risk communication:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendations for management of suspected ADRs by dose interruption/reduction is included in SmPC Section 4.2. Recommendation that an oral examination should be performed prior to initiation of cabozantinib and periodically during cabozantinib therapy and cabozantinib should be used with caution in patients receiving agents associated with ONJ, such as bisphosphonates, is included in SmPC Section 4.4. Recommendation that cabozantinib treatment should be held at least 28 days prior to scheduled dental surgery or invasive dental procedures, if possible and cabozantinib treatment should be discontinued in patients who experience ONJ is included in SmPC Section 4.4. Recommendation to inform the doctor if the patient has had surgery within the last month or if surgical procedures are planned, including dental surgery, included in PL Section 2. Warning that bone damage in the jaw is an uncommon side effect and details for reporting side effects included in PL Section 4. **Other routine risk minimisation measures beyond the Product Information:** **Legal status:** Restricted medical prescription.

Safety concern	Routine risk minimisation activities
Important potential risks	
Renal failure	**Routine risk communication:** SmPC Section 4.2 SmPC Section 4.8 SmPC Section 5.2 PL Section 2 PL Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendations that cabozantinib should be used with caution in patients with mild or moderate renal impairment and should not be used in patients with severe renal impairment are included in SmPC Section 4.2. What patients need to know or tell their doctor or pharmacist before taking Cabometyx is included in PL Section 2. Warnings that changes in blood tests used to monitor general health and function of the organs (including the kidney) and low levels of electrolytes are very common side effects, with protein in urine listed as a common side effect, and details for reporting side effects included in PL Section 4. **Other routine risk minimisation measures beyond the Product Information:** **Legal status:** Restricted medical prescription.
Hepatotoxicity	**Routine risk communication:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 SmPC Section 5.2 PL Section 2 PL Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Statements that in patients with mild hepatic impairment, no dose adjustment is required, since only limited data are available for patients with moderate hepatic impairment (Child Pugh B), no dose recommendation can be provided and that cabozantinib is not recommended for use in patients with severe hepatic impairment (Child Pugh C) are included in SmPC Section 4.2. Recommendation for management of hepatotoxicity by dose interruption and to consider use of corticosteroids if immune-mediated reaction is suspected when cabozantinib is used in combination with nivolumab in RCC and that treatment should be re-initiated with a single medicine or sequential re-initiating with both medicines after recovery in SmPC Section 4.2. Recommendation that liver function tests should be performed before initiation of and periodically throughout treatment with cabozantinib, that patients with mild or moderate hepatic impairment are monitored closely during treatment and that higher frequencies of Grades 3 and 4 ALT and AST elevations have been reported in patients with advanced RCC treated with cabozantinib in combination with nivolumab relative to cabozantinib monotherapy in SmPC Section 4.4. What patients need to know or tell their doctor or pharmacist before taking Cabometyx is included in PL Section 2. Warnings that change in blood tests used to monitor general health and function of the organs (including the liver) is a very common side effect and that an increase in the level of bilirubin in the blood is a common side effect are included in PL Section 4. Details for reporting side effects are included in PL Section 4. **Other routine risk minimisation measures beyond the Product Information:** **Legal status:** Restricted medical prescription.

Safety concern	Routine risk minimisation activities
Embryotoxicity	**Routine risk communication:** SmPC Section 4.5 SmPC Section 4.6 SmPC Section 5.3 PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation to use an additional contraceptive method, such as a barrier method, as unchanged contraceptive effect may not be guaranteed is included in SmPC Sections 4.5 and 4.6. Recommendation for women of child-bearing potential and female partners of male patients taking cabozantinib to avoid pregnancy by using effective methods of contraception during therapy and for at least 4 months after completing therapy is included in SmPC Section 4.6. Recommendation that cabozantinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with cabozantinib is included in SmPC Section 4.6. Nonclinical studies have shown embryo–foetal and teratogenic effects below human exposure levels at intended therapeutic doses (SmPC Section 5.3). Warning that oral contraceptives may be ineffective while taking cabozantinib and therefore a barrier contraceptive should also be used while taking cabozantinib and for at least 4 months after treatment has finished (PL Section 2). Recommendation to seek advice from a doctor before taking cabozantinib if a patient, or their partner, is planning to have a baby after treatment has finished is included in PL Section 2. **Other routine risk minimisation measures beyond the Product Information:** **Legal status:** Restricted medical prescription.
Carcinogenicity	**Routine risk communication:** SmPC Section 5.3 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Cabozantinib was not carcinogenic in the nonclinical studies performed in rasH2 mouse model at a slightly higher exposure than the intended human therapeutic exposure. The clinical relevance of the observed neoplastic lesions in rats is uncertain, but likely to be low (SmPC Section 5.3). **Other routine risk minimisation measures beyond the Product Information:** **Legal status:** Restricted medical prescription.

ADR=adverse drug reaction; ALT=alanine aminotransferase; AST=aspartate transaminase; GI=gastrointestinal; ONJ=osteonecrosis of jaw; PL=package leaflet; PRES=posterior reversible encephalopathy syndrome; RCC=renal cell carcinoma; SmPC=summary of product characteristics.

a Data in this section relate to events of pulmonary embolism, venous thrombosis and arterial thrombosis.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 Routine Risk Minimisation Measures, are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

A summary of risk minimisation measures for cabozantinib is presented in Table 50.

Table 50 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Gastrointestinal perforation	**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	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.
Gastrointestinal and nongastrointestinal fistula	**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	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.
Thromboembolic events	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8[a] PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.
Haemorrhage (Grade ≥3)	**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	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.
Wound complications	**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	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Posterior reversible encephalopathy syndrome (PRES)	**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	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.
Osteonecrosis	**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	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.
Important potential risks		
Renal failure	**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	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.
Hepatotoxicity	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 SmPC Section 5.2 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.
Embryotoxicity	**Routine risk minimisation measures:** SmPC Section 4.5 SmPC Section 4.6 SmPC Section 5.3 PL Section 2 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Carcinogenicity	**Routine risk minimisation measures:** SmPC Section 5.3 Restricted medical prescription **Additional risk minimisation measures:** None	Routine pharmacovigilance activities Additional pharmacovigilance activity: None.

PL= package leaflet; PRES=posterior reversible encephalopathy syndrome; SmPC=summary of product characteristics.

a Data in this section relate to events of pulmonary embolism, venous thrombosis and arterial thrombosis.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

This is a summary of the 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 and uncertainties (missing information).

Cabometyx's SmPC and its package leaflet (PL) 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 of 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 is it Used for

Cabometyx is authorised as monotherapy for the treatment of advanced RCC in adults following prior VEGF-targeted therapy and in treatment-naïve adults with intermediate or poor-risk and for the treatment of HCC in adults who have previously been treated with sorafenib (see SmPC for the full indication).

Cabometyx is authorised for the first-line treatment of advanced RCC in adults in combination with nivolumab (see SmPC for the full indication).

Cabometyx is authorised as monotherapy for the treatment of adult patients with locally advanced or metastatic DTC, refractory or not eligible to RAI who have progressed during or after prior systemic therapy.

The proposed expanded indication for Cabometyx is for the treatment of adult patients with unresectable or metastatic, well differentiated extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumours, who have progressed following at least one prior systemic therapy other than somatostatin analogues.

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 as 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 PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Cabometyx is not yet available, it is listed under 'missing information' below.

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 nongastrointestinal fistula • Thromboembolic events • Haemorrhage (Grade ≥3) • Wound complications • Posterior reversible encephalopathy syndrome (PRES) • 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 GI perforation was identified from cabozantinib clinical studies. Additional data confirming the risk were from postmarketing use of cabozantinib. Gastrointestinal perforation has been reported in Studies XL184-308, A031203, CA2099ER, XL184-309, XL184-311 and A021602 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.

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

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

Important identified risk – Gastrointestinal and nongastrointestinal 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, XL184-311 and A021602, 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 nonGI 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=package 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. Arterial thromboembolism events were reported in Studies XL184-308, A031203, CA2099ER, XL184-309, XL184-311 and A021602. 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 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; HCC=hepatocellular carcinoma; PL=package leaflet; 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, XL184-311 and A021602. A similar risk was observed with other VEGF-TKIs 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.

Important identified risk – Haemorrhage (Grade ≥3)	
	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=package leaflet; RCC=renal cell carcinoma; 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 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, XL184-311 and A021602, confirmed by wound complications 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.
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 (buildup 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=package 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 (PRES)	
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 the Studies XL184-311 and A021602 two subjects experienced PRES in cabozantinib arm, 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 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None

PL=package leaflet; PRES=posterior reversible encephalopathy syndrome; RCC=renal cell carcinoma; 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 (bone damage in the jaw) was reported in Studies XL184-308, CA2099ER and XL184-311. Osteonecrosis of the jaw was not seen in Studies A031203 or XL184-309 and A021602. Six subjects in the cabozantinib arm of the Study A021602 had an event included in the ETM list of osteonecrosis. Osteonecrosis of the jaw 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

ETM=event to monitor; ONJ=osteonecrosis of the jaw; PL=package leaflet; RCC=renal cell carcinoma; SmPC=summary of product characteristics.

Important identified risk – Osteonecrosis	
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, XL184-309, XL184-311 and A021602. 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=package 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 and A021602[a]. 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 4patients 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 4.8

Important potential risk – Hepatotoxicity	
	SmPC Section 5.2 PL Section 2 PL Section 4 Restricted medical prescription **Additional risk minimisation measures:** None

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; PL=package leaflet; SmPC=summary of product characteristics; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor.

a The reported AEs of ALT increased and AST increased from the Study A021602 are considered expected and their presence/absence should be solicited, per the study protocol.

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 28 November 2023. 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 child-bearing potential or female partners of male patients treated with cabozantinib. <u>Risk factor in cancer patients receiving chemotherapy</u> 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 4.5 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 28 November 2023. 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 Post-authorisation Development Plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation.

II.C.2 Other studies in post-authorisation development plan

[redacted]

PART VII: ANNEXES

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Annex 4 – Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Not applicable