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:	2
Product concerned (brand name):	Cabometyx® and Cometriq®

Data lock point (DLP) for this RMP: 28 November 2025
Version Number: 9.1
Date of final sign off: 09 April 2026

Rationale for submitting an updated RMP:

- In line with GVP module V Revision 2, all safety concerns for cabozantinib (Cabometyx and Cometriq) have been removed from the RMP, as they no longer meet the criteria for an important identified risk or important potential risk. As no additional risk minimisation measures or additional PV activities are required, their inclusion in the RMP is no longer justified.
- This RMP for cabozantinib represents the merger of the separate RMPs for cabozantinib marketed under both products (Cabometyx (tablet formulation) and Cometriq (capsule formulation)) by Ipsen Pharma into one consolidated RMP.

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.

CCI

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		This part was updated to merge the cabozantinib products, Cabometyx and Cometriq, which share the same active substance and are marketed by the same Marketing Authorisation Holder. The product overview reflects both products, their respective indications, dosages and pharmaceutical forms. Neuroendocrine tumours (NET) indication status changed from proposed to approved for Cabometyx.
Part II Safety Specification	**Module SI** Epidemiology of the Indication(s) and Target Population(s)	This part was updated to merge the epidemiology information of both the products (Cabometyx and Cometriq). Epidemiology information for medullary thyroid carcinoma (MTC) indication from Cometriq RMP was added. Neuroendocrine tumours (NET) indication changed from "proposed expanded indication" in Cabometyx RMP version 9.0 to an approved indication in this updated RMP, with the indication wording remaining unchanged.
	Module SII Nonclinical Part of the Safety Specification	This part was updated to merge the nonclinical safety data of both products (Cabometyx and Cometriq).
	Module SIII Clinical Trial Exposure	This part was updated to merge the clinical trial exposure data of both products (Cabometyx and Cometriq). Clinical trial exposure data from Cometriq development programme for MTC indication was included.
	Module SIV Populations Not Studied in Clinical Trials	This part was updated to merge the information on populations not studied across both products (Cabometyx and Cometriq) clinical development programmes.

Part	Module/Annex	Significant changes in this RMP
	Module SV Post-authorisation-authorisation Experience	This part was updated to merge the post-authorisation experience data of both products (Cabometyx and Cometriq). Post-authorisation exposure was updated on the basis of most recent periodic safety update report data (data lock point 28 November 2025). Updated cumulative patient exposure data for Cabometyx and Cometriq. Included combined total cabozantinib exposure (both formulations). Updated NET indication status from proposed to approved for Cabometyx.
	Module SVI Additional European Union (EU) Requirements for the Safety Specification	No change.
	Module SVII Identified and Potential Risks	Merged safety concern from initial Cometriq RMP. All safety concerns including important identified risks and important potential risks were removed. Rationale for the removal of these risks from the RMP was provided.
	Module SVIII Summary of the Safety Concerns	All safety concerns including important identified risks and important potential risks were removed. Rationale for the removal of these risks from the RMP was provided.
Part III Pharmacovigilance Plan (including post-authorisation safety studies)		This part was updated to merge the pharmacovigilance plans of both products (Cabometyx and Cometriq).
Part IV Plans for Post-authorisation Efficacy Studies		No change.
Part V Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)		This part was updated to remove all risk minimisation measures as all safety concerns have been removed from the RMP.
Part VI Summary of the RMP		This part was updated to merge information from both products (Cabometyx and Cometriq). Updated NET indication from “proposed” to “authorised” for Cabometyx.

Part	Module/Annex	Significant changes in this RMP
Part VII Annexes	Annex 1 EudraVigilance Interface	No change.
	Annex 2 Tabulated Summary of Planned, Ongoing and Completed Pharmacovigilance Study Programme	This part was updated to merge the pharmacovigilance study programmes of both products (Cabometyx and Cometriq). Added new Table 43 “Planned and Ongoing Studies” showing “None” as ongoing studies. Expanded Table 44 (formerly Table 51) “Completed Studies” to include completed studies from both Cabometyx and Cometriq programmes.
	Annex 3 Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan	No change.
	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)	This part was updated to merge the supporting data of both products (Cabometyx and Cometriq). Removed “MedDRA Terms Used for Postmarketing Surveillance of Identified and Potential Risks” as all safety concerns have been removed from the RMP. Added new references related to MTC epidemiology information from Cometriq RMP.

Part	Module/Annex	Significant changes in this RMP
	Annex 8 Summary of Changes to the RMP Over Time	This part was updated to merge the RMP version histories of both products (Cabometyx and Cometriq). Added "Summary of Changes to the Cometriq Risk Management Plan Over Time" documenting complete RMP version history for Cometriq. Retained complete Cabometyx RMP version history. Added entry for current Version 9.1.

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

Cabometyx	
Version number	9.0
Approved with procedure	EMEA/H/C/004163/II/0040
Date of approval (opinion date)	23 July 2025
Cometriq	
Version number	5.5
Approved with procedure	EMEA/H/C/002640/II/0044
Date of approval	16 September 2021

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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
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
GI	Gastrointestinal
GVP	Good Pharmacovigilance Practices
HCC	Hepatocellular carcinoma
ICI	Immune checkpoint inhibitor
INN	International Nonproprietary Name
IV	Intravenously
MA	Marketing authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MAP	Managed access programme
MedDRA	Medical Dictionary for Regulatory Activities
MTC	Medullary thyroid carcinoma/cancer
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
RMM	Risk minimisation measure
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	Ipsen Pharma
Medicinal products to which this RMP refers	Two
Invented name(s) in the European Economic Area (EEA)	Cabometyx® and Cometriq®
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 Cabometyx: Tablet content: *Active substance:* Cabozantinib *Excipients:* Microcrystalline cellulose Anhydrous lactose Hydroxypropyl cellulose Croscarmellose sodium Colloidal anhydrous silica Magnesium stearate Film-coating: Hypromellose 2910 Titanium dioxide (E171) Triacetin Iron oxide yellow (E172) Cometriq: Capsule content *Active substance:* Cabozantinib *Excipients:* Microcrystalline cellulose Croscarmellose sodium Sodium starch glycolate Silica colloidal anhydrous Stearic acid Capsule shell Gelatin Black iron oxide (E172) (20 mg capsules only) Red iron oxide (E172) (80 mg capsules only) Titanium dioxide (E171) Printing ink Shellac Black iron oxide (E172) Propylene glycol
Hyperlink to the Product Information	Cabometyx Product Information Cometriq Product Information

Indication(s) in the EEA	Current: Cabometyx: 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. 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. Cometriq: Medullary Thyroid Carcinoma (MTC) Cometriq is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma. Proposed (if applicable): Cabometyx: Not applicable Cometriq: Not applicable

Dosage in the EEA	Current: Cabometyx: *Cabometyx as monotherapy* For RCC, HCC, DTC and NET, 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 solution for infusion administered intravenously at either 240 mg every 2 weeks or 480 mg every 4 weeks, or with nivolumab solution for injection administered subcutaneously at either 600 mg every 2 weeks or 1200 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). Cometriq: The recommended dose of Cometriq is 140 mg once daily, taken as one 80 mg orange capsule and three 20 mg grey capsules. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.
	Proposed (if applicable): Cabometyx: Not applicable Cometriq: Not applicable
Pharmaceutical form(s) and strengths	Current: Cabometyx: Film-coated tablets containing cabozantinib (S)-malate equivalent to either 20 mg, 40 mg or 60 mg cabozantinib. Cometriq: Hard capsules containing cabozantinib (S)-malate equivalent to either 20 mg or 80 mg cabozantinib.
	Proposed (if applicable): Cabometyx: Not applicable Cometriq: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

ATC=anatomical therapeutic chemical; DTC=differentiated thyroid carcinoma; EU=European Union; FLT3=Fms like tyrosine kinase-3; Gas6= growth arrest-specific gene 6; HCC=hepatocellular carcinoma; MA=marketing authorisation;

MET=mesenchymal epithelial transition; MTC=medullary thyroid carcinoma; 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; TIE-2=tyrosine kinase with immunoglobulin-like and EGF-like domains 2; 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.

- **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 approved indication for Cometriq is:

- **Medullary Thyroid Carcinoma (MTC)**

Cometriq is indicated for the treatment of adult patients with progressive, unresectable, locally advanced or metastatic MTC.

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) [1]. Renal cell carcinoma is the main type of kidney cancer, which comprises more than 90% of kidney cancer [2, 3]. • The global incidence of kidney cancer is approximately 431,000 in 2020 and results in about 179,000 deaths [1]. • In the USA, the incidence rate of kidney cancer has generally increased (approximately 0.6% annually) over the past decade. For example, the incidence

Incidence of target indication	Advanced RCC in adult patients
	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 [4]. • In Europe, the incidence of kidney cancer is approximately 138,000 in 2020 [5].
Prevalence of target indication	• The 5-year prevalence numbers were highest in Asia (409,111) and lowest in Oceania (17,044) by GLOBOCAN 2020 [1]. • In 2019, 599,072 people were reported living with kidney and renal pelvis cancer in the USA by the SEER programme [6]. • According to GLOBOCAN 2020, the 5-year prevalence (all ages) was 405,983 in Europe (all regions) [5].
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) [7]. • 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) [1]. • 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) [6].
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 [7]. 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 [8]. 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 [9]. Chronic kidney disease and end-stage renal disease is attributed in the increased risk of kidney cancer [10, 11]. Additionally, a meta-analysis of cohort studies (1996-2010) indicates a positive association between diabetes and kidney cancer with an excess risk of 40% [12]. 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 [13, 14]. Tobacco smoking is classified as carcinogenic for the kidney cancer by the International Agency for Research on Cancer [15]. 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 [16]. Several studies conclude the risk of alcohol consumption of (moderate intake) is lower compared to non-drinkers or occasional drinkers. cancer [17, 18, 19]. Among environmental exposures, trichloroethylene used most as metal cleaner and degreaser is identified as a human carcinogen causing kidney cancer based on sufficient evidence.[15] Additionally, other environmental exposures such as the ingestion of Aristolochia plants is historically linked to carcinomas of the urinary tract [20]. Majority of the kidney cancers are sporadic with 3-5% with a familial context.[17] 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

Incidence of target indication	Advanced RCC in adult patients
	the kidney cancers. [21] Genome-wide association studies (GWAS) additionally have identified 13 loci at-risk for the development of kidney cancer [22].
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. • 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.

Incidence of target indication	Advanced RCC in adult patients
	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 [23, 24, 25]. 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 [26, 27, 28]. • 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. [26] Vascular endothelial growth factor is present in most RCC cells with no difference among the RCC types [29]. • 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 [26]. • 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 [30, 31, 32]. 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 [33, 34].
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 [7, 22].

ASR=age-standardised 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; HLRCC=hereditary leiomyomatosis renal cell carcinoma; 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; Pvhl=von Hippel-Lindau protein; 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;

Incidence of target indication	**Advanced RCC in adult patients**

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) [35, 36]. • 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 [37, 38]. • 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 [39]. • The incidence in the EU was 87,630 cases in 2020 [40, 41]. The estimated incidence of liver cancer in the USA in 2023 is approximately 41,210 cases [32]. • The global prevalence of HCC increased from an estimated 437,408 cases in 1990 to 714,600 new cases in 2002 [42]. • In 2020, there were an estimated 905,700 cases of liver cancer globally [38].
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 [40, 41]. • 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 [43]. • 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) [44]. • 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 [44].
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; [44, 45]), alcoholic liver disease [46] NAFLD such as NASH [47, 48, 49], tobacco [50, 51] and genetic susceptibility [52, 53]. • 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 [47]. • Some degree of cirrhosis is present in 80% to 90% of patients with HCC [36].
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

Indication/target population	HCC in adult patients
	tumour is recommended in patients with early-stage disease and preserved liver function [54]. • 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 [55]. • 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) [56]. • 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 and advanced liver disease or co-morbidities that restrict treatment to best supportive care [57]. • 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 [58, 59, 60]. • 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 [60]. • 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 [61]. • 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 [62]. 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 [63]. • In subsequent lines, the targeted therapies cabozantinib (CELESTIAL trial) [64] and regorafenib (RESORCE trial) [65] as well as the VEGFR2-targeting antibody ramucirumab (REACH-2 trial) [66] 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 [67]. • 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 [67]. • The histopathologic appearance of HCC exhibits substantial heterogeneity, with varied morphologic subtypes observed. Such subtypes include

Indication/target population	HCC in adult patients
	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 [67]. • Patients with HCC often experience no symptoms until their disease is advanced. HCC becomes severely debilitating as it progresses: patients may report symptoms, which are severe enough to affect their quality of life such as sleep disorders, sexual dysfunction, gynaecomastia, pruritus, fatigue and muscle cramps [68]. • In 2020, 830,200 deaths due to liver cancer occurred worldwide [69]. • The estimated mortality rate of liver cancer in the USA in 2023 will be approximately 29,380 cases [70], while mortality in the EU was 78,415 cases in 2020 [71]. • 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) [72]. • 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) [73].
Important co-morbidities	• Hepatocellular carcinoma is frequently complicated by the presence of co-morbid conditions, which can compromise liver function and affect outcomes [74], including liver cirrhosis, infection with HBV or HCV [67, 75], and metabolic co-morbidities, e.g. diabetes mellitus [76]. • 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 [77]. • 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 [78]. • Hepatic encephalopathy can be present in 18% of patients at the initial diagnosis of HCC [79], while at the end stages of HCC, intractable encephalopathy almost invariably occurs in most patients [79].

AFP=alpha-fetoprotein; CTLA 4=Cytotoxic T-Lymphocyte-Associated protein 4; 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% [80]. • In 2020, over 87,000 new cases and over 6000 deaths were reported in Europe [81]; 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 [82]. 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 [83]. • Thyroid cancer is about 2.5 times more common in women than in men, and the incidence has doubled from 2000 through 2019 [82].
Risk factors for the disease	• Risk factors for DTC include a diet low in iodine and environmental radiation exposure [84]. • 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 [84].

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 [84]. • Patients who develop RAI-refractory DTC have a very poor prognosis with an estimated median survival time of 2.53.5 years [84]. • 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 [84]. • 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 [85, 86]. • 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 [87]. 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 [84]. 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 [84]. • 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 [83].
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 [88].

EMA=European Medicines Agency; ESMO=European Society for Medical Oncology; NTRK=neurotrophic tyrosine receptor kinase; RAI= radioactive iodine; RET=rearranged during transfection; TKI=Tyrosine kinase inhibitors; 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 [89]. • 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 [90]. • 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 [91]. • 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% [92]. • 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 [89]. • 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 [92].
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%) [91]. • Additionally, 10,102 NEN patients from seven 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 [93].
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 [94]. • 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 [95].

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 [96, 97]. 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 [96]). • 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 [96]. 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 [96]. • For patients with progressive pancreatic NET, approved treatment options include the mTOR inhibitor everolimus, the tyrosine kinase inhibitor sunitinib [98, 99] and for patients with SSTR+ disease, the peptide receptor radionuclide therapy (PRRT) lutetium-177 (Lu-177) dotatate [100]. For patients with progressive gastrointestinal NET, approved treatment options include everolimus and Lu-177 dotatate for SSTR+ disease [100, 101]. For patients with lung NET, the only approved treatment is everolimus [101]. • 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 [96].
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% [102]. The 5-year survival of GI NET was 98% in localised tumours and 68% in distant [103]. The 5-year survival in pulmonary NET was 89% [104]. • 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 [105]. • The speed of tumour growth in general slow for NET with roughly 50% of NET originating within the GI system including the pancreas [106]. • Neuroendocrine tumours patients often have symptoms related to hormonal hypersecretion which commonly come in the forms of diarrhoea, flushing, bronchospasm, and hypertension [107, 108].
Important co-morbidities	• Chronic pancreatitis is linked to pancreatic NET, but clear literature is difficult to identify [109]. • 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 [110].

BMI=body mass index; EMA=European Medicines Agency; ESMO=European Society for Medical Oncology; GI=gastrointestinal; IQR-interquartile range; mTOR=mammalian target of rapamycin; NEC=neuroendocrine carcinoma; NEN=neuroendocrine neoplasm; NET=neuroendocrine tumour; US=United States; WHO=World Health Organization.

SI.1.5. Medullary Thyroid Carcinoma (MTC)

The epidemiology of thyroid cancer, per se, is well-characterised and understood. The epidemiology of the MTC subset is less well described. In general, the medullary subtype comprises anywhere from <5% to 10% of all thyroid carcinomas [111, 112, 113]. Accordingly, many of the figures in the discussion below naturally arise from extrapolation of published numbers. The risk factors for MTC are becoming known and are outlined below, as are the concomitant medicines that are commonly used and the symptoms experienced by individuals with this cancer. Finally, due to recent clinical trial activity in the realm of advanced and metastatic MTC, the symptoms experienced by the individuals inflicted with this disease have been elucidated, as has the natural course of the disease. These data are valuable in understanding this subset of thyroid carcinoma.

The incidence, prevalence, natural history (including morbidity and mortality), risk factors, demographics, treatment options and important co-morbidities are summarised in Table 8.

Table 8 Epidemiology of Patients with Medullary Thyroid Carcinoma

Indication/ target population	**MTC in adult patients**
Incidence of target indication	• MTC accounts for 5% to 10% of thyroid cancer cases [112, 113]
Prevalence of target indication	• Approximately half of the patients with MTC present with disease localised to the thyroid gland, one third of patients present with locally invasive tumours or clinically apparent spread to the regional lymph nodes and distant metastases are observed at presentation in 7% to 23% of MTC cases [111, 113, 114]. • The best estimates of incidence and prevalence arise from a compilation of the data and extrapolation from a number of different sources including Orphanet, Cancer Research UK and the NCI's SEER database. These data show that EU incidence is <2000 per year with a prevalence of <7/100,000. In the United States of America incidence is <2000 annually with a prevalence of 8.6/100,000. • In 2012, there were an estimated 300,000 new cases of thyroid cancer diagnosed worldwide. The highest incidence rates were seen in selected countries of South and North America, Italy, Japan and the Pacific Islands [115].
Natural history, including mortality and morbidity	• The 10-year disease-specific survival of MTC is about 75%. Prognostic factors that predict adverse outcome include advanced age at diagnosis, extent of primary tumour nodal disease and distant metastases [116]. • Patients with disease localised to the thyroid gland have a 10-year survival rate of 95.6% [113]. Patients with regional disease (locally invasive or clinically apparent spread to the regional lymph nodes) have a 5-year OS rate of 75.5% [113]. • Once distant metastases occur, survival is about 20% to 40% at 10 years [113, 117, 118, 119]. • In the cabozantinib phase III MTC study, an interim analysis of OS conducted at 75% of the events required for final analysis showed a median of 20.3 months in the placebo arm, which may be reflective of the natural history of this disease in patients who have progressive locally advanced or metastatic MTC. • A common specific activating point mutation in the RET gene, M918T, appears to be a strong negative prognostic indicator for both metastasis-free survival and OS. Ten-year survival was approximately 55% in subjects with a confirmed M918T mutation, while it is reported to be as high as 85% when the mutation is absent [120].

Indication/ target population	MTC in adult patients
	• The natural history and prognostic factors of MTC were studied in 161 patients seen at the University of Texas M. D. Anderson Hospital and Tumor Institute in Houston, Texas between 1944 and 1983. In these patients, 77.6% had the sporadic variety of MTC, 19.3% had MEN 2A and 3.1% had MEN 2B. The 5- and 10-year adjusted survival rates of all the patients with MTC were 78.2% and 61.4%, respectively. Patients with MEN 2A had much better rates than patients with sporadic disease (p=0.0005), who were 7.74 times more likely to die of MTC. The stage of the disease at presentation was a major prognostic factor. Patients with Stage III or IV disease were 7.31 times more likely to die of MTC than those with Stage I or II. There was no significant difference in survival between patients with Stage I versus Stage II, or Stage III versus Stage IV. The presence of cervical lymph node metastases did not affect the survival adversely. Direct extension with tissue involvement was a poor prognostic sign. Patients younger than 40 years old at the time of diagnosis of MTC had a significantly better adjusted survival rate than those who were older than 40. Women had a better prognosis than men, who were 1.89 times more likely to die of MTC. Diarrhoea was a poor prognostic sign; however, it occurred more frequently in patients with advanced stages of the disease and larger tumour mass [121]. • In a separate analysis of a 37-year retrospective study on 157 patients with MTC at a single centre (Padova University), the overall 10-year survival rate in the whole series was 72%. Seventy-four per cent of patients had sporadic MTC, 19.1% were affected by a MEN 2A syndrome, 3.8% were affected by MEN 2B syndrome and 2.5% were affected by familial MTC [122].
Risk factors for the disease	• The risk factors for this disease are largely familial/ hereditary but these apply only to about 20% of cases [113].
Demographic profile of target population	• Patients with MTC (N=1070) were identified in the SEER database from 12 population-based cancer registries in the United States between 1973 and 2000. The average age at diagnosis was 50.3 years. Most patients with MTC were Caucasian (87.0%) and women (59.7%) [123]. • Aschebrook-Kilfoy et al [124] recently used the SEER programme (based on 13 registries) to investigate patterns for the four major histologic subtypes of thyroid cancer (including MTC) by gender, race/ethnicity and age in the United States for thyroid cancer cases diagnosed during 1993 to 2006. Of note, there were 959 cases of MTC diagnosed during this period and among those 559 were in women and 400 in men, confirming the slight female preponderance. Among women, MTC incidence rates were highest among whites (0.22 per 100,000 woman-years) and Hispanics (0.21 per 100,000 woman-years). Among men, MTC rates were highest among Hispanics (0.18 per 100,000 man-years). • Age-specific incidence of disease curves for men and women revealed consistently rising rates between both genders until the oldest age groups. The incidence of the disease increases for males between 40 to 60 years of age and starts decreasing after 70 years of age. For females, the incidence of the disease similarly increases, albeit with a less pronounced slope between 40 to 60 years of age, and starts decreasing after 60 years of age among the white population.

Indication/ target population	MTC in adult patients
Main treatment options	• **Complete surgical resection** is the only curative treatment for MTC. The primary treatment of clinically apparent hereditary or sporadic MTC is total thyroidectomy with dissection of ipsilateral and central neck compartments with the aim of removing all neoplastic tissue; contralateral dissection is frequently but not unanimously, recommended [111]. • Recurrent disease in the neck and mediastinum is frequently amenable to surgery with either curative or palliative intent and some patients may benefit from external beam radiation therapy [114]. • **Additional non-surgical therapeutic options** include administration of somatostatin analogue (octreotide), radioligand therapy (131Iodine-labelled meta-iodobenzylguanidine, 131Iodine-labelled anti-carcinoembryonic antigen and 90yttrium-labelled octreotide) and chemoembolisation of liver metastasis [125]. None of these options have been evaluated in randomised studies and their effect on disease outcome is unclear. • **Cytotoxic chemotherapy (single agent or combination**) has demonstrated limited proven efficacy with no demonstrated improvement in PFS or OS. Different chemotherapeutic protocols have included bleomycin, doxorubicin, cisplatin, cyclophosphamide, dacarbazine, fluorouracil and vincristine [126]. • **Vandetanib** has been approved in the EU as a systemic treatment for aggressive, symptomatic MTC. Vandetanib was evaluated in a randomised placebo-controlled phase III study with the primary endpoint of PFS. Vandetanib resulted in significant improvement of PFS compared to placebo [127]. • **Several kinase inhibitors** are under evaluation in clinical trials and preliminary evidence largely based on the observation of tumour response indicates that there may be clinical activity.
Important co-morbidities	**Important co-morbidities found in MTC include:** • Local tumour invasion of the aerodigestive tract and recurrent laryngeal nerve, leading to loss of speech and/or impairment of swallowing. This has been reported in up to 15% of patients with sporadic disease [111, 128]; • Distant metastases in organs such as the lungs, bone and liver [111] that give rise to symptoms such as bone pain, dyspnoea and signs and symptoms associated with tumour burden in the organ; • Systemic symptoms, such as diarrhoea, due to hormonal secretion by the tumour (e.g. calcitonin). In addition, MTC disease progression may be associated with weight loss, fatigue and bone pain [111]. Other important co-morbidities include MEN 2A and MEN 2B associated endocrine disorders (e.g. phaeochromocytoma) and hypertension [88]. **Important iatrogenic co-morbidities from treatment of MTC include:** • Hypothyroidism; • Iatrogenic hypoparathyroidism; • Hypocalcaemia; • Scar tissue in the neck; • Recurrent laryngeal nerve damage or paralysis due to thyroid surgery.

EU=European Union; MEN=multiple endocrine neoplasia; MTC=medullary thyroid carcinoma; NCI=National Cancer Institute; OS=overall survival; PFS=progression free survival; RET=rearranged during transfection; SEER=Surveillance, Epidemiology and End Results database; UK=United Kingdom.

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 9.

Table 9 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 53- to 66-fold higher than expected in humans at approved clinical doses (40 to 140 mg). 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 approved clinical doses.	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 approved clinical doses across all indications (RCC, HCC, DTC, NET and MTC).
• 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 ageing). Steady-state plasma concentrations were approximately 1.7- to 2-fold higher than expected in humans at approved clinical doses (40 to 140 mg). 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 approved clinical doses. 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 steady-state plasma exposures estimated to be >3.5- to >6-fold higher than those expected in humans as a metabolite at approved clinical doses.	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. A reversible proteinuria has been reported clinically in subjects with solid tumours receiving cabozantinib; however, the overall frequency of proteinuria was low (2%) in MTC subjects receiving cabozantinib in the pivotal XL184-301 phase III study. 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 approved clinical doses. 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 approved cabozantinib doses across all indications.
• 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 2.4- to 3-fold (males) and 0.7- to	Cabozantinib has the potential to impair reproductive function and affect fertility in humans, based on results of nonclinical safety studies. Clinical studies have not been conducted to assess the effects of cabozantinib on reproductive toxicity and therefore nonclinical data is extrapolated.

Key safety findings (from nonclinical studies)	Relevance to human usage
1-fold (females) of those expected in humans at approved clinical doses (40 to 140 mg).. 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 approved clinical doses.	
• Developmental toxicity In rats, cabozantinib caused increased post implantation loss at steady-state plasma concentrations ≥0.8-fold of those expected in humans at approved clinical doses 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 approved clinical doses. 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. Clinical studies have not been conducted to assess the effects of cabozantinib on developmental toxicity and therefore nonclinical data is extrapolated. 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 [129] and Study ADVL 1622). The safety and efficacy of cabozantinib in children and adolescents aged <18 years have not been established.
• Nephrotoxicity Nephrotoxic changes observed in rats dosed daily for 14 days included dose-related effects on kidney weights (slightly increased), urinalysis 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 ageing 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 1.6- to 2-fold higher than expected	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, 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

Key safety findings (from nonclinical studies)	Relevance to human usage
in humans at approved clinical doses (40 to 140 mg)..	(<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. In the pivotal phase III XL184-301 study, the overall frequency of AEs of proteinuria (Grade 3 or 4) was low (0.5%) in subjects with MTC receiving cabozantinib. Three cabozantinib-treated subjects in Study XL184-301 had renal failure, two of which were Grade 3 and two of which were SAEs (one a Grade 3 SAE reported concurrently with nephrotic syndrome considered possibly related by the investigator and a Grade 2 SAE considered not related to study treatment). In addition, two subjects had acute renal failure, both non-serious, one of which was Grade 3.
• 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 aminotransferase (AST) values, and	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 studies do not indicate a clinical risk of hepatotoxicity from cabozantinib at clinically-relevant exposures.

Key safety findings (from nonclinical studies)	Relevance to human usage
histopathological changes in gallbladder (accumulation of secretions)) at steady-state plasma concentrations approximately 16- to 20-fold higher than expected in humans at approved clinical doses (40 to 140 mg). 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 1.6- to 2-fold higher than expected in humans at approved clinical doses.	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%). Grade 4 and Grade 5 events of hepatic failure (one each) were also reported which were assessed as not related to

Key safety findings (from nonclinical studies)	Relevance to human usage
	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. .
• 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 across all the approved indications (RCC, HCC, DTC, NET or MTC).
• 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 administered cabozantinib at approved clinical doses (40 to 140 mg). 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 1.6- to 2-fold higher than those measured at steady-state in subjects administered cabozantinib at approved clinical doses. Finally, levels of genotoxic impurities in cabozantinib drug product are also being monitored in order to not exceed specified limits.	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 [81], 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 [129]. While pheochromocytomas are frequent in rats (up to 20% in males), this is a rare tumour in humans [129]. In humans, both MEN 2A and MEN 2B predispose patients to pheochromocytoma. 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 across all the approved indications (RCC, HCC, DTC, NET, and MTC).. 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 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

Key safety findings (from nonclinical studies)	Relevance to human usage
	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- to ≥5-fold higher than expected at steady-state at approved clinical doses (40 to 140 mg). Cabozantinib administration resulted in no adverse effects on neurobehavioural or respiratory system functions in rats at plasma exposures approximately 10- to 60-fold higher than expected at steady-state at approved clinical doses (40 to 140 mg).	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 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	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
exceeded the assay incubation solubility 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; AUC=area under the plasma drug concentration-time curve; BCRP=breast cancer resistance protein; BSEP=bile salt export pump; C_{max}=maximum plasma concentration; CYP=cytochrome P450; DDI=drug-drug interaction; DTC=differentiated thyroid carcinoma; GI=gastrointestinal; HCC=hepatocellular carcinoma; IC_{50}=half-maximal inhibitory concentration; Ki=inhibition constant; MATE=multidrug and toxin extrusion protein; MEN=multiple endocrine neoplasia; MRP2=multidrug resistance associated protein; MTC=medullary thyroid carcinoma; NET=neuroendocrine tumours; 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; RMP=risk management plan; SAE=serious adverse event; SmPC=summary of product characteristics.

Based on the nonclinical studies conducted with cabozantinib the primary toxicities were observed in the reproductive, gastrointestinal (GI), bone marrow, lymphoid tissues, adrenal gland and renal organs and systems (Module 2.4.4 in the Marketing Authorisation Application (MAA)).

There are no important identified risks from the specific observations in nonclinical studies. While Embryotoxicity and Carcinogenicity were initially considered as important potential risks related to nonclinical information, these risks are no longer retained as safety concerns for the RMP in accordance with GVP Module V Revision 2 (see SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP).

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.

- **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), Study XL184-311 (DLP 08 February 2021) and Study A021602 (DLP 24 August 2023) were the basis for the marketing authorisation for Cabometyx.

The approved indication for Cometriq is:

- **Medullary Thyroid Carcinoma (MTC)**

Cometriq is indicated for the treatment of adult patients with progressive, unresectable, locally advanced or metastatic MTC.

The original pivotal trial Study XL184-301 (DLP 28 August 2014) was the basis for the marketing authorisation for Cometriq.

The DLP for post-authorisation exposure was 28 November 2025 (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 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
≥124 weeks	12 (3.6)	1619
≥128 weeks	7 (2.1)	986

Duration of exposure	Study XL184-308 N=331	
	Persons n (%)	Person time (person weeks)
≥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		
Total	66 (84.6)	2537

Gender Age group	Study A031203 N=78	
	Persons n (%)	Person time (person weeks)
<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

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

SIII.2.6. Neuroendocrine Tumours

Phase III Study A021602 involved the use of cabozantinib for the treatment of adult patients with advanced epNET (i.e. carcinoid tumours) and 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

Duration of exposure	Study A021602 N=195	
	Persons n (%)	Person time (person weeks)
≥52 weeks	45 (23.1%)	3482
≥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

Gender Age group	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).

SIII.2.7. Medullary Thyroid Carcinoma

Primary safety data for the MTC indication are presented for subjects from the phase III study XL184-301. These subjects received a 140 mg once daily dose of cabozantinib capsules (marketed as Cometriq), which is the approved dose for the MTC indication.

The safety analysis set included in this RMP for cabozantinib includes three efficacy and/or safety studies that were included in Module 5 of the MAA for MTC. Using these three studies as the basis of this RMP was discussed and agreed to by the European Medicines Agency (EMA) in the presubmission meeting (May 2012). An overview of the subjects included in these three clinical studies is provided in Table 28. In these studies, 295 subjects were exposed to cabozantinib at the proposed commercial dose of 140 mg (as the freebase weight, equivalent to 175 mg malate salt weight). Additionally, other ongoing single-agent cabozantinib studies (N=807) were evaluated to ensure that important safety signals seen in these other single-agent cabozantinib studies are represented by the three key clinical studies. Clinical pharmacology studies were also conducted in approximately 421 subjects without cancer (363 healthy volunteers, 26 hepatic-impaired subjects and 32 renal-impaired subjects) and subjects with cancer (N=40).

Study XL184-001 enrolled subjects with various solid tumours that were metastatic or unresectable and were no longer responding to therapies or had disease for which no standard therapy exists.

Study XL184-201 enrolled subjects with radiographic evidence of progressive or recurrent glioblastoma in the first or second relapse. These subjects could have received up to two prior systemic antitumour therapies.

Study XL184-301 enrolled subjects with unresectable, locally advanced or metastatic MTC and documented radiographic disease progression within 14 months of randomisation. There were no requirements for prior therapies.

These studies all enrolled subjects who had an Eastern Cooperative Oncology Group performance status ≤2 or Karnofsky Performance Scale of ≥60% and adequate renal, hepatic and haematologic function.

These 295 subjects represent the population exposed to cabozantinib used for the analysis of risks. Their exposure to cabozantinib is summarised in Table 28 to Table 31 below. The

database lock point is 15 June 2011 for all studies except XL184-301, which had a DLP of 28 August 2014. Data are provided in total for the three studies as well as for the indication of MTC (Study XL184-301 only) as agreed to by the EMA at the presubmission meeting. Exposure in the single-dose normal healthy volunteer clinical pharmacology studies is not included. Subjects from Studies XL184-001, XL184-201 and XL184-301 on 140 mg of cabozantinib were considered for this summary. Person time in weeks for duration of exposure is summarised categorically and was calculated as the sum of exposure in weeks over all subjects who received at least one dose of cabozantinib in the particular indication/s. For each subject, duration of exposure was calculated as time from first dose of study treatment until last dose. For subjects still on study treatment the last dose was assumed to be the cut-off date for the database.

Table 28 Subjects in Clinical Studies that Comprise the Safety Analysis Set

Study	Phase	Number of subjects treated	
		Cabozantinib 140 mg	Placebo
XL184-001	Phase I	35 (25 MTC, 10 non-MTC)	None
XL184-201	Phase II	46 (glioblastoma)	None
XL184-301	Phase III	214 (MTC)	109 (MTC)
Total (Safety Analysis Set)		295 (239 MTC, 56 non-MTC)	109 (109 MTC)

MTC=medullary thyroid cancer.
Cut-off date: 15 June 2011 (the latest cut-off date in the clinical study report) or 28 August 2014 (XL184-301).

Table 29 Duration of Exposure (by Indication)

Duration of exposure	Persons		Person time	
Indication 1	Cabozantinib is indicated for the treatment of adult patients with progressive, unresectable, locally advanced or metastatic medullary thyroid cancer			
Duration of exposure	Combined results for cabozantinib treatment (140 mg qd) (n=295)		Indication: MTC Study XL184-301 (n=214)	
	Persons n (%)	Person time (person weeks)	Persons n (%)	Person time (person weeks)
≤4 weeks	31 (10.5)	81.4	14 (6.5)	35.7
≤8 weeks	57 (19.3)	236.9	28 (13.1)	125.0
≤12 weeks	78 (26.4)	466.0	42 (19.6)	277.9
≤16 weeks	102 (34.6)	802.1	56 (26.2)	466.9
≤20 weeks	112 (38)	980.4	59 (27.6)	519.6
≤24 weeks	118 (40.0)	1119.7	62 (29.0)	589.4
≤28 weeks	131 (44.4)	1456.6	73 (34.1)	871.4
≤32 weeks	140 (47.5)	1730.0	79 (36.9)	1053.4
≤36 weeks	149 (50.5)	2043.9	88 (41.1)	1367.3
≤40 weeks	156 (52.9)	2304.3	95 (44.4)	1627.7
≤44 weeks	163 (55.3)	2599.6	102 (47.7)	1923.0
≤48 weeks	173 (58.6)	3063.9	111 (51.9)	2341.1
≤52 weeks	177 (60.0)	3262.6	115 (53.7)	2539.9
≤56 weeks	183 (62.0)	3590.4	120 (56.1)	2814.6
≤60 weeks	188 (63.7)	3888.4	125 (58.4)	3112.6
≤64 weeks	193 (65.4)	4194.3	130 (60.7)	3418.4
≤68 weeks	198 (67.1)	4522.0	134 (62.6)	3678.7
≤72 weeks	206 (69.8)	5077.4	139 (65.0)	4026.7
≤76 weeks	209 (70.8)	5298.6	142 (66.4)	4247.9
≤80 weeks	211 (71.5)	5455.7	144 (67.3)	4405.0
>80 weeks	84 (28.5)	12323.0	70 (32.7)	10,899.4
Overall exposure	295 (100)	17778.7	214 (100)	15,304.4

MTC=medullary thyroid cancer; qd=once daily.
Note: For subjects on studies as of the respective data cut-off, the last dose date is assumed to be the respective data cut-off date for the study.

Table 30 Exposure by Age Group and Gender (by Indication)

Gender Age group	Combined results for cabozantinib treatment (140 mg qd) (N=295)		Indication: MTC Study XL184-301 (N=214)	
	Persons n (%)	Person time (person weeks)	Persons n (%)	Person time (person weeks)
Female **Total**	89 (30.2)	5381.0	65 (30.4)	4629.6
≤65 years	71 (24.1)	4022.9	51 (23.8)	3404.3
>65 years	18 (6.1)	1358.1	14 (6.5)	1225.3
Male **Total**	206 (69.8)	12397.7	149 (69.6)	10674.9
≤65 years	165 (55.9)	10237.1	116 (54.2)	8721.6
>65 years	41 (13.9)	2160.6	33 (15.4)	1953.3

MTC=medullary thyroid cancer; qd=once daily.
Note: For subjects on studies as of the respective data cut-off, the last dose date is assumed to be the respective data cut-off date for the study.

Table 31 Exposure by Ethnic Origin (Totals)

Ethnic origin	Combined results for cabozantinib treatment (140 mg qd) (n=295)		Indication: MTC Study XL184-301 (N=214)	
	Persons n (%)	Person time (person weeks)	Persons n (%)	Person time (person weeks)
Total population	295 (100.0)	17,778.7	214 (100.0)	15304.4
Asian	11 (3.7)	537.7	9 (4.2)	481.4
Black or African American	6 (2.0)	175.1	1 (0.5)	7.0
White	262 (88.8)	16,393.0	192 (89.7)	14160.7
Other	8 (2.7)	157.3	5 (2.3)	143.7
Not reported	8 (2.7)	515.6	7 (3.3)	511.6

MTC=medullary thyroid cancer; qd=once daily.
Note: For subjects on studies as of the respective data cut-off, the last dose date is assumed to be the respective data cut-off date for the study.

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. Exclusionary criteria during clinical trials evolved as safety and tolerability knowledge increased during the development of cabozantinib. Clinical trials were also aimed to protect subjects that may be at risk for certain AEs and to increase the chance of a patient to benefit from treatment and to give enough time for the effectiveness observations to occur. Exclusionary criteria provided a homogenous and relevant group of patients who mirror the realities of medical practice across the indications.

Common and indication-specific exclusion criteria for subjects in the cabozantinib clinical studies are summarised in Table 32.

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

Table 32 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	Cabozantinib is contraindicated in these patients (Cabometyx and Cometriq SmPCs 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 Cabometyx and Cometriq SmPCs. The interaction of cabozantinib with warfarin is provided in Section 4.5 of Cabometyx and Cometriq SmPCs: 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	In Study XL184-301), the median age of subjects was 55 years, with approximately 75% subjects over the age of 45. Only a small number of female patients are expected to be of childbearing potential. The risk is included as a warning and precaution for use of cabozantinib in women of childbearing potential and breastfeeding females. Section 4.6 of the Cabometyx and Cometriq SmPCs. <u>Pregnancy</u> There are no studies in pregnant women using cabozantinib. Studies in animals have shown embryofoetal and teratogenic effects (see Section 5.3 of the SmPCs). The potential risk for humans is unknown. Cabozantinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with cabozantinib. <u>Breastfeeding</u> It is not known whether cabozantinib and/or its metabolites are excreted in human milk. Because of the potential harm to the infant, mothers should discontinue breastfeeding during treatment with cabozantinib and for at least 4 months after completing therapy.

Exclusion criteria	Reason for exclusion	Missing information (Yes/No)	Is it considered to be missing information? If No, rationale
Paediatric age patients (<18 years old)	There is no cabozantinib experience in the paediatric population.	No	Medullary thyroid cancer and other indications (RCC, HCC, DTC, NET) requiring systemic therapy are very rare in a paediatric population. The following information is included in Section 4.2 of Cabometyx and Cometriq SmPCs as to the lack of safety information in this population: The safety and efficacy of cabozantinib in children and adolescents <18 years have not been established. No data are available. Studies in paediatric varied indications have been conducted 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. Detailed exposure estimates in the paediatric population are not available (cabozantinib PSUR DLP 28 November 2025).

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, thromboembolic events, clinically significant cardiac arrhythmias or a recent history of significant disease such as either symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction or transient ischaemic attack); 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, unhealed wounds from recent surgery or fracture; malabsorption syndrome; uncompensated symptomatic hypothyroidism requirement for dialysis, solid organ transplant, or psychiatric illness	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 Cabometyx and Cometriq SmPCs (Special warnings and precautions for use) as conditions that may put a patient at risk for a serious adverse reaction.

Exclusion criteria	Reason for exclusion	Missing information (Yes/No)	Is it considered to be missing information? If No, rationale
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. Criterion in place due to lack of experience in hepatic impaired patients	No	Hepatic impairment Study XL184-003 has been completed and Cometriq SmPC was updated on 23 April 2015. Section 4.2 of Cabometyx SmPC: 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 dosing recommendations can be provided. Close monitoring of overall safety is recommended in these patients (SmPC Sections 4.4 and 5.2). There is no clinical experience in patients with severe hepatic impairment (Child Pugh C), so cabozantinib is not recommended for use in these patients (SmPC Section 5.2). Section 4.2 of Cometriq SmPC: In patients with mild or moderate hepatic impairment the recommended dose of cabozantinib is 60 mg once daily. Close monitoring of overall safety is recommended in these patients (see Section 5.2) as dose adjustment or interruption may be required. Cabozantinib is not recommended for use in patients with severe hepatic impairment as safety and efficacy have not been established in this population.
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 (Section 4.2 of Cabometyx and Cometriq SmPCs).
Inability to swallow tablets or capsules.	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.

Exclusion criteria	Reason for exclusion	Missing information (Yes/No)	Is it considered to be missing information? If No, rationale
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 (Section 4.4 of Cabometyx and Cometriq SmPCs).
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. In order to better assess the safety and efficacy profile of cabozantinib in a specific indication in clinical studies, subjects with other malignancies were excluded. Approved indication (Section 4.1 of Cabometyx and Cometriq SmPCs) will be for the population studied in phase II and phase III.

Exclusion criteria	Reason for exclusion	Missing information (Yes/No)	Is it considered to be missing information? If No, rationale
Renal impairment	Criterion in place due to concern of proteinuria and lack of experience in renal impaired patients.	No	Renal impairment Study XL184-017 has been completed and Cometriq SmPC was updated on 23 April 2015. Section 4.2 of Cabometyx and Cometriq SmPCs: Cabozantinib should be used with caution in patients with mild or moderate renal impairment. Cabozantinib is not recommended for use in patients with severe renal impairment as safety and efficacy have not been established in this population.
Haemorrhage	Identified risk with cabozantinib.	No	Information is included in Section 4.4 of Cabometyx and Cometriq SmPCs. Section 4.4 of Cabometyx SmPC: Severe haemorrhage, sometimes fatal, has been observed with cabozantinib. Patients who have a history of severe bleeding prior to treatment initiation should be carefully evaluated before initiating cabozantinib therapy. Cabozantinib should not be administered to patients that have or are at risk for severe haemorrhage. Section 4.4 of Cometriq SmPC: Severe haemorrhage, sometimes fatal, has been observed with cabozantinib. Patients who have evidence of involvement of the trachea or bronchi by tumour or a history of haemoptysis prior to treatment initiation should be carefully evaluated before initiating cabozantinib therapy. Cabozantinib should not be administered to patients with serious haemorrhage or recent haemoptysis.
Urine protein/creatinine ratio	Proteinuria is an identified risk with cabozantinib.	No	The following information is included in Section 4.4 of Cabometyx and Cometriq SmPCs: Proteinuria has been observed with cabozantinib. Urine protein should be monitored regularly during cabozantinib treatment. Cabozantinib should be discontinued in patients who develop nephrotic syndrome. Proteinuria is included as a common ADR in Section 4.8 of Cabometyx and Cometriq SmPCs.

Exclusion criteria	Reason for exclusion	Missing information (Yes/No)	Is it considered to be missing information? If No, rationale
Active infections	To optimise the benefit-risk ratio for the subjects and to not confound safety observations associated with treatment with cabozantinib.	No	The risks and benefits of cabozantinib treatment will have to be evaluated before treating someone with concurrent infection. Certain treatments for infection are advised to not be used due to potential drug interactions (Section 4.4 and 4.5 of Cabometyx and Cometriq SmPCs).
HIV infection	To optimise the benefit-risk ratio for the subject and to not confound safety observations associated with treatment with cabozantinib.	No	The risks and benefits of cabozantinib treatment will have to be evaluated before treating someone with concurrent HIV infection. Certain treatments for HIV are advised to not be used due to potential drug interactions (Section 4.4 and 4.5 of Cabometyx and Cometriq SmPCs).
Prior recent or extensive radiation	Criterion was used to avoid potential safety and efficacy confounders of the pivotal study.	No	Ongoing complications from radiation exposure are highlighted in Section 4.4 of Cometriq SmPC (Special warnings and precautions for use) for GI perforations and fistulae.
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 Cabometyx 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.

Exclusion criteria	Reason for exclusion	Missing information (Yes/No)	Is it considered to be missing information? If No, rationale
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 Cabometyx 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 Cabometyx 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 Cabometyx 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; AE=adverse event; CD=cluster of differentiation; CNS=central nervous system; CTLA-4=cytotoxic T-lymphocyte-associated protein 4; CYP=cytochrome P450; DLP=data lock point; DTC=differentiated thyroid carcinoma; ECG=electrocardiogram; GI=gastrointestinal; HCC=hepatocellular carcinoma; HIV=human immunodeficiency virus; INR=international normalised ratio; LMWH=low molecular weight heparin; MET=mesenchymal epithelial transition factor; NET=neuroendocrine tumour; 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. In MTC studies (XL184-001, XL184-201 and XL184-301), 295 subjects were exposed to cabozantinib 140 mg. In the pivotal placebo-controlled Study XL184-301, 214 subjects were exposed to cabozantinib and 109 exposed to placebo. 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,in the DTC population with a frequency less than approximately 1 in 48 and in the MTC population with a frequency less than approximately 1 in 72 based on DLP at initial submission would be unlikely to be detected with a data set of this size. Adverse drug reactions occurring in the MTC population with a frequency of >1/1000, which would be considered uncommon, rare and very rare events would not be detected. Therefore, it may be appropriate to choose ADRs that occur at lower frequencies in this population. 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, 6355 subjects have been exposed to cabozantinib (including 2014 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 2025). 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 Cabometyx 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, 53 subjects (27.2%) in Study A021602 and 103 subjects (48.1%) in Study XL184-301 (MTC) 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, 99 subjects (50.8%) in Study A021602 and 152 subjects (71.0%) in Study XL184-301 (MTC) 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 XL184-311,164 weeks as of the DLP of 24 August 2023 for the Study A021602 and >80 weeks (32.7% of subjects) as of the DLP of 28 August 2014 for Study XL184-301 (MTC). 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. Adverse drug reactions in subjects with MTC, which require an exposure of longer than 80 weeks to develop, may 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), or 80 weeks (Study XL184-301 for MTC), 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. Adverse drug reactions occurring in the DTC population treated with cabozantinib for more than 6 months with a frequency less than approximately 1 in 32 (96/3) would be unlikely to be detected, Adverse drug reactions occurring in the NET population treated with cabozantinib for more than 6 months with a frequency less than approximately 1 in 33 (99/3) would be unlikely to be detected, and ADRs occurring in the MTC population treated with cabozantinib for more than 6 months with a frequency less than approximately 1 in 51 (152/3) would be unlikely to be detected with a data set of this size. In Study A021602, 192 ADRs (98.5%) were reported.

Although the MTC population treated is small, the duration of exposure appears to be in line with what would be expected postmarketing and no significant safety trends are apparent. Subjects with longer term exposure had no different safety profile than subjects with shorter term exposure. The population is still small and although no trends have been identified, pharmacovigilance in subjects dosed chronically should continue.

There have been no signals detected regarding specific events that may have long latency or as a result of cumulative exposure to cabozantinib, based on the duration of exposure experienced in clinical trials. However, the population is still small and, although no trends have been identified to date, pharmacovigilance in subjects dosed chronically will continue.

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 33.

Table 33 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. One partner pregnancy was reported in Study XL184-301, with

Type of special population	Exposure
	no reported AEs. It is not known whether cabozantinib is excreted in human milk. Therefore, lactating females were excluded from clinical trials of cabozantinib and avoidance of breastfeeding for at least 4 months after the last dose is recommended. Cabometyx and Cometriq SmPCs includes language in Section 4.6 for women of childbearing potential to avoid pregnancy while on cabozantinib and states precautions for women who are breastfeeding. Female partners of male patients taking cabozantinib must also avoid pregnancy. Effective methods of contraception should be used by male and female patients and their partners during therapy and for at least 4 months after completing therapy. Because oral contraceptives might possibly not be considered as effective methods of contraception, they should be used together with another method, such as a barrier method.
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 AUCs (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 Cabometyx and Cometriq SmPCs Section 4.2.
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. Additionally, a dedicated study in hepatically impaired adult subjects was concluded (Study XL184-003). The single 60 mg dose of cabozantinib was well tolerated in both healthy and mild and moderately hepatic impaired subjects (no subjects with severe hepatic impairment were enrolled in the study); no difference in the incidence and severity of treatment emergent AEs was observed in the subjects with mild or moderate hepatic impairment when compared to the known safety profile for cabozantinib and no new safety concerns were identified in the study. The results from the hepatic

Type of special population	Exposure
	impairment study indicate that exposure ($AUC_{0\text{-}inf}$) increased by 81% and 63% in subjects with mild and moderate hepatic impairment, respectively. Based on safety and PK data, the decision was made that no subjects were to be recruited into the severe hepatic impairment group. Patients with hepatic impairment show high inter subject variability in cabozantinib exposure and higher cabozantinib exposure has been associated with earlier dose modification [130]. These data indicate that cabozantinib can be administered to patients with mild to moderate hepatic impairment, provided that the patient is monitored by the treating physician for emergent toxicity associated with the higher exposure. 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. Cabozantinib is not recommended for use in patients with severe hepatic impairment (Section 4.2 of Cabometyx and Cometriq SmPCs).
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 for cabozantinib across all indications (RCC, HCC, DTC, NET, MTC).
Patients with a disease severity different from inclusion criteria in clinical trials	There were few subjects with ECOG status outside of the protocol inclusion criteria but with the data available, there is no indication of safety differences based on ECOG status across the clinical development programme. <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

Type of special population	Exposure
	spread and/or macrovascular invasion at baseline compared to those who did not. DTC in adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma following prior systemic therapy and refractory to radioactive iodine 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. Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy 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	Advanced RCC and HCC in adults Clinical information is limited. A population PK analysis did not identify clinically relevant differences in the PK of cabozantinib based on race. Advanced RCC in adults following prior VEGF-targeted therapy 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. Advanced RCC in treatment-naïve adults with intermediate or poor-risk 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. Advanced RCC in combination with nivolumab in treatment-naïve adults 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%). HCC in adults who have previously been treated with sorafenib 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%). 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
	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%). Progressive extra-pancreatic and pancreatic neuroendocrine tumours in adults after prior systemic therapy 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%). MTC in adults with progressive, unresectable, locally advanced or metastatic medullary thyroid carcinoma (Studies XL184-001, XL184-201, XL184-301) In the cabozantinib studies (XL184-001, XL184-201 and XL184-301) baseline subject demographics included subjects mostly of White race (85.7% to 89.9%) with a minority of other races (Asian 2.2% to 5.5%; Black or African American 0.5% to 6.5%; other race 0.9% to 5.7%). Given the data available, there is no indication of safety differences between racial categories.
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. MTC in adults with progressive, unresectable, locally advanced or metastatic medullary thyroid carcinoma Medullary thyroid carcinoma is a disease in which the majority of patients harbour a genetic mutation. Almost all patients diagnosed with hereditary MTC harbour an activating mutation in the RET gene and a subset, approximately 50% to 70% of patients with the sporadic form of MTC have been found to express such a mutation [131]. In Study XL184-301, the majority of the population were RET mutation positive: 51.2% (169/330) of all enrolled subjects were determined to be RET mutation positive (107/219, 48.9% of those randomised to cabozantinib), 34.8% (115/330) could not have RET mutation status determined (77/219, 35.2% cabozantinib) and 13.9% (46/330) were determined to be RET mutation negative (16.0%, 35/219 cabozantinib).

Type of special population	Exposure
	Safety Profile by RET Mutation Status: Frequent AEs in the RET mutation positive subgroup were similar to the most frequent events in the entire population and the RET mutation negative population (for example, diarrhoea, palmar-plantar erythrodysaesthesia syndrome, decreased weight, decreased appetite, fatigue). Several of these events were also the events of Grade ≥3 severity that occurred most frequently. The incidence of serious events in the cabozantinib treated RET mutation positive subgroup was not greatly different from that found in RET mutation negative population. Efficacy by RET mutation status: The three main RET mutational subgroups (RET mutation positive, negative, unknown) were evaluated for PFS, response rate and OS. The PFS hazard ratios for the RET mutation positive, RET mutation unknown and RET mutation negative groups all favoured cabozantinib (unstratified Cox regression HR=0.23, 0.30 and 0.53, respectively). The tumour response rates were similar across groups: 32%, 25% and 22% in RET mutation positive, RET mutation unknown and RET mutation negative subjects, respectively, as determined in subjects with measurable disease. A significant improvement in OS was observed in the subgroup of RET M918T mutation positive subjects (n=81/219 cabozantinib arm): 44.3 months in the cabozantinib arm versus 18.9 months in the placebo arm (HR = 0.60, p=0.0255). There was no improvement in OS for the RET M918T negative and unknown subgroups. RAS mutation analysis: RAS mutations have recently been described in the subset of patients lacking RET mutations (for example, [132, 133]); therefore, clinical benefit based on the presence of RAS mutations was evaluated. A total of 16 subjects with RAS mutations were identified out of the 85 who were evaluated, including 13 from the RET mutation negative subgroup. For subjects with RAS mutations, the median PFS in the cabozantinib group was 47 weeks versus 8 weeks in the placebo group (log rank HR = 0.15). Supporting cabozantinib activity in this small subpopulation was a tumour response rate of 31%. Conclusion: Overall, the safety profile of cabozantinib in patients with MTC treated with Cometriq is similar between the RET mutation negative and RET mutation positive/unknown subgroups and thus largely independent of the mutational state of the tumour. Benefit in cabozantinib treated subjects was observed independent of RET mutational status. While the benefit may not have been as pronounced or significant in the RET mutation negative group, it appears RET mutation negative subjects harbouring RAS mutations had duration of PFS and tumour response rates similar to the RET mutation positive and unknown groups.
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 (ADVL1211) 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, MTC, RCC, hepatoblastoma or epithelial- myoepithelial carcinoma, were exposed to cabozantinib. Forty-one MTC paediatric subjects were enrolled in this study. The safety profile observed in this study appeared to be in line with the safety profile of cabozantinib as observed in adults. A phase II study (ADVL1622) to determine the activity of cabozantinib in children and young adults was concluded.

Type of special population	Exposure
	As cabozantinib is an antiangiogenic agent, growth plate evaluation is included in the 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 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 been established. However, HCC is a very rare entity in children and represents a different biologic disease compared to HCC in adults [129]. 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 [134]. 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 [134]. 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 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 [135]. MTC in adults with progressive, unresectable, locally advanced or metastatic medullary thyroid carcinoma The safety and efficacy of cabozantinib in children and adolescents have not been established. Forty-one MTC paediatric subjects were enrolled in the phase I study XL184-011 (ADVL-1211) as part of the approved PIP.
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 or screening 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.

Type of special population	Exposure
	In addition to their anticancer therapy, patients with cancer 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 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

Type of special population	Exposure
	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 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. MTC in adults with progressive, unresectable, locally advanced or metastatic medullary thyroid carcinoma (Studies XL184-001, XL184-201, XL184-301) Among the 295 subjects exposed to cabozantinib (140 mg once daily orally) in the three key clinical trials, 61 (20.7%) were ≥65 years old, including 13 (4.4%) subjects who were ≥75 years old. While the number of subjects age 75 and above is small, the number of total and related SAEs was not higher in the subjects 75 years and above compared to the number in age groups 74 years or below and no unique safety signals were identified in the older population. Sixteen SAEs regardless of relationship to study treatment were observed in eight of 13 (61.5%) subjects 75 years and older compared to 314 SAEs in 128 out of 281 (45.6%) subjects 74 years and younger. Fifteen of these 16 events were for causes other than progressive disease; they were experienced in seven subjects 75 years and above. These 15 events were events of fatigue (two subjects), weakness, hip pain, elevated lipase, hyponatraemia, suspicion of transient ischaemic attack, atrial fibrillation, ascites, pancreatitis, pneumonia, clostridia infection and pulmonary embolisms (one subject each). These events were also experienced by subjects in age groups below 75, indicating that the age group 75 years and above experienced a

Type of special population	Exposure
	similar SAE profile compared to younger age groups and that there were no unique safety signals in this population. Of all the 16 SAEs, one event was fatal (general deterioration due to progressive disease). None of the related events in the age group 75 years and older had an outcome of fatal.
Adverse drug reactions of special concern	The incidence of the frequency of AEs and the AEs of interest, including GI perforation, GI fistula, intra-abdominal abscesses, non-GI fistula, haemorrhage, osteonecrosis, ATE and VTE was evaluated by age group: <65 years, 65 and <75 years and ≥75 years. There were no notable age-related differences in the safety profile in the elderly population, compared with the non-elderly population use in different age ranges, for example, 65 to 74, 75 to 84, >85.
Effect of multiple medications	In addition to their anticancer therapy, patients with cancer are usually on numerous medications, which may include levothyroxine, antimotility agents and somatostatin analogues, antihypertensive agents, pain medications, bisphosphonates, vitamin D and calcium supplements and medications for the control of cortisol levels (particularly relevant for MTC patients). The use of these medications was reflected in the populations studied in clinical trials with cabozantinib. In the elderly population, no specific safety trends or events related to multiple concomitant medicinal products have been identified.

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; C_{max}=maximum plasma concentration; CHF=congestive heart failure; CI=confidence interval; CNS=central nervous system; CSR=clinical study report; DTC=differentiated thyroid carcinoma; ECOG=Eastern Cooperative Oncology Group; epNET=extra-pancreatic neuroendocrine tumour; ETM=event to monitor; GI=gastrointestinal; HCC=hepatocellular carcinoma; HR=hazard ratio; LS=least-squares; KPS=karnofsky performance status; MTC=medullary thyroid carcinoma; NET=neuroendocrine tumour; OS=overall survival; PD-L1=programmed death-ligand 1; PFS=progression free survival; PIP=Paediatric Investigation Plan; PK=pharmacokinetic(s); pNET=pancreatic neuroendocrine tumour; PPES=palmar-plantar erythrodysesthesia syndrome; PS=performance status; PT=preferred term; RAS=rat sarcoma; RCC=renal cell carcinoma; RET=rearranged during transfection; 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.

Ipsen Pharma is the Marketing Authorisation Holder (MAH) for both Cometriq and Cabometyx in the European Union for all approved indications. In the United States (US), Exelixis is the MAH and is responsible for distribution of both 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 covering both capsule (Cometriq) and tablet (Cabometyx) formulations. Signal detection and management activities are performed by Exelixis on all data generated from the use of cabozantinib in both formulations and across all indications worldwide. Pharmacovigilance agreements are in place between the different parties involved, primarily between Exelixis and Ipsen to ensure coordinated safety monitoring and reporting for all indications of cabozantinib in the EU.

SV.1 Post-authorisation Exposure

Cabozantinib is authorised in two formulations: Cabometyx (tablet formulation) and Cometriq (capsule formulation).

Cometriq received EU authorisation on 21 March 2014 through the centralised procedure for the treatment of progressive, metastatic MTC and is registered across the 27 EU Member States,

as well as the European Economic Area countries of Norway, Iceland and Liechtenstein. Cometriq is currently approved and commercially available in the US on 24 January 2013 for the treatment of progressive, metastatic MTC and in the EU and United Kingdom for the treatment of progressive, unresectable locally advanced or metastatic MTC. Cometriq is supplied as 20 mg and 80 mg hard gelatin capsules. The recommended daily dose of Cometriq is 140 mg orally.

Cabometyx is authorised in the EU as first-line monotherapy in adult patients with intermediate or poor-risk RCC, 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, 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 and for the treatment of adult patients with unresectable or metastatic, well differentiated epNET and pNET, who have progressed following at least one prior systemic therapy other than somatostatin analogues 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. On 26 March 2025, the US Food and Drug Administration approved Cabometyx for patients aged 12 years and older with previously treated, unresectable, locally advanced or metastatic, well differentiated pNET and epNET that are not surgically resectable. 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, NET and 40 mg orally for advanced RCC in combination with nivolumab.

Both formulations are also made available in certain countries by Ipsen via Managed Patient Access Programmes (managed access programme (MAP) and global access programme (GAP)).

SV.1.1. Method Used to Calculate Exposure

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

Information provided is as of the DLP for the global PSUR for cabozantinib (Cabometyx+Cometriq) of 28 November 2025.

Commercial Cabometyx exposure was calculated as follows:

- In the US, the number of patients receiving commercial Cabometyx was obtained from 11 Specialty Pharmacies in the US and was based on individual patient prescriptions as submitted to these 11 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.

- 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 (7 months). It should be noted that some patients received free commercial product as part of an access programme (i.e, 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 (7 months). Patients enrolled in Ipsen-sponsored NISs receive commercial product and are included in the estimated exposure to Cabometyx in the marketed setting.

Commercial Cometriq exposure was calculated as follows:

- In the US, the number of patients receiving commercial Cometriq was obtained from Diplomat Specialty Pharmacy and Rx Crossroads and was based on individual patient prescriptions as submitted to these two Specialty Pharmacies and also includes a patient estimate for product shipments to group oncology providers.
- Outside of the US, the number of patients receiving commercial Cometriq was based on the cumulative or interval number of sold Cometriq commercial units shipped by Ipsen and adjusted for an average exposure duration (7 months). It should be noted that some patients received free commercial product as part of an access programme (i.e. MAP_MTC). Cumulative or interval access programme exposure was based on the number of free Cometriq units shipped by Ipsen and adjusted for average exposure duration (7 months). This does not include patients who received Cometriq through the Swedish Orphan Biovitrum (SOBI) named-patient use (NPU) programme.

SV.1.2. Exposure

Cumulative worldwide Cabometyx exposure (through 28 November 2025) in the marketed setting and MAPs is provided in Table 34. The cumulative patient exposure to Cabometyx in the marketed setting is 273,574 (including 102,847 patients in the EU, 89,456 patients in the US, 24,288 patients in Japan and 56,983 patients in the rest of the world (ROW)). In addition, cumulatively 4095 patients outside of the US and Japan received Cabometyxas part of MAP and GAP programmes (751 patients in the EU and 3344 patients in the ROW).

Table 34 Estimated Worldwide Commercial Patient Exposure for Cabometyx as of 28 November 2025 by Region

By country	
All indications	
	Cumulative exposure through 28 November 2025
Marketed	
EU	102,847
US	89,456
Japan	24,288
ROW [a]	56,983
Total	**273,574**
MAP/GAP	
EU	751
US	0
Japan	0
ROW [a]	3344
Total	**4095**
Total exposure (marketed and MAP/GAP)	**277,669**

EU=European Union; GAP=global access programme; MAP=market access programme; 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 Cabometyx in the commercial setting: Algeria, Australia, Bahrain, Brazil, Canada, Colombia, Egypt, French Polynesia, Hong

Kong, Israel, Jordan, Kazakhstan, Kuwait, Lebanon, Malaysia, Mexico, Morocco, New Caledonia, New Zealand, Oman, Panama, Qatar, Russian Federation, Saudi Arabia, Serbia, Singapore, South Africa, South Korea, Switzerland, Taiwan, Thailand, Turkey, Ukraine, United Arab Emirates and United Kingdom.

Cumulative worldwide Cometriq exposure (through 28 November 2025) in the marketed setting and MAPs is provided in Table 35. The cumulative patient exposure to Cometriq in the marketed setting is 5161 (including 1312 patients in the EU, 3467 patients in the US, no patients in Japan and 382 patients in the ROW). In addition, cumulatively 181 patients outside of the US and Japan received as part of MAP and GAP programmes (154 patients in the EU and 27 patients in the ROW).

Table 35 Estimated Worldwide Commercial Patient Exposure for Cometriq as of 28 November 2025 by Region

By country	
All indications	
	Cumulative exposure through 28 November 2025
Marketed	
EU	1312
US	3467
Japan	0
ROW [b]	382
Total	**5161**
MAP/GAP	
EU	154
US	0
Japan	0
ROW [a]	27
Total	**181**
Total exposure (marketed and MAP/GAP)	**5342**

EU=European Union; GAP=global access programme; MAP=market access programme; 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 Cometriq in the commercial setting: Canada, Israel, Serbia, Switzerland, United Arab Emirates, and United Kingdom.

Cumulative worldwide to combined cabozantinib (Cabometyx+Cometriq) exposure (through 28 November 2025) in the marketed setting and MAPs is provided in Table 36. The cumulative patient exposure to combined cabozantinib (Cabometyx+Cometriq) in the marketed setting is 278,735 (including 104,159 patients in the EU, 92,923 patients in the US, 24,288 patients in Japan and 57,365 patients in the ROW). In addition, cumulatively 4276 patients outside of the US and Japan received cabozantinib as part of MAP and GAP programmes (905 patients in the EU and 3371 patients in the ROW).

Table 36 Estimated Worldwide Commercial Patient Exposure to Combined Cabozantinib (Cabometyx + Cometriq) as of 28 November 2025 by Region

By country	
All indications	
	Cumulative exposure through 28 November 2025
Marketed	
EU	104,159
US	92,923
Japan	24,288
ROW [c]	57,365
Total	**278,735**
MAP/GAP	
EU	905
US	0

By country	
All indications	
	Cumulative exposure through 28 November 2025
Japan	0
ROW [a]	3371
Total	**4276**
Total exposure (marketed and MAP/GAP)	**283,011**

EU=European Union; GAP=global access programme; MAP=market access programme; 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 combined cabozantinib (Cabometyx+Cometriq) in the commercial setting: Algeria, Australia, Bahrain, Brazil, Canada, Colombia, Egypt, French Polynesia, Hong Kong, Israel, Jordan, Kazakhstan, Kuwait, Lebanon, Malaysia, Mexico, Morocco, New Caledonia, New Zealand, Oman, Panama, Qatar, Russian Federation, Saudi Arabia, Serbia, Singapore, South Africa, South Korea, Switzerland, Taiwan, Thailand, Turkey, Ukraine, United Arab Emirates and United Kingdom.

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

The prescribing information obtained for patients who were dispensed Cabometyx by the Specialty Pharmacies showed that 73% had an underlying kidney or hepatocellular cancer; other malignancies were also reported including thyroid cancer and neuroendocrine tumour (Table 37).

Table 37 Patterns of Cabometyx Use for Indications Reported in the Marketed Setting in the United States through 28 November 2025

Reported indication	Number of patients
Renal cancer	35,231
Hepatocellular carcinoma	3384
Thyroid cancer	1070
Neuroendocrine tumour	644
Other cancers (off label)	4856
Unknown cancer	7972

The prescribing information obtained for patients who were dispensed Cometriq by the Specialty Pharmacies is provided in Table 38.

Table 38 Patterns of Cometriq Use for Indications Reported in the Marketed Setting in the United States through 28 November 2025

Reported indication	Number of patients
Thyroid cancer/Renal cancer/Hepatocellular carcinoma	2407
Other cancers (off label)	745

Information on patient indication from the postmarketing setting outside of the US is not available for both Cabometyx and Cometriq.

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 39.

Table 39 Summary of Safety Concerns from the First Approved EU RMP for Cabometyx

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

EU=European Union; RMP=Risk Management Plan.

The safety concerns presented in the first approved EU RMP for Cometriq (Version 1) are provided in Table 40.

Table 40 Summary of Safety Concerns from the First Approved EU RMP for Cometriq

Important identified risks	• GI perforation • GI and non-GI fistula • Intra-abdominal and pelvic abscess • Thromboembolic events • Haemorrhage • Wound complications • Hypertension • Osteonecrosis • PRES • Diarrhoea • Palmar-plantar erythrodysaesthesia syndrome • Proteinuria
Important potential risks	• QTc prolongation • Renal failure • Hepatotoxicity • High-dose toxicity • Fertility impairment • Embryotoxicity • Medication errors • Drug-drug interactions • Food-drug interactions
Missing information	• Use in Paediatric population • Use in Patients with ethnicities other than White • Use in Patients with hepatic impairment • Use in Patients with renal impairment • Use in Patients with cardiac impairment • Use in pregnant or lactating women • Drug interactions - Individual drug transporters including P-glycoprotein substrates - Drugs affecting gastric pH - Drugs affecting enterohepatic recirculation • Toxicity of metabolite EXEL-1644 • Carcinogenicity

EU=European Union; GI=gastrointestinal; QTc=corrected QT interval; PRES=Posterior Reversible Encephalopathy Syndrome; RMP=Risk Management Plan.

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 41.

Table 41 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).	Arthralgia, blood ALP increased, thrombocytopenia, decreased appetite, hypocalcaemia, hypomagnesaemia, hypokalaemia, dysgeusia, headache, dizziness, dysphonia, nausea, vomiting, stomatitis, constipation, abdominal pain, dyspepsia, rash, pain in extremity, fatigue, mucosal inflammation, asthenia, serum ALT increased, AST increased and weight decreased are very common ADRs of cabozantinib treatment and are included in Section 4.8 of the Cabometyx and Cometriq SmPC.

Reason for risk(s) not being considered important	Justification [a]
	Anaemia, hypoalbuminaemia, dyspnoea, cough and peripheral oedema are very common ADRs of cabozantinib treatment and are included in Section 4.8 of the Cabometyx SmPC. Dysphagia, glossodynia, oropharyngeal pain, hair colour changes, dry skin, alopecia, erythema, muscle spasms, blood LDH increased and blood TSH increased very common ADRs of cabozantinib treatment and are included in Section 4.8 of the Cometriq SmPC. 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 ALT, increased AST, 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 Cabometyx SmPC. Abscess (including visceral, skin, tooth), pneumonia, neutropenia, lymphopenia dehydration, hyperbilirubinaemia, hypophosphataemia, peripheral neuropathy (including sensory), tinnitus, hypotension, haemorrhoids, hyperkeratosis, proteinuria, blood creatinine increased and lipase increased are common ADRs of cabozantinib treatment and are included in Section 4.8 of the Cabometyx and Cometriq SmPCs. Allergic rhinitis, flatulence, hyponatraemia, hyperkalaemia, hyperglycaemia, hypoglycaemia, gastroesophageal reflux disease, oral pain, dry mouth, dysphagia, pruritus, alopecia, dry skin, erythema, hair colour change, muscle spasms, GGT increased, amylase increased, , blood cholesterol increased, white blood cell count decreased, 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 Cabometyx SmPC. Folliculitis, fungal infection (including skin, oral and genital), hypoalbuminaemia, anxiety, depression, confusional state, paraesthesia, ageusia, tremor, vision blurred, ear pain, pallor, peripheral coldness, anal inflammation, cheilitis, cholelithiasis, acne, blister, hair growth abnormal, skin hypopigmentation, musculoskeletal chest pain, dysuria, haematuria, chills and face oedema are common ADRs of cabozantinib treatment and are included in Section 4.8 of the Cometriq SmPCs. Abnormal dreams, ataxia, disturbance in attention, hepatic encephalopathy, speech disorder, cataract, conjunctivitis, hypoacusis, supraventricular tachycardia, atelectasis, pharyngeal oedema, oesophagitis, skin ulcer, telangiectasia, amenorrhoea, vaginal haemorrhage, cyst, facial pain, localised oedema, activated partial thromboplastin time shortened, eosinophil count increased and platelet count increased are uncommon ADRs of cabozantinib treatment and are included in Section 4.8 of the Cometriq SmPC. Eosinophilia, dehydration, peripheral neuropathy, tinnitus, dry eye, blurred vision, tachycardia, epistaxis, pleural effusion, dry mouth, gastritis, oral pain, haemorrhoids, hepatitis, 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 Cabometyx 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 Cabometyx SmPC. Fertility impairment is considered to have minimal clinical impact on patients (in relation to the severity of the indication treated).

Reason for risk(s) not being considered important	Justification [a]
	Medication error with cabozantinib monotherapy is considered to have minimal clinical impact on patients (in relation to the severity of the indications treated). (Cabometyx and Cometriq SmPCs 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.	Pancreatitis is a common ADR of cabozantinib treatment and is included in Section 4.8 of the Cabometyx and Cometriq SmPCs. Pneumothorax is an uncommon ADR of cabozantinib treatment and is included in Section 4.8 of the Cabometyx and Cometriq SmPCs. Convulsion, cerebrovascular accident, acute myocardial infarction, cardiac failure, pneumothorax and hepatitis cholestatic are uncommon ADRs of cabozantinib treatment and are included in Section 4.8 of the Cabometyx SmPC. Aneurysm, artery dissections and cutaneous vasculitis are ADRs of cabozantinib treatment that occur at an unknown frequency and are included in Section 4.8 of the Cabometyx and Cometriq SmPCs. Cerebrovascular accident, atrial fibrillation, cardiac failure, pneumonia aspiration, anal fissure and skin exfoliation are common ADRs of cabozantinib treatment and are included in Section 4.8 of the Cometriq SmPC. Aspergilloma and renal failure acute are uncommon ADRs of cabozantinib treatment and are included in Section 4.8 of the Cometriq SmPC. Hypertensive crisis will be described in Section 4.4, occurs at an uncommon frequency and is included in Section 4.8 of the Cabometyx and Cometriq SmPCs. Delirium, loss of consciousness, angina pectoris, pneumonitis and rhabdomyolysis are uncommon ADRs of cabozantinib treatment and are included in Section 4.8 of the Cometriq 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, pneumothorax, pancreatitis, and nephritis are uncommon ADRs of cabozantinib in combination with nivolumab treatment and included in Section 4.8 of the Cabometyx SmPC. Myocardial infarction is an ADR of cabozantinib treatment that occurs at an unknown frequency and is included in Section 4.8 of the Cometriq SmPC. Vanishing bile duct syndrome and cutaneous vasculitis are ADRs of cabozantinib in combination with nivolumab treatment that occur at an unknown frequency and are included in Section 4.8 of the Cabometyx 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, are very common ADRs, venous thrombosis (including DVT), gastrointestinal perforation (including fatal), GI and non-GI fistula (including tracheal, pneumomediastinum, tracheo-oesophageal), pulmonary embolism is a common ADR and PRES, embolism arterial are uncommon ADRs of cabozantinib treatment and included in Section 4.8 of the Cabometyx and Cometriq SmPCs. Hypothyroidism, arterial thrombosis and GI haemorrhage, respiratory tract haemorrhage (including pulmonary, bronchial, tracheal), impaired wound healing and osteonecrosis of the jaw are common ADRs of cabozantinib treatment and are included in Section 4.8 of the Cometriq SmPC. Hypothyroidism and haemorrhage are very common ADRs, hepatic encephalopathy, embolism,are common ADRs and arterial thrombosis, wound complications and osteonecrosis of the jaw are uncommon ADRs, of cabozantinib treatment, and included in Section 4.8 of the Cabometyx SmPC. Hypertension, diarrhoea, hypothyroidism, hyperthyroidism, and PPES are very common ADRs, thrombosis, pulmonary embolism are common ADRs and embolism arterial, small intestine perforation (including fatal), fistula and osteonecrosis of the jaw are uncommon ADRs of cabozantinib in combination with nivolumab treatment and included in Section 4.8 of the Cabometyx 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; ALT=alanine aminotransferase; AST=aspartate aminotransferase; DVT=deep vein thrombosis; EU=European Union; GGT=gamma-glutamyl transpeptidase; GI=gastrointestinal; HCC=hepatocellular carcinoma; LDH=lactate dehydrogenase; PPES=palmar-plantar erythrodysaesthesia syndrome; PRES=reversible encephalopathy syndrome; RCC=renal cell carcinoma; RMP=risk management plan; SmPC=summary of product characteristics; TSH=thyroid stimulating hormone; 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

There are no identified risks, potential risks or missing information considered important for inclusion as safety concerns for this RMP.

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

The 11 safety concerns identified for cabozantinib (both Cabometyx and Cometriq) are reclassified and removed as they no longer meet the criteria of important identified risks or important potential risks as per Good Pharmacovigilance Practices (GVP) guidance Module V

Revision 2. These risks are adequately managed by routine risk minimisation and well described in the EU SmPCs and Patient Information Leaflets for Cabometyx and Cometriq. Cumulative overviews have been performed for each of the safety concerns cumulative to 28 November 2025. Based on these cumulative reviews, there are no additional RMMs warranted and routine pharmacovigilance is considered sufficient to monitor and manage these risks. Data from the most recent EU PSUR (29 November 2021 to 28 November 2024) and non-EU PSUR (29 November 2024 to 28 November 2025) did not reveal any new safety information. Furthermore, the voluntary post-authorisation safety study, CASSIOPE (FR-60000-001) completed on 24 March 2023, did not identify any new safety concerns and the safety profile of cabozantinib in this study remained consistent with its known safety profile. No additional pharmacovigilance activities were proposed to monitor the safety profile.

SVII.2.1. Important Identified Risks Removed from the Updated Risk Management Plan

Gastrointestinal perforation was previously classified as an important identified risk. The risk of GI perforation is a clinically well understood class effect of tyrosine kinase inhibitors and adequately described in the Warnings and Precautions section of the Cometriq and Cabometyx EU SmPCs and GI perforation is an ADR for Cabozantinib. A cumulative overview of the available safety data has been performed and based on this review; it can be concluded that there are no additional RMMs nor additional pharmacovigilance activities required to further characterise the risk. Gastrointestinal perforation events are monitored via routine pharmacovigilance, namely through signal detection and adverse reaction reporting. The Company proposes to remove this risk from the list of safety concerns from the RMP to align with GVP Module V Revision 2. Gastrointestinal perforation events will continue to be monitored through routine pharmacovigilance.

Gastrointestinal and nongastrointestinal fistula was previously classified as an important identified risk. The risk of GI fistula and non-GI fistula is adequately described in the Warnings and Precautions section of the Cometriq and Cabometyx EU SmPCs and GI fistula is an ADR for Cabozantinib. A cumulative overview of the available safety data has been performed, and based on this review, it can be concluded that there are no additional RMMs nor additional pharmacovigilance activities required to further characterise the risk. Gastrointestinal fistula and non-GI events are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting. The Company proposes to remove this risk from the list of safety concerns from the RMP to align with GVP Module V Revision 2. Fistula events will continue to be monitored through routine pharmacovigilance.

Thromboembolic events was previously classified as an important identified risk. The risk of thromboembolic events is adequately described in the Warnings and Precautions section of the Cometriq and Cabometyx EU SmPCs and thromboembolic events is an ADR for Cabozantinib. A cumulative overview of the available safety data has been performed, and based on this review, it can be concluded that there are no additional RMMs nor additional pharmacovigilance activities required to further characterise the risk. Thromboembolic events are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting. The Company proposes to remove this risk from the list of safety concerns from the RMP to align with GVP Module V Revision 2. Thromboembolic events will continue to be monitored through routine pharmacovigilance.

Haemorrhage (Grade ≥3) was previously classified as an important identified risk. The risk of haemorrhage is clinically well known and adequately described in the Warnings and Precautions section of the Cometriq and Cabometyx EU SmPCs and haemorrhage is an ADR for Cabozantinib. A cumulative overview of the available safety data has been performed, and based on this review, it can be concluded that there are no additional RMMs nor additional

pharmacovigilance activities required to further characterise the risk. Haemorrhagic events are followed up via routine pharmacovigilance activities. The Company proposes to remove this risk from the list of safety concerns from the RMP to align with GVP Module V Revision 2. Haemorrhagic events will continue to be monitored through routine pharmacovigilance.

Wound complications was previously classified as an important identified risk. The risk of wound complications is adequately described in the Warnings and Precautions section of the Cometriq and Cabometyx EU SmPCs and wound complication is an ADR for Cabozantinib. A cumulative overview of the available safety data has been performed, and based on this review, it can be concluded that there are no additional RMMs nor additional pharmacovigilance activities required. Wound complications events are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting. The Company proposes to remove this risk from the list of safety concerns from the RMP to align with GVP Module V Revision 2. Wound complications events will continue to be monitored through routine pharmacovigilance.

Posterior reversible encephalopathy syndrome (PRES) was previously classified as an important identified risk. The risk of PRES is adequately described in the Warnings and Precautions section of the Cometriq and Cabometyx EU SmPCs and PRES is an ADR for Cabozantinib. A cumulative overview of the available safety data has been performed, and based on this review, it can be concluded that there are no additional RMMs nor additional pharmacovigilance activities required to further characterise the risk. Posterior reversible encephalopathy syndrome events are monitored via routine pharmacovigilance, namely through signal detection and adverse reaction reporting. The Company proposes to remove this risk from the list of safety concerns from the RMP to align with GVP Module V Revision 2. Posterior reversible encephalopathy syndrome events will continue to be monitored through routine pharmacovigilance.

Osteonecrosis was previously classified as an important identified risk. The risk of osteonecrosis is adequately described in the Warnings and Precautions section of the Cometriq and Cabometyx EU SmPCs and osteonecrosis is an ADR for Cabozantinib. A cumulative overview of the available safety data has been performed, and based on this review, it can be concluded that there are no additional RMMs nor additional pharmacovigilance activities required to further characterise the risk. Events with osteonecrosis are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting. The Company proposes to remove this risk from the list of safety concerns from the RMP to align with GVP Module V Revision 2. Osteonecrosis will continue to be monitored through routine pharmacovigilance.

SVII.2.2. Important Potential Risks Removed from the Updated Risk Management Plan

Renal failure was previously classified as an important potential risk. The risk of renal failure is adequately described in the Warnings and Precautions (proteinuria) section of the Cometriq and Cabometyx EU SmPCs and renal failure (proteinuria) is an ADR for Cabozantinib. A cumulative overview of the available safety data has been performed, and based on this review, it can be concluded that there are no additional RMMs nor additional pharmacovigilance activities required to further characterise the risk. Renal failure events are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting. The Company proposes to remove this risk from the list of safety concerns from the RMP to align with GVP Module V Revision 2. Renal failure events will continue to be monitored through routine pharmacovigilance.

Hepatotoxicity was previously classified as an important potential risk. The risk of hepatotoxicity is adequately described in the Warnings and Precautions section of the Cometriq and Cabometyx EU SmPCs. A cumulative overview of the available safety data has been performed, and based on this review, it can be concluded that there are no additional RMMs nor additional pharmacovigilance activities required to further characterise the risk. Hepatotoxicity events are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting. The Company proposes to remove this risk from the list of safety concerns from the RMP to align with GVP Module V Revision 2. Hepatotoxicity events will continue to be monitored through routine pharmacovigilance.

Embryotoxicity was previously classified as an important potential risk. The results of the embryofoetal development studies are included in Sections 5.3 (Preclinical safety data) of the current Cabometyx and Cometriq EU SmPCs. Section 4.6, Fertility, pregnancy and lactation of the EU SmPCs provide clear guidance on contraception in women of childbearing potential receiving cabozantinib and female partners of male patients receiving cabozantinib. 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. This section also provides guidance on cabozantinib use during pregnancy, noting that there are no studies in pregnant women using cabozantinib. The potential risk for humans is unknown, and Cabozantinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with cabozantinib. A cumulative overview of the available safety data has been performed, and based on this review, it can be concluded that there are no additional RMMs nor additional pharmacovigilance activities required to further characterise the risk. Embryotoxicity events are monitored via routine pharmacovigilance, namely through signal detection and adverse reaction reporting. The Company proposes to remove this risk from the list of safety concerns from the RMP to align with GVP Module V Revision 2. Embryotoxicity events will continue to be monitored through routine pharmacovigilance.

Carcinogenicity was previously classified as an important potential risk. Given the limited number of reported cases, there is currently no substantial evidence to support an association between cabozantinib and carcinogenicity. No evidence that would suggest a causal link and nonclinical findings have not been clinically translated in patients. Information on the potential risk of carcinogenicity is described in the Sections 5.3 (Preclinical safety data) of the current Cabometyx and Cometriq EU SmPCs. A cumulative overview of the available safety data has been performed, and based on this review, it can be concluded that there are no additional RMMs nor additional pharmacovigilance activities required to further characterise the risk. Carcinogenicity events are monitored via routine pharmacovigilance, namely through signal detection and adverse reaction reporting. The Company proposes to remove this risk from the list of safety concerns from the RMP to align with GVP Module V Revision 2. Carcinogenicity events will continue to be monitored through routine pharmacovigilance.

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

Previously classified important identified risks and important potential risks are removed from this updated RMP; therefore this section is not applicable.

Part II: Module SVIII – Summary of the Safety Concerns

Summary of Ongoing Safety Concerns

A summary of safety concerns for cabozantinib is presented in Table **42**.

Table 42 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
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 cabozantinib (Cabometyx and Cometriq) 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

There are no planned or ongoing additional pharmacovigilance activities for cabozantinib.

III.3 Summary Table of Additional Pharmacovigilance Activities

There are no planned or ongoing additional pharmacovigilance activities for cabozantinib.

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

The section is not applicable as there are no safety concerns.

V.1 Routine Risk Minimisation Measures

The section is not applicable as there are no safety concerns.

V.2 Additional Risk Minimisation Measures

The section is not applicable as there are no safety concerns.

V.3 Summary of Risk Minimisation Measures

The section is not applicable as there are no safety concerns.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

This is a summary of the RMP for cabozantinib (Cabometyx and Cometriq). The RMP details how more information will be obtained about cabozantinib's safety profile.

The SmPCs and its package leaflets (PLs) for Cabometyx and Cometriq give essential information to healthcare professionals and patients on how cabozantinib should be used.

This summary of the RMP for cabozantinib should be read in the context of all this information including the assessment reports of the evaluations and their plain-language summaries, all of which is part of the European Public Assessment Reports (EPARs).

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

Cabometyx is authorised 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.

Cometriq is authorised for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC (see SmPC for the full indication).

Both products contain cabozantinib as the active substance and are given by oral administration.

Further information about the evaluation of cabozantinib's benefits can be found in the EPARs for Cabometyx and Cometriq, including in their plain-language summaries, available on the EMA website, under the medicine's webpage:

Cabometyx:

https://www.ema.europa.eu/en/medicines/human/EPAR/cabometyx.

Cometriq:

https://www.ema.europa.eu/en/medicines/human/EPAR/cometriq.

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

The measures to minimise the risks of cabozantinib are outlined below:

- 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 RMMs.

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.

II.A List of Important Risks and Missing Information

Important risks of cabozantinib 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 cabozantinib. 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	None
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

There are no important identified or potential risks for cabozantinib.

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

CCI

PART VII: ANNEXES

Table of contents

Annex 4 – Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

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

Not applicable