Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Cabozantinib

Proprietary Product Name: Cabometyx

Sponsor: Ipsen Pty Ltd

October 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of common abbreviations

Abbreviation	Meaning
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the plasma concentration-time curve from time 0 to 24-hours
AUC_{0-t}	Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
AUC_{0-inf}	Area under the plasma concentration-time curve from time 0 extrapolated to infinity
Bid	Twice daily
BMI	Body Mass Index
BP	Blood Pressure
^{14}C	Carbon-14 isotope
C_{max}	Observed maximum plasma concentration
µCi	Micro Curies
CI	Confidence Interval
CL/F	Apparent total body clearance
CP	Childs-Pugh
CRF	Case report form
CT	Computed tomography
CV	Coefficient of variation
CTCAE	Common toxicity criteria for adverse events
dL	Decilitre
ECOG	Eastern Cooperative Oncology Group
g	Grams
GLS	Geometric least square

Abbreviation	Meaning
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FBE	Free Base Equivalent
FDA	Food and Drug Administration (US)
FT4	Free T4
h	Hours
HGF	Hepatocyte growth factor
ICF	Informed consent form
IC_{50}	Concentration require for 50% inhibition
IRC	Independent Radiology Committee
ITT	Intent to treat
KPS	Karnofsky Performance Status
kg	Kilograms
L	Litres
LLOQ	Lower limit of quantitation
LSM	Least square mean
m	Metres
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Millilitres
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
ng	Nanograms
ONJ	Osteonecrosis of the Jaw

Abbreviation	Meaning
PD	Pharmacodynamic
PFS	Progression free survival
PK	Pharmacokinetic
PIB	Powder in bottle
PITT	Primary endpoint intent to treat
qd	Once daily
QTcF	Fridericia's correction of QT interval
RBC	Red blood cell
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
SoD	Sum of lesion diameter
T_{max}	Time to reach maximum plasma concentration
TEAE	Treatment emergent adverse event
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal
UPCR	Urine protein creatinine ratio
VEGF(R)	Vascular endothelial growth factor (receptor)
V/F	Apparent total volume of distribution
WCC	White cell count

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	18 January 2018
Date of entry onto ARTG:	19 January 2018
ARTG number:	283800
Active ingredient:	Cabozantinib
Product name:	Cabometyx
Sponsor's name and address:	Ipsen Pty Ltd Brandon Office Park, 540 Springvale Road Glen Waverley Victoria 3150
Dose forms:	Film coated tablet
Strength(s):	20 mg, 40 mg and 60 mg film coated tablets
Container:	Bottle
Pack size:	30 tablets
Approved therapeutic use:	Cabometyx is indicated for the treatment of advanced renal cell carcinoma (RCC) in adults following prior treatment with vascular endothelial growth factor targeted therapy
Route of administration:	Oral (PO)
Dosage:	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.

Product background

This AusPAR describes the application by the sponsor to register cabozantinib, a new chemical entity, as Cabometyx, for the following indication:

> *For the treatment of advanced renal cell carcinoma (RCC) in adults following prior treatment with vascular endothelial growth factor targeted therapy.*

The proposed dosing regimen involves oral administration of 60 mg once daily. The draft Product Information (PI) document states that treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

Cabozantinib is a vascular endothelial growth factor (VEGF) inhibitor and inhibits multiple receptor tyrosine kinases implicated in tumour growth and angiogenesis, pathologic bone

remodelling, drug resistance, and metastatic progression of cancer. Cabozantinib belongs to the same pharmacological class as pazopanib, sunitib, sorafenib and axitinib, which have been approved for a similar indication by the TGA.

Renal cell carcinoma (RCC) originates in the renal cortex and constitutes 80% to 85% of primary renal neoplasms. RCC can be classified as:

- Localised disease when it is confined to the renal cortex.
- Advanced disease when the tumour invades beyond the renal fascia or extends into the associated adrenal gland.

Many patients present with advanced or unresectable disease at initial diagnosis and up to one third of patients relapse after surgical treatment with curative intent of initially localised disease.

Diagnosis is usually established by radiographic detection of a renal mass. The extent and location of tumour metastases in patients with advanced RCC contribute to significant morbidity. Metastatic symptoms include airway obstruction, venous thromboembolism, bone pain, skeletal related events (SRE) and hypercalcaemia. In addition, paraneoplastic syndromes (hypertension and disorders of the endocrine, hepatic, and neuromuscular systems) impact quality of life of patients with advanced RCC. Patients with advanced RCC may also develop brain metastases during the disease; these cause debilitating neurological symptoms and shorten survival. The median overall survival (OS) for patients with advanced RCC ranges from about 8 months (poor risk score) to 4 years (favourable risk score). The most frequent locations of metastases are the lungs, mediastinum, bone, liver, and brain. Among solid cancer types, RCC has the second highest incidence of brain metastases.

Current treatment options

There is no curative treatment regime for advanced renal cell carcinoma (RCC) at this time: aims of treatment are to reduce symptom burden, reduce the rate of progression and prolong survival. Median OS in advanced RCC patients has improved with the advent of targeted therapy.[1] Median OS with first-line therapy with sunitinib in a 2009 study was over 24 months.[2]

The clinical reference UpToDate recommends high dose interleukin 2 (IL-2) (aldesleukin) first line in patients able to tolerate it, and anti-VEGF targeted therapy or anti-programmed death 1 (PD1)/anti-programmed cell death ligand 1 (PDL1) trial participation if not.[3] IL-2 is not registered in Australia. Both National Comprehensive Cancer Network (NCCN, United States) guidelines and UpToDate recommend pazopanib or sunitinib as first line choice of anti-VEGF therapy.[4] After first-line immunotherapy, UpToDate currently recommends second line axitinib or sorafenib if axitinib is not available. After first-line anti-VEGF therapy, UpToDate recommends second line nivolumab or second line cabozantinib as an alternative: the two have not been directly compared but nivolumab is thought to be preferable as it appears to have less toxicity. Different side effect profiles are also seen between the individual anti-VEGF agents and

[1] Li P, Wong Y, Armstrong K, et al. Survival among patients with advanced renal cell carcinoma in the pretargeted versus targeted therapy eras. Cancer Medicine. 2016;5(2):169-181. doi:10.1002/cam4.574. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4735783/

[2] Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009;27(22):3584-3590. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3646307/

[3] UpToDate topic, 'Overview of the treatment of renal cell carcinoma.' https://www.uptodate.com/contents/overview-of-the-treatment-of-renal-cell-carcinoma

[4] NCCN guidelines for the treatment of kidney cancer. Version 1.2018, dated 27 September 2017. Accessed 11/10/2017: https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf

choice of therapy depends partly on co-morbidities and patient profile. For example, a lower incidence of hand-foot syndrome, fatigue and myelosuppression but a higher incidence of hepatic injury is seen with pazopanib than sunitinib.[5] In Australia, pazopanib and sunitinib are subsidised for first line therapy of RCC.

Table 1 summarises the products currently registered on the Australian Register of Therapeutic Goods (ARTG) for the treatment of advanced RCC.

Table 1: Products on the ARTG for the treatment of RCC

INN	Indication
Axitinib	Treatment of patients with advanced renal cell carcinoma after failure of one prior systemic therapy
Bevacizumab	in combination with interferon alfa-2a is indicated for treatment of patients with advanced and/or metastatic renal cell cancer
Everolimus	Treatment of advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib
Nivolumab	Treatment of patients with advanced clear cell renal cell carcinoma after prior anti-angiogenic therapy in adults
Pazopanib	Treatment of advanced and/or metastatic renal cell carcinoma
Sorafenib	Treatment of patients with advanced renal cell carcinoma
Sunitinib	Treatment of advanced renal cell carcinoma.

INN = International Non-proprietary Name

Regulatory status

This is an application to register a new chemical entity on the ARTG.

Cabozantinib was approved for use of treatment of RCC by the US Food and Drug Administration (FDA) on 25 April 2016 and by the European Medicines Agency (EMA) centralised procedure on 9 September 2016. There do not appear to be any differences in the dosage regimen or proposed patient population between the jurisdictions.

Table 2: Summary of overseas regulatory status in Europe and the United States

	Cabometyx (tablets)	Cometriq (capsules)
Australia (TGA)	Current application (new active substance)	Not applicable
United States (FDA)	*For the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.*	Approved 29 November 2012: *For the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC)*

[5] Mitchell CC, Parikh OA. Factors involved in treatment preference in patients with renal cancer: pazopanib versus sunitinib. Patient preference and adherence. 2014;8:503-511. doi:10.2147/PPA.S38989. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4003261/

	Cabometyx (tablets)	Cometriq (capsules)
Europe (EMA)	*For the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy*	Approved 21 March 2014 *For the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma*

A boxed warning in the Cometriq (but not Cabometyx) FDA label concerns gastrointestinal (GI) perforations, fistulas and haemorrhage (including fatal cases), which were seen in the metastatic thyroid cancer (MTC) pivotal trial.[6,7] In an FDA publication, the following explanation is given:[8]

> *The safety profile of cabozantinib in RCC appeared similar to the previously characterized profile of the capsule formulation of cabozantinib in the MTC population. Patients treated with the 60-mg tablet formulation used in the RCC study experienced fewer events, such as gastrointestinal perforations and fistulas, compared with those treated with the 140-mg capsule formulation in the MTC trial.*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR and Attachment 2.

Table 3: Registration time line

Description	Date
Submission dossier accepted and first round evaluation commenced	31 January 2017
First round evaluation completed	30 June 2017
Sponsor provides responses on questions raised in first round evaluation	3 July 2017
Second round evaluation completed	12 October 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	31 October 2017

[6] Cometriq FDA label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203756lbl.pdf
[7] Cabometyx FDA label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208692s000lbl.pdf
[8] Singh H, Brave M, Beaver JA et al. FDA Approval Summary for Cabozantinib for RCC. Clin Cancer Res; 23(2) January 15, 2017. DOI: 10.1158/1078-0432.CCR-16-1073. http://clincancerres.aacrjournals.org/content/23/2/330

Description	Date
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	18 January 2018
Completion of administrative activities and registration on ARTG	19 January 2018
Number of working days from submission dossier acceptance to registration decision*	198

*Statutory timeframe for standard applications is 255 working days

III. Quality findings

Neither the drug substance nor the finished product is the subject of a monograph in the British or European Pharmacopoeia (BP/Ph. Eur.) or the US Pharmacopeia (USP).

Drug substance (active ingredient)

Cabozantinib (S)-malate is a new chemical entity with the proposed trade name Cabometyx.

Proposed Name

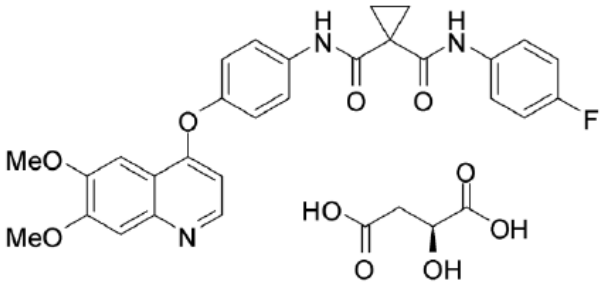
There are two Australian approved names (AANs): 'Cabozantinib (S)-malate' and 'cabozantinib'. The international non-proprietary name (INN) is 'cabozantinib'.

The chemical name is N-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-N′-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate.

Structure

The chemical structure is somewhat similar to other TKIs, including regorafenib and sorafenib. The chemical structure of cabozantinib (S)-malate is provided below.

Figure 1: Chemical structure of cabozantinib (S)-malate



Molecular Formula: C28H24FN3O5·C4H6O5

Molecular Weight: 635.6 Daltons (S-malate salt) 501.5 Daltons (freebase).

Structural isomerism

Cabozantinib contains no asymmetric centres. The counterion, (S)-malate contains one stereogenic centre and is the enantio-pure form as shown (that is, not racemic).

Control of materials

Cabozantinib (S)-malate is the final drug substance and controlled to set specifications. A critical step in the final manufacturing step is control of crystalline form. Cabozantinib (S)-malate can exist as N-1 or N-2 crystal forms, where the commercial process is designed to produce the N-2 form.

The physicochemical properties of the drug substance, including polymorphic form and solubility have been described. Of note, the active pharmaceutical ingredient (API) has poor aqueous solubility across the physiological pH range.

Polymorphism

The sponsor has demonstrated the ability to clearly distinguish the polymorphic forms, and it is routinely controlled.

Drug product

The proposed drug product is film coated tablets which contain either 20 mg, 40 mg or 60 mg of cabozantinib as the (S)-malate salt. Cabozantinib 20 mg tablets are yellow film-coated round tablets, debossed with 'XL' on one side and '20' on the other side of the tablet. Cabozantinib 40 mg tablets are yellow film-coated triangle-shaped tablets, debossed with 'XL' on one side and '40' on the other side of the tablet. Cabozantinib 60 mg tablets are yellow film-coated oval-shaped tablets, debossed with 'XL' on one side and '60' on the other side of the tablet. The tablets are proposed to be packaged in HDPE bottles with 30 tablets, three 1 g silica gel desiccant canisters, polyester coil and child-resistant closure.

Cabometyx was initially provided as a powder-in-bottle oral suspension formulation for initiation of the Phase I Study XL184-001. A capsule formulation was later developed and used in Phase II studies, a Phase III study and various clinical pharmacology studies. A tablet formulation was later developed and used in other Phase III efficacy and/or safety studies, including pivotal Study XL184-308.

Container closure system

The product is proposed to be stored in high-density polyethylene (HDPE) bottles. The tablets have been demonstrated to be very slightly sensitive to oxidation but stable to humidity and light. The container closure system is therefore appropriate.

Specifications

The proposed specifications are identical at release and expiry, except for the specification for the XL184-1-1 genotoxic impurity (GTI) which has a tighter limit at release than expiry.

The proposed specification for appearance is acceptable.

The proposed specification acceptance criteria for identification involves comparing sample to reference standard using high pressure liquid chromatography (HPLC)

(retention time) and ultra violet spectral analysis. This is acceptable to the relevant guideline.[9]

The content uniformity test method has been validated for specificity, filter bias, linearity, accuracy, precision, solution stability, and robustness. The proposed limit for water content is in line with batch and stability data and is considered acceptable.

The proposed specification limits for microbial content are in line with relevant guidelines;[9] and USP 1111, and are acceptable.

Stability was assessed at long-term storage condition of 25°C/60% RH (up to 36 months) and accelerated condition of 40°C/75% RH (up to 6 months). The stability test parameters included appearance, potency, impurities, water content, dissolution (as a profile over time with mean and range) and genotoxic impurities. Microbial limit testing was tested only under long-term test conditions.

Photostability studies were conducted in accordance with the relevant guideline on one batch of 20 mg tablets and one batch 100 mg tablets.[10]

Forced degradation studies were conducted on one batch of 20 mg tablets.

Recommended shelf-life

The sponsor has demonstrated that the proposed 36 month shelf life stored at 25°C is appropriate.

Photostability

Cabozantinib 20 mg tablets and 100 mg tablets were assessed for photostability under relevant guideline conditions.[9] The tablets were tested for appearance, potency, impurities, genotoxic impurities, water content, and dissolution. There was no significant difference between dark control and exposed tablets for all parameters. Therefore cabozantinib tablets are considered to be photo stable.

Biopharmaceutics

Overview of biopharmaceutic studies

The cabozantinib tablet formulation that was used in 'pivotal' (as stated by sponsor) Phase III Study XL184-308 in subjects with renal cell carcinoma (RCC) is the proposed commercial formulation. The cabozantinib tablet formulation was also used in the Phase III Studies XL184-306 and XL184-307 in subjects with castrate-resistant prostate cancer (CRPC).

Prior to the tablet formulation, cabozantinib was provided as capsules using the same cabozantinib drug substance. Capsules were dosed in the first-in-human Study XL184-001, clinical pharmacology studies, and Phase III Study XL184-301 in medullary thyroid cancer (MTC). Study XL184-001 also dosed cabozantinib as a powder-in-bottle (PIB) oral suspension. Cabozantinib capsules consist of the cabozantinib drug substance blended with excipients and encapsulated into hard gelatine capsules. There were three biopharmaceutic studies (Studies XL184-004, XL184-016, and XL184-010) in which cabozantinib capsules were administered. Study XL184-010 was designed to evaluate the

[9]ICH Q6A.Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances.
[10] ICH Q1B: Stability testing: Photostability testing of new drug substances and products.

bioequivalence of the tablet and capsule formulations, whereas Studies XL184-004 and XL184-016 are related to the drug substance.

In the Phase III RCC Study XL184-308, the daily 60 mg cabozantinib dose was administered as one 60 mg tablet. Dose reduction to a 40 mg cabozantinib dose was administered as a combination of two 20 mg tablets (commercially will be one single 40 mg tablet). The cabozantinib exposures associated with the 20 mg, 40 mg and 60 mg tablets were evaluated clinically in PK Study XL184-020.

There were no tablet formulation changes that necessitated biopharmaceutic studies.

The following biopharmaceutics studies were evaluated:

- Study XL184-010
  - an open-label, randomised, single-dose, comparative, two-period, two-sequence crossover bioequivalence study that compared the capsule formulation of cabozantinib to the tablet formulation of cabozantinib.
- Study XL184-004
  - an open-label, randomised, single-dose, comparative, two-period, two-sequence crossover Phase 1 study that evaluated the effect of food (high-fat meal) on the plasma PK of XL184 dosed as capsules (1 x 80 mg + 3 x 20 mg capsules).
- Study XL184-016
  - an open-label, randomised, single-dose, comparative, two-period, two-sequence crossover bioequivalence study that compared different mixtures of crystal forms in cabozantinib drug substance (an approximate 1:1 mixture of N-1 and N-2 crystal forms versus primarily the N-2 crystal form) administered as the capsule formulation.

Justification for lack of absolute bioavailability study

The product has very low solubility over most of the pH range. The sponsor has not discussed a microdose absolute bioavailability study. This issue will be drawn to the attention of the Delegate.

The sponsor has provided a relative bioavailability study of tablets compared to an oral solution of cabozantinib. The relative BA study demonstrated that cabozantinib (S)-malate in solution had an earlier time to maximum plasma concentration (T_{max}) and a higher observed maximum plasma concentration (C_{max}). Mean area under the concentration versus time curve from time zero to infinity (AUC_{inf}) for tablets were 97% of the AUC_{inf} for solution suggesting that the tablet formulation is close to being 'optimally formulated'.

Bioequivalence of tablet strengths

The 'pivotal' clinical study for this application (XL184-308) used 20 mg and 60 mg tablets but not 40 mg tablets. All cabozantinib tablets are immediate release, direct scales and made from a common blend. The 40 mg tablets are effectively bracketed by the 20 mg and 60 mg tablets. Additionally, a dose-linearity study (XL184-020) demonstrated proportional changes in C_{max}, AUC_t, AUC_{24}, AUC_{inf} and half-life ($t_{½}$) with increasing dose. Therefore the 40 mg tablet is accepted as equivalent to the 20 mg and 60 mg tablets on a dose-adjusted basis. However, the sponsor has not provided comparative dissolution data

across the physiological pH range comparing the product strengths, as discussed in the relevant EU guideline[11]. This will be requested from the sponsor.

As discussed in the relevant guideline[11] to support a biowaiver for the 40 mg tablet strength, the sponsor should provide comparative dissolution data at pH 1.2, 4.5 and 6.8 between additional strengths (40 mg) and the strengths used for bioequivalence testing (20 mg and 60 mg tablets).

Study XL184-010 (capsule versus tablet formulation)

- A Phase I, open label, randomised, single dose, two treatment, two way crossover bioequivalence study of cabozantinib (XL184) tablet and capsule formulations in healthy adult subjects.

The study demonstrated that the tablet formulation is bioequivalent to the capsule formulation for the AUC parameter. However the tablet formulation had considerably higher C_{max} compared to capsules, and the bioequivalence criterion was not met for the C_{max} parameter. This will be drawn to the attention of the clinical Delegate.

Study XL184-016 (effect of polymorphic form)

- A Phase I, open label, randomised, single dose, two treatment, two way crossover bioequivalence study of XL184 (cabozantinib) capsules in healthy adult subjects. The clinical study site was identical to Study XL184-010. The study was run between 2 May 2011 and 6 July 2011.

In conclusion, this study provided evidence that Treatment A (100 mg XL184 capsule containing an approximate 1:1 mixture of N- 1 and N-2 crystal forms) and Treatment B (100 mg XL184 capsule containing primarily N-2 crystal form) met bioequivalence acceptance criteria for AUC, but not C_{max} (with high variability). It is unclear what 'primarily N-2 crystal form' exactly refers to in terms of quantitative polymorphic form ratio. Therefore, it is unclear how useful this study is for setting acceptable specification limits for API polymorphic form ratio.

Study XL184-004 (food effect on capsules)

- A Phase I open label, randomised, single dose, two treatment, and two way crossover study to assess the effect of food on the bioavailability of XL184 (cabozantinib) in healthy adult subjects. The clinical study site was identical to Study XL184-016. The study was run between 12 April 2011 and 15 June 2011.

In conclusion, this study has demonstrated a significant food effect on cabozantinib capsules whereby C_{max} and AUC were higher under fed conditions compared to fasted. The median T_{max} was also longer under fed conditions. The food effect is reflected in the proposed PI which states: 'Patients should be instructed to not eat anything for at least 2 hours before through 1 hour after taking Cabometyx'.

Quality summary and conclusions

The application and the supporting data relating to the composition, development, manufacture, quality control, stability and bioavailability of the product have been assessed and checked for compliance, as applicable, with Australian legislation and

[11] EMEA. Committee for Proprietary Medicinal Products (CPMP), 26 July 2001. Note for Guidance on the Investigation of Bioavailability and Bioequivalence. CPMP/EWP/QWP/1401/98.

requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA.

The proposed shelf life for the finished product is 36 months below 25°C.

The proposed trade name Cabometyx appears to have been adopted internationally (for tablets; Cometriq seems to be used for a capsule formulation not proposed in Australia). Note Cosentyx (secukinumab rch injection prefilled syringe or vial, for psoriasis / psoriatic arthritis / ankylosing spondylitis) which is similar but a very different dosage form. The acceptability of the tradename is a clinical decision.

The draft PI is acceptable from a pharmaceutical chemistry perspective.

Approval was recommended from a chemistry and quality perspective with certain conditions of registration recommended at this time to:

- Amend the specification for L-malic acid to include the residue on ignition (ROI) test.
- Set tighter limits on particle size.
- Tighten the release limit for one impurity (depending on toxicological advice).

IV. Nonclinical findings

Introduction

The submitted nonclinical data was in accordance with the relevant guideline for the nonclinical assessment of anticancer pharmaceuticals.[12] The overall quality of the dossier was reasonable with all pivotal safety studies conducted under Good Laboratory Practice (GLP) conditions.

Pharmacology

Primary pharmacology

In vitro

Cabozantinib is a multiple receptor kinase inhibitor, inhibiting VEGFR2 (also known as kinase insert domain receptor (KDR); 50% inhibitory concentration (IC_{50}) or Ki 35-50 pM), MET, VEGFR1, VEGFR3 receptor tyrosine kinases ((RET) KIT, fms like tyrosine kinase 3 (FLT-3), TIE-2[13], Axl, tropomyosin receptor kinase B (TrkB), FMS, MER, ROS1 and RSE (TYRO3)) at clinically relevant concentrations (IC_{50} 2 to 15 nM). Aberrant function of some of these kinases has been shown to be involved in tumour growth (for example, MET, Flt1, RET, KIT, Axl, FMS, ROS1 and RSE), angiogenesis (for example, VEGFR2, MET, Flt4), bone remodelling (for example, VEGFR2), drug resistance to VEGFR inhibitors (for example, Axl, MET) and metastatic progression of cancer (for example, MET). Cabozantinib retained some inhibitory activity against a small number of Flt3, KIT, RET and MET mutants. At clinically relevant concentrations, cabozantinib inhibited cellular proliferation in multiple tumour cell lines with a reliance of signalling through MET (IC_{50} 13 to 149 nM), endothelial cell migration in response to VEGF (substrate for VEGFR2; IC_{50} 12 nM), HGF (substrate for MET) and angiopoietin-1 (substrate for TIE-2; IC_{50} 23 nM), and tumour cell invasion and migration in response to HGF (IC_{50} 12 to 53 nM).

[12] ICH S9 Nonclinical evaluation for anticancer pharmaceuticals
[13] Transmembrane tyrosine-protein kinase receptor for Angiopoietin(ANGPT) 1, ANGPT2 and ANGPT4

There are 4 major human metabolites of cabozantinib: EXEL5162 (N oxidation product), EXEL5366 (amide cleavage product), EXEL1644 (sulfation of desmethyl EXEL5366) and EXEL1646 (monohydroxy sulphation product). EXEL5162 and EXEL5366 had poor to no inhibitory activity at various kinases and on MET autophosphorylation, and limited anti-proliferative activity. No clinically-relevant inhibitory activity was seen with EXEL1644 and EXEL1646 at any of the kinases cabozantinib had inhibitory activity towards. Therefore, none of the major human metabolites of cabozantinib are expected to contribute to efficacy.

In vivo

The anti-tumour efficacy of cabozantinib was examined in numerous mouse xenograft models of cancer: medullary thyroid cancer, glioma, human breast carcinoma, human lung carcinoma and cancers reliant on RET, MET, VEGFR, TIE-2 or Flt3 signalling. In general, steady state plasma levels of cabozantinib approximately 1500 to 2400 ng/mL, similar to the clinical steady state C_{max}[14], were needed for > 90% tumour growth inhibition. It had low activity against KIT in mice with the xenograft of human lung adenocarcinoma Calu6/KIT AC(D10C) cells. Tumour growth inhibition and/or regression were observed in most models and histological evaluation of tumour tissue indicated a decrease in micro vessel density. Cabozantinib (VEGFR/MET inhibitor) treatment did not promote metastasis like sunitinib (also a multi kinase inhibitor with activity against VEGFR, PDGFR, KIT, RET and Flt3 but not MET) in an experimental model of lung metastasis. Published data indicate that simultaneous inhibition of MET and VEGFR can reduce tumour invasion and metastasis.[15]

There were no efficacy studies in animal models of advanced renal cell carcinoma, so it is difficult to compare efficacious doses/plasma concentrations with that proposed for the current indication.

Resistance

No studies were conducted to identify spontaneous resistance mutations. Cabozantinib is not a substrate for P-glycoprotein (see Pharmacokinetic drug interactions); therefore over expression of this transporter is expected to have minimal effect on cabozantinib efficacy. If efficacy of cabozantinib is dependent on the inhibition of multiple kinases, the incidence of resistance is expected to be lower than would be the case if efficacy was dependent on activity at a single kinase.

Secondary pharmacodynamics and safety pharmacology

No clinically relevant activity was observed with cabozantinib at 37 other receptor kinases and 74 non-kinase receptors, ion channels and transporters. No clinically-relevant inhibitory activity was observed with EXEL1644 and EXEL1646 at 42 to 47 receptor kinases and 79 non-kinase receptors, ion channels and transporters at 1 μM except for EXEL1644 against a Met mutant, Aurora-B, Axl and Tie2 with (IC_{50} 50 to 90 nM (> 10 times the predicted clinical free C_{max}).[16] Off-target effects are not predicted with EXEL1644 and EXEL1646.

Dedicated safety pharmacology studies assessed effects on the cardiovascular, respiratory and central nervous systems. No significant inhibition of the potassium (hERG K^+) tail current was observed with cabozantinib, EXEL5162, EXEL1646, EXEL5366 or EXEL1644 at 30 μM (> 1000 times the free clinical C_{max}). There was no evidence of QTc

[14] Mean clinical $C_{max, ss}$ 905 to 1186 ng/mL in white male, female and Asian male patient groups
[15] Sennino B. et al. (2012) Suppression of tumor invasion and metastasis by concurrent inhibition of c-Met and VEGF signaling in pancreatic neuroendocrine tumors. Cancer Discov. 2: 270-287.
[16] Predicted clinical free fraction Cmax: 24 nM for canozantinib, 3.6 nM for EXEL1646, 2.1 nM for EXEL5162, 1.2 nM for EXEL5366, 4.53 for EXEL1644.

prolongation;[17] or other electrocardiogram (ECG) abnormalities in dogs treated with ≤ 1000 mg/kg PO cabozantinib (predicted C_{max} 23 times the clinical C_{max}).[18] Cabozantinib is not predicted to prolong the QTc interval during clinical use. In this study, peak plasma levels of metabolites EXEL5162 and EXEL5366 are predicted to exceed those expected clinically. Peak plasma levels of EXEL1646 and EXEL1644 are predicted to be below those expected clinically, so cardiovascular abnormalities aside from QTc prolongation cannot be dismissed by the absence of findings in dogs. Increased blood pressure was observed in dogs treated with 1000 mg/kg PO cabozantinib (No observable effect level (NOEL) 150 mg/kg; predicted C_{max} 7 times the clinical C_{max}).[19] This is not expected to be of clinical concern.

No adverse effects on central nervous system (CNS) or respiratory function were seen in rats treated with ≤ 300 mg/kg PO and ≤ 900 mg/kg PO cabozantinib, respectively. The predicted C_{max} at the no effect level is approximately 65 times the clinical C_{max} for cabozantinib.[20] Peak plasma concentrations for metabolites EXEL5162, EXEL1646 and EXEL5366 are predicted to adequately exceed the expected peak levels for these metabolites in patients. While the peak levels of EXEL1644 are predicted to be subclinical in the dedicated safety pharmacology studies in rats, there were no clinical signs of effects on the central nervous and respiratory systems in rats treated with ≤ 30 mg/kg/day SC EXEL1644 in a 2 week repeat dose toxicity study (C_{max} far exceeding the expected clinical C_{max} for this metabolite[21]). Therefore, CNS and respiratory effects are not predicted during clinical use.

Pharmacokinetics

The rate of oral absorption was reasonably rapid in mice, rats (at doses ≤ 100 mg/kg/day), dogs, monkeys and humans (Tmax generally 0.5 to 4 h). Peak plasma concentrations occurred later at higher doses (≥ 300 mg/kg/day) in rats. Oral bioavailability was dependent on formulation, ranging from 42 to 62% in mice, 58 to 111% in rats, 18 to 87% in dogs and 13 to 73% in monkeys. Absolute bioavailability was not assessed in human subjects. Following IV dosing, the terminal plasma half-life was moderate in mice, dogs and monkeys (t½ 3 to 6 h) and longer in rats (t½ 9 to 14 h). Following PO dosing to human subjects, the t½ was very long in human subjects (t½ 99 h). Clearance (CL) was similar in mice, dogs and monkeys following IV dosing (0.23 to 0.64 L/kg/h) and lower in rats (IV dosing) and humans (PO dosing, CL/F) (t½ 0.03 to 0.05 L/kg/h). Exposures (AUC) were dose proportional in mice and rats (up to 100 mg/kg/day) and generally less than dose proportional in dogs (30 to 120 mg/kg/day). Saturation of absorption was evident in dogs at ≥ 400 mg/kg/day. Dose proportionality was not assessed in monkeys. There were no consistent sex differences in exposures in mice and dogs but female rats generally had higher exposures than male counter parts (by approximately 1.5 fold), associated with lower formation of the sulfate metabolite EXEL1646 in female rats (AUC 1.85% of parent

[17] The QT interval is the time from the start of the Q wave to the end of the T wave. It represents the time taken for ventricular depolarisation and repolarisation, effectively the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation. The QT shortens at faster heart rates. An abnormally prolonged QT is associated with an increased risk of ventricular arrhythmias, especially Torsades de Pointes. The recently described congenital short QT syndrome has been found to be associated with an increased risk of paroxysmal atrial and ventricular fibrillation and sudden cardiac death.

[18] Predicted C_{max} in dogs at 1000 mg/kg, 27.5 µg/mL, based on data in Study XL184-NC-004

[19] Predicted C_{max} in dogs at 150 mg/kg, 7.8 µg/mL, based on data (6.2 µg/mL at 120 mg/kg) in Study XL184-NC-001.

[20] Based on data in Study XL184-NC-007 where a Cmax of 78.5 µg/mL was observed for a 900 mg/kg PO dose in rats and pharmacokinetic data from Study XL184-NC-003 suggesting a similar Cmax for a 300 mg/kg and 900 mg/kg dose in rats (note the Cmax for a 300 mg/kg dose was 80.6 µg/mL and 900 mg/kg dose 86.6 µg/mL in this study).

[21] EXEL1644 C_{max} at 30 mg/kg/day in rats was ~100 µg/mL, compared to predicted clinical C_{max} 0.2 µg/mL.

as comparted to 9.4% in male rats in a 5 day study). There was no evidence of accumulation following repeated dosing in mice and dogs, and there was some accumulation in rats.

There were 4 major human metabolites: EXEL5162, EXEL1646, EXEL1644 and EXEL5366. Exposures (AUC) to these metabolites relative to the parent are shown in Table 4.

Table 4: Major human metabolites in human plasma relative to cabozantinib based on AUC

Species	EXEL5162 (M1)	EXEL1646 (M4)	EXEL1644 (M12)	EXEL5366 (M8)
Mouse	3–11%	0.15–3%	0.24–1.4%	2.4–4%
Rat	1–3%	2–9%	0.02–0.07%	0.25–0.4%
Dog	4–5.5%	0.24%	0	2%
Human	15%	43%	150%	10%

Protein binding by cabozantinib was very high in the plasma of mice, rats and humans (> 99% bound fraction). Protein binding by EXEL1644 was similarly high to very high in the plasma of these species (97 to 100% bound fraction) with some concentration-dependence observed at 125 to 500 µM. Protein binding in human plasma was > 99% at all tested concentrations. The volume of distribution was similar to total body water in mice and rats (0.4 to 0.93 L/kg) and larger than total body water in dogs, monkeys and humans (2.1 to 6.4 L/kg). Tissue distribution studies were assessed in rats. Given the difference in the volume of distribution observed in rats and human subjects, it is unclear how predictive the tissue distribution in rats is to the human situation. Nonetheless, in rats, aside from tissues involved in absorption and excretion, relatively high exposures were seen in the adrenal and Harderian glands and the uveal tract in the eye. The high exposures in the uveal tract suggested some affinity to this tissue; however, there was no specific retention of drug-related material in pigmented skin. There was minimal penetration of the blood-brain barrier (tissue: blood AUC, approximately 0.1).

The metabolism of cabozantinib was generally similar in rats, dogs and humans and involved N oxidation (to EXEL5162), monohydroxy sulfation (to EXEL1646), amide cleavage (to EXEL5366 and p-fluoroaniline) and sulfation of the desmethyl amide cleavage product (to EXEL1644). However, EXEL1644 does not appear to be formed in dogs. Minor metabolites in human plasma included glucuronide conjugates of demethylated cabozantinib and a methyl ester of EXEL5366. Glucuronide conjugates of demethylated and other minor metabolites were also metabolites in rats and dogs. In vitro studies demonstrated a significant role of cytochrome P450 (CYP) isozyme CYP3A4 in the metabolism of cabozantinib (EXEL5162 was shown to be formed by CYP3A4). Sulfation of cabozantinib monohydroxy (to EXEL1646) and cabozantinib mono-desmethyl hydroxyl amide cleavage product (to EXEL1644) was shown to involve multiple human sulfotransferases (SULT1A1, 1A2, 1A3 and 2A1 to form EXEL1646; SULT1A1, 1A2, 1A3, 1E1 and 2A1 to form EXEL1644) and the relative involvement was dependent on the substrate concentration. The amide cleavage product, EXEL5366, is likely formed by (an) amidase(s).

Excretion of cabozantinib and/or its metabolites was predominantly via the faeces in rats, dogs and humans. Urinary excretion of drug related material was more prominent in humans. Biliary excretion was demonstrated in both of the laboratory animal species. There was minimal urinary and biliary excretion of unchanged drug.

The animals used in the toxicity studies (mice, rats and dogs) are typical species used to assess the toxicity of human pharmaceuticals. However, there are some limitations or unknowns with respect to the pharmacokinetics of cabozantinib in these species to ascertain their suitability as models for the assessment of drug toxicity in humans. The extent of plasma protein binding is unknown in dogs. This is probably not a major concern as the percentage of free fraction in dogs is unlikely to be lower than that in human plasma and relative total exposure (free and plasma protein bound) in dogs to that in human subjects will either be similar to or under-estimate (be conservative) to comparisons based on free fractions alone. It is unclear how predictive the tissue distribution profile in rats is to the distribution of drug-related material in human subjects, based on significant differences in the volume of distribution between the two species. This may suggest a difference in sensitivity to the toxic effects of cabozantinib between the two species. The sulphated metabolites, EXEL1646 and EXEL1644, were not prominent metabolites in animal species. To overcome this limitation in animals, specific safety studies (safety pharmacology, general toxicity and genotoxicity studies) were conducted with these metabolites. This is considered appropriate. Overall, the limitations and unknowns cited above are not considered to detract significantly from the relevance of the submitted toxicity studies.

Pharmacokinetic drug interactions[22]

As CYP3A4 has a significant role in the metabolism of cabozantinib, inducers/inhibitors of this enzyme may affect cabozantinib exposures. No clinically relevant inhibition of other CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4 was seen with cabozantinib or EXEL1644 in in vitro studies. EXEL1644 was not a mechanism-dependent inhibitor of CYP3A4. In human hepatocytes, no consistent induction (> 2-fold) of CYP1A2, 2B6 or 3A4 activity was observed with cabozantinib at clinically relevant concentrations. In rats, there was no significant induction of CYP proteins (CYP1A1, 2B, 2C and 3A) (< 2.5-fold induction at the highest dose, 100 mg/kg/day PO cabozantinib). Cabozantinib is not expected to affect exposures to co-administered drugs by interactions with CYP450 enzymes.

Cabozantinib was not apparently a substrate for organic anion transporter (OAT) 1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, breast cancer resistance protein (BCRP), bile salt export pump (BSEP) or P-glycoprotein. Cabozantinib is likely a substrate for multidrug resistance associated protein 2 (MRP2). EXEL1644 was not a substrate for OAT1, organic cation transporter (OCT) 1, OCT2 or BSEP but was a substrate for OAT3, OATP1B1, BCRP, MRP2 and a likely substrate for OATP1B3. Results regarding P glycoprotein were inconclusive. There was no clinically-relevant inhibition of BCRP, OCT1, OCT2, BSEP, OAT1, OAT3, OATP1B1, OATP1B3, multidrug and toxin extrusion (MATE) 1 or MATE2-K with cabozantinib or EXEL1644 in in vitro studies (no inhibition or IC_{50} >> clinical free fraction C_{max}). Inhibition of intestinal MRP2 and P glycoprotein (both intestinal and systemic) by cabozantinib cannot be dismissed based on the available data (P-gp: IC_{50} 0.5 or 7 μM in two different assays, and MRP2: no inhibition at the maximum test concentration 15 μM, compared to estimated intestinal concentration of 479 μM). EXEL1644 is not predicted to

[22] The following assumptions were made:

- cabozantinib: molecular weight, 501.5; dose, 60 mg; Cmax, 2.36 μM (total); free fraction, 1%; intestinal volume, 0.25 L; absorption rate constant, 0.1 min-1; bioavailability, 100%; kdeg for CYP3A, 0.0005 min-1
- EXEL1644: molecular weight, 470.4; Cmax, 453 nM (total); free fraction, 1%
- for intestinal CYP (CYP3A) and intestinal transporters (P-glycoprotein and BCRP): if the IC50 is ≤0.1-fold the intestinal concentration, an in vivo interaction is considered possible
- for systemic CYP, renal uptake and efflux transporters, and hepatic efflux transporters (OAT1, OAT3, OCT2, MRP2, BCRP, P-glycoprotein, BSEP, MATE1 and MATE2K): if the IC50 is ≤50-fold the unbound clinical C_{max}, an in vivo interaction is considered possible
- for hepatic uptake transporters (OCT1, OATP1B1 and OATP1B3): if the IC50 is ≤25-fold the unbound hepatic inlet concentration, an in vivo interaction is considered possible.

have any meaningful inhibitory activity on MRP2 or P glycoprotein (MRP2: IC_{50} 78.5 μM; P-gp: no inhibition at 250 μM).

Toxicology

Acute toxicity

Single dose toxicity studies were conducted in rats and dogs. A 14 day observation period was included in the Good Laboratory Practice (GLP) compliant studies. Rats appeared to be more sensitive than dogs to the toxic effects of cabozantinib at equivalent doses, probably due to differences in bioavailability in the two species. The maximum non-lethal dose in rats was 100 mg/kg PO (C_{max} 44.7 μg/mL, AUC 1213 μg·h/mL) with drug related deaths observed at ≥ 300 mg/kg PO (C_{max} 80.6 μg/mL, AUC 2807 μg·h/mL), indicating a moderate order of acute oral toxicity in this species. Target organs for toxicity in this species were the adrenal glands, lymphoid tissues, gastrointestinal tract, pancreas, lungs, kidneys, bone marrow and male reproductive organs. There were also signals of hepatic and muscle damage, indicated by increased serum creatinine kinase (CK), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactose dehydrogenase (LDH), Gamma-glutamyltransferase (GGT; also γ-glutamyltransferase) and total bilirubin in rats at all dose levels but there were no histological lesions in liver or skeletal muscle (examined only in rats dosed with 100 or 300 mg/kg). Serum ALT and AST were also increased in dogs receiving escalating doses 30, 60 and 120 mg/kg over 15 days. The maximum non-lethal dose in dogs was the highest tested dose, 2000 mg/kg PO (C_{max} 20.7 μg/mL, AUC 382 μg·h/mL), suggesting a low order of acute oral toxicity in this species. No target organs for toxicity were identified in dogs.

Repeat-dose toxicity

Repeat-dose toxicity studies by the oral route of up to 6 months duration were conducted in rats and dogs. All pivotal studies were GLP compliant and were conducted with the malate salt of cabozantinib. A 4 week dose-ranging study in mice was conducted to determine doses in a carcinogenicity study. The duration of the pivotal studies is considered adequate given the indication.[23] Exposures to cabozantinib achieved in mice and rats are considered adequate being a few multiples of the clinical AUC at the highest tested doses (Table 5). Exposures achieved in dogs were approximately equivalent to the clinical AUC at the highest tested dose. The maximum tolerated dose was clearly achieved in all species. The species chosen are generally acceptable from a pharmacokinetic perspective, though the predicted exposures to the metabolite EXEL1644 were subclinical in the studies listed in Table 5. Predicted exposures to EXEL5162 and EXEL5366 were approximately similar to that expected clinically in the 4 week repeat-dose toxicity study in mice and subclinical in the rat and dog studies. Predicted exposures to EXEL1646 in male rats in the 14 day study were similar to the predicted exposure in patients.[24] Separate repeat-dose toxicity studies were conducted in mice and rats with the EXEL1644 metabolite (see *Metabolites*). Therefore the toxicity of all the 4 metabolites is considered to have been assessed by the submitted toxicity studies.

[23] ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals
[24] Based on toxicokinetic data (AUC0-last for EXEL1646: 21.7 μg*h/mL) in a 5-day repeat dose study at 10 mg/kg/day, compared to predicted clinical AUC 10.7 μg*h/mL.

Table 5: Relative exposure in repeat-dose toxicity and carcinogenicity studies

Species	Study duration [Study no.]	Dose mg/kg/day PO	AUC_{0-24h}^ µg·h/mL	Exposure ratio#
Mouse (RasH2)	4/26 weeks [carcinogenicity Study XL184-NC-042][a]	2	11.6	0.5
		5	28.9	1.2
		15	89.4	3.6
		50	115	5
Rat (SD)	14 days [Study XL184-NC-005]	1	11.0	0.4
		5	52.2	2.1
		15	513	21
	6 months [Pivotal; Study XL184-NC-013]	0.1	3.69	0.1
		0.3	11.1	0.4
		1	36.9	1.5
	2 years [carcinogenicity Study XL184-NC-036]	0.1	2.85	0.1
		0.3	8.57	0.3
		1	25.9	1.0
Dog (Beagle)	6 months [Pivotal; Study XL184-NC-012]	0.2	0.31	0.01
		1	2.02	0.1
		5	7.04	0.3
	6 months [Pivotal; Study XL184-NC-018]	20	21.8	0.9
Human	steady state	[60 mg]	24.9	–

= animal: human plasma AUC_{0-24h}; ^ = data are for the sexes combined at the last sampling occasion;
[a]data predicted from a 4 week study (Study XL184-NC-035)

Major toxicities

The majority of the toxicities observed with cabozantinib are similar to those reported previously with other TKIs (for example, pazopanib, regorafenib, lenvatinib and crizotinib) and can be attributed to the pharmacological action of cabozantinib. Given the low exposures at which these toxicities were observed, all of these findings may be considered clinically relevant. However, the bone and teeth effects are not considered relevant for an adult patient group. These toxicities included:

- Inflammation of the GI tract in rats treated with 15 mg/kg/day PO cabozantinib for 14 days with necrosis of the ileum observed at ≥5 mg/kg/day (exposure ratio based on AUC (ERAUC) at the NOEL 0.4). Findings in mice treated with 50 mg/kg/day for 4 weeks included decreased parietal/chief cells in the fundus, metaplasia of mucous cells in the pylorus, epithelial hyperplasia and chronic active inflammation of the gastroduodenal junction (ERAUC at the NOEL approximately 1). Epithelial hyperplasia of the glandular stomach and duodenum was observed in the short-term carcinogenicity study in mice at 15 mg/kg/day. Intestinal inflammation was also seen in dogs treated with ≥ 100 mg/kg/day PO (ERAUC 8).
- Cortical and medullary necrosis and cortical angiectasis were observed in the adrenals of treated rats (≥ 5 mg/kg/day for 14 days; ERAUC at the NOEL, 0.4). Similar effects have been observed with pazopanib. VEGF receptors (R1 and R2) are expressed in endothelial cells of the adrenal cortex[25] and proliferation of vascular endothelial cells is a requirement for adrenal cortex development and differentiation.[26] Therefore, these effects may be attributed to the pharmacological action of cabozantinib.
- Bone marrow depletion, hypocellularity and/or congestion/haemorrhage were seen in mice and rats treated with ≥ 5 mg/kg/day PO cabozantinib for 4 and 2 weeks, respectively (ERAUC at the NOEL approximately0.5) and in dogs at ≥ 100 mg/kg/day for 2 weeks (ERAUC 8). This was accompanied by some decreases in haematological parameters including reticulocytes. MET has a role in the proliferation of myeloid and erythroid progenitor cells in the bone marrow.[27] As most currently registered VEGFR inhibitors have not been reported to inhibit MET, the findings indicate a greater risk for anaemia and possibly other cytopaenias in patients receiving cabozantinib as compared to other VEGFR inhibitors.
- There were effects on lymphoid tissues in all animal species. Thymic necrosis and splenic necrosis were seen in rats treated with ≥5 mg/kg/day PO cabozantinib for 14 days (ERAUC at the NOEL 0.4) and lymphocyte depletion were seen in mice treated with 15 mg/kg/day PO cabozantinib for 26 weeks (ERAUC at the NOEL approximately 1). Lymphoid necrosis and depletion was also evident in dogs at ≥ 100 mg/kg/day for 2 weeks and at 20 mg/kg/day for 6 months (ERAUC at the NOEL 0.1).
- The male and female reproductive organs were target organs for toxicity. Testicular hypoplasia and hypospermatogenesis associated with decreased testis and epididymidis weights was seen in dogs treated with ≥ 1 mg/kg/day PO cabozantinib for 6 months (ERAUC at the NOEL 0.01). These effects were still evident after a 4 week treatment free period. Seminiferous tubule degeneration/atrophy was seen in mice treated with ≥ 15 mg/kg/day PO cabozantinib for 4 weeks (ERAUC at the NOEL approximately 1). Adverse effects on functional fertility were evident in rats in a dedicated fertility study (see *Reproductive toxicity*). Effects on female reproductive organs (absence of corpora lutea, reduction in glandular tissue of the ovaries, uterus and mammary glands, and low organ weights) were evident in dogs treated for 6 months (≥ 0.2 mg/kg/day PO cabozantinib; NOEL not established), uterine dilatation in the 2 year carcinogenicity study in rats at 1 mg/kg/day (ERAUC at the NOEL 0.3) and in a postnatal study in rats (delayed vaginal opening).

[25] Vittet D, Ciais D, Keramidas M, De Fraipont F, Feige JJ (2000). Paracrine control of the adult adrenal cortex vasculature by vascular endothelial growth factor. Endocrine Research, 26:843-52.
[26] Katoh R (2003). Angiogenesis in endocrine glands: Special reference to the expression of vascular endothelial growth factor. Microscopy Research and Technique, 60:181-5.

[27] Ikehara, S. (1996) Role of hepatocyte growth factor in hemopoiesis. Leukemia Lymphoma 23: 297–303. Kmiecik, T.E., J.R. Keller, E. Rosen and G.F. Vande Woude. (1992) Hepatocyte growth factor is a synergistic factor for the growth of hematopoietic progenitor cells. Blood 80: 2454–2457.

- Skin effects observed in dogs treated with ≥ 5 mg/kg/day PO cabozantinib for 6 months included clinical signs of grey skin and white hair coat hypopigmentation and microscopic lesions of hyperkeratosis, hyperplasia and exudate (ERAUC at the NOEL 0.1).
- Vascular inflammation in various tissues (tongue, mesenteric lymph node, testis, GI tract and pancreas) was observed in the long term rat study at doses ≥ 0.3 mg/kg/day PO cabozantinib (ERAUC at the NOEL 0.1).
- Zymogen depletion was observed in the pancreas of mice treated with 15 mg/kg/day for 26 weeks (ERAUC at the NOEL approximately1) and pancreatic necrosis was seen in rats treated with 15 mg/kg/day for 14 days (ERAUC at the NOEL approximately 2). Similar effects have been reported with others in this pharmacological class.
- An increased incidence and severity of chronic progressive nephropathy were observed in rats in the 6 month study and 2 year carcinogenicity study at all doses (0.1 to 1 mg/kg/day; ERAUC 0.1 to 1.5), with increased incidence of tubular vacuolation in all treated male groups in the 2 year study. Increased serum blood urea nitrogen (BUN) and renal tubular degeneration were also seen in rats treated with 15 mg/kg/day PO.
- Increased serum AST (> 2-fold) and ALT (2.5- to 9-fold) levels were seen in rats treated with ≥ 5 mg/kg/day PO cabozantinib for 14 days, associated with hepatocyte hypertrophy and bile duct hyperplasia in one 14 day study at 1 to 15 mg/kg/day but not in another 14 day study at 1 to 5 mg/kg/day (ERAUC at 1 mg/kg/day 0.4). Interestingly, both studies showed lower liver weights (liver/body weight ratio) at ≥ 5 mg/kg/day. Liver toxicity was not evident in the 6 month rat study, but increased karyomegaly/multinucleated hepatocytes were observed in the 2-year carcinogenicity study in female rats at ≥ 0.3 mg/kg/day (ERAUC 0.3). Serum levels of ALT, AST, and/or sorbitol dehydrogenase (SDH) were also increased in dogs at ≥ 100 mg/kg/day for 14 days and at 20 mg/kg/day for 6 months. Given the magnitude of the increase in serum transaminases and other parameters for liver toxicity, a potential for hepatic injury exists even in the absence of histological changes.[28] Unlike most of the currently-registered VEGFR inhibitors, cabozantinib inhibits MET at clinically relevant concentrations. MET signalling plays a role in liver regeneration and studies in conditional MET knockout mice indicate inhibition of this signalling pathway delays healing after liver injury, thereby enhancing liver damage by increasing apoptosis/necrosis of hepatocytes.[29,30] Therefore, greater hepatotoxicity may be expected with concomitant use of drugs that cause any form of liver injury.
- Necrosis was observed in the pituitary of rats treated with 15 mg/kg/day PO cabozantinib for 14 days (ERAUC at the NOEL approximately 2).
- Increased trabecular bone thickness was seen in rats treated with ≥ 0.1 mg/kg/day PO cabozantinib for 2 years. Similar effects have been reported in rodent studies with pazopanib, regorafenib and lenvatinib. Unlike primates significant postpubertal growth of rodent physes occurs and these effects are not considered to be a concern for an adult patient group. They are, however, a concern for a paediatric patient group (see also *Paediatric use*).

[28] EMEA/CHMP/SWP/150115/2006: Reflection paper on non-clinical evaluation of drug-induced liver injury (DILI)
[29] Huh, C.-G., V.M. Factor, A. Sánshez, K. Uchida, E.A. Conner and S.S. Thorgeirsson. (2004) Hepatocyte growth factor/c-met signaling pathway is required for efficient liver regeneration and repair. Proc. Natl. Acad. Sci. USA 101: 4477–4482..
[30] Nakamura, T., K. Sakai, T. Nakamura and K. Matsumoto. (2011) Hepatocyte growth factor twenty years on: Much more than a growth factor. J. Gastroent. Hepatol. 26: 188–202

- As with other VEGFR inhibitors, teeth effects were observed in rodents treated with cabozantinib. These effects included broken teeth/white teeth and/or malocclusion in rats treated with ≥ 0.1 mg/kg/day for 0.5 to 2 years (NOEL not established). Microscopic examination showed degeneration/necrosis of odontoblasts and enamel organ and altered dentin matrix (presence of odontoblasts within the dentin matrix, distortion, degeneration/absence of the dentin matrix) in the 2 year study. Since adult rat incisors are growing continuously, incisor growth is a potential target secondary to vascular disruption due to a VEGFR2 inhibitory activity of cabozantinib. These effects are not considered relevant for an adult patient group, but are relevant for a paediatric patient group (see also *Paediatric use*).
- Mineralisation was observed in multiple tissues (kidney, glandular stomach, tongue and mesenteric lymph node) in rats treated with 1 mg/kg/day PO cabozantinib for 2 years (ERAUC at the NOEL 0.3). There was also vessel inflammation in multiple tissues (glandular stomach, lymph nodes, testis, intestines and pancreas) in rats at subclinical exposures.

Findings not observed with others in the pharmacological class are listed below. These effects were only seen in life-time studies in rats. No such long term studies have been conducted with others in the class, so it is unclear if these are specific for cabozantinib or are class effects:

- An increased incidence of adrenal hyperplasia was seen in female rats treated with ≥ 0.1 mg/kg/day PO cabozantinib for 2 years. There was also an increased incidence of adrenal tumours seen in this study (see *Carcinogenicity*).

Genotoxicity

The genotoxic potential of cabozantinib was assessed in bacterial and mammalian mutagenicity assays and in vitro (in human lymphocytes) and in vivo (mouse bone marrow) clastogenicity assays. All studies were adequately conducted. Negative results were returned in all assays. Metabolites EXEL5162, EXEL1644 and EXEL1646 were not mutagenic in a bacterial mutagenicity assay. Cabozantinib is not expected to pose a genotoxic risk.

Carcinogenicity

While not considered necessary for the proposed indication, the sponsor submitted a 6 month short term carcinogenicity study in transgenic RasH2 mice and a 2 year study in rats. The choice of a long term and a short term carcinogenicity study in a wild-type and a transgenic mouse model, respectively, is considered acceptable to assess carcinogenicity, according to the ICH guideline S1B.[31] Group sizes used and the duration of dosing were appropriate for the test species (ICH 3BS7a).[32] Dual negative control groups were included in both studies. Dose selection was adequate based on significant toxicity observed at the highest tested doses. No treatment-related neoplastic findings were seen after oral dosing of ≤ 15 mg/kg/day cabozantinib for 6 months to transgenic mice (ERAUC approximately 4). In rats, compared with concurrent negative control groups, there was an increased incidence of benign pheochromocytomas in the adrenal gland of male rats treated with ≥ 0.1 mg/kg/day cabozantinib (ERAUC 0.1) and female rats treated with ≥ 0.3 mg/kg/day cabozantinib (ERAUC 0.3). An increased incidence of the preneoplastic lesion, adrenal hyperplasia, was observed at the lower dose of 0.1 mg/kg/day PO in females. There was no clear increase in malignant phaeochromocytomas compared to concurrent controls. No carcinogenicity studies have been conducted with any of the currently-registered VEGFR

[31] ICH S1B: Note for guidance on carcinogenicity: testing for carcinogenicity of pharmaceuticals.
[32] ICH 3BS7a: Note for guidance on carcinogenic potential.

inhibitors, so it is unclear if the increase in adrenal tumours is a class effect or specific for cabozantinib. Rats are more prone to the development of pheochromacytomas than other species. Pheochromacytoma is induced in rats by a variety of chemicals (including xylitol, retinol and phenylbutazone) and is rarely seen in humans.[33] The clinical relevance is unclear. Nonetheless, the tumour findings are not considered a specific concern for the proposed patient group but may need to be considered if the proposed indications for cabozantinib were extended to other patient groups.

Reproductive toxicity

A standard set of GLP compliant reproductive toxicity studies was submitted and examined potential effects on fertility (in rats), embryofetal toxicity (rats and rabbits) and pre-/postnatal development (rats). Adequate animal numbers were used in the pivotal studies and treatment periods were appropriate. The malate salt was used in all studies. Exposures to cabozantinib were subclinical in the embryofetal development and pre- and post-natal studies (Table 6); however doses were sufficient for adverse effects to be seen. Exposures in the fertility study were up to 5 times the clinical AUC. Exposures to the metabolites EXEL1644, EXEL1646, EXEL5366 and EXEL5162 are estimated to be subclinical in rats but unknown in rabbits. This is not considered a major deficiency, given the adverse effects observed in all of the pivotal studies.

Relative exposure

Table 6: Relative exposure in reproductive toxicity studies

Species	Study [Study no.]	Dose (mg/kg/day PO)	AUC_{0-24h} (µg·h/mL)	Exposure ratio[#]
Rat (SD)	Fertility [Study XL184-NC-020][a]	1	17.2/19.3	0.7/0.8
		2.5	40.6/73.2	1.6/2.9
		5	102/148	4/6
	Embryofetal development [Study XL184-NC-022]	0.01	0.168	0.01
		0.03	0.469	0.02
		0.1	1.49	0.06
	Pre-/postnatal development [Study XL184-NC-040][b]	0.03	0.469	0.02
		0.1	1.49	0.06
		0.3	4.47	0.18
Rabbit (NZW)	Embryofetal development [Study XL184-NC-024]	0.3	0.274	0.01
		1	0.984	0.04
		3	4.24	0.17

[33] Greaves P. ed. (2012) Chapter 13: Endocrine Glands: adrenal gland. In: Histopathology of preclinical toxicity studies, 4th edn. Amsterdam: Academic Press. pp.740-761.

Species	Study [Study no.]	Dose (mg/kg/day PO)	AUC_{0-24h} (µg·h/mL)	Exposure ratio#
Human	steady state	[60 mg]	24.9	–

= animal: human plasma AUC_{0-24h}; [a] male/female data; b estimated from data in Study XL184-NC-022

Reduced testes weights and hypospermia were seen in male rats treated with ≥ 1 mg/kg/day PO cabozantinib (ERAUC 0.7). Epididymis, prostate and seminal vesicle weights were also decreased at ≥ 2.5 or 5 mg/kg/day. When treated males (≥ 2.5 mg/kg/day) were mated with treated females, no pregnancies were observed. An increase in pre and post implantation loss with a consequent reduction in the number of viable fetuses was seen at 1 mg/kg/day (NOEL not established). Angiogenesis mediated by VEGF is critical for the development and function of the corpus luteum.[34] Cabozantinib treatment may be expected to affect fertility in male and female patients.

Cabozantinib crossed the placenta in rats and rabbits with fetal plasma levels 18 to 23% and 25 to 40% maternal levels in rats and rabbits, respectively. Embryofetal toxicity and lethality were seen at non maternotoxic doses when pregnant rats and rabbits were treated with cabozantinib during the period of organogenesis. An increase in post implantation loss was seen in rats treated with ≥0.03 mg/kg/day and rabbits treated with 3 mg/kg/day PO cabozantinib. Reduced fetal weights were seen in rabbits when dams were treated with ≥1 mg/kg/day cabozantinib. Fetal cardiac abnormalities (heart/ventricular septal defect and absent aortic arch) and skeletal variations (bipartitie vertebral centrum, an increased incidence of rudimentary ribs) were seen at doses ≥ 0.01 mg/kg/day in rats. Additionally, fetal oedema, cleft palate/lip, dermal aplasia and kinked or rudimentary tail were observed in a pilot study in rats at 0.6 mg/kg/day. Fetal anomalies in rabbits (at ≥ 1 mg/kg/day) included swollen hind paw, an increased incidence of intermediate lobe of lung missing, reduced spleen size, misaligned, fused and/or absent vertebrae, bipartite vertebrae, an increased incidence of angulated hyoid wing, hemicentrum and incomplete ossification. All adverse embryofetal effect occurred at subclinical exposures. Cabozantinib inhibits MET and VEGFR2, both of which play a role in embryofetal development and survival.[35,36] Therefore, the adverse embryofetal effects are likely associated with the pharmacological action of cabozantinib.

Significant levels of cabozantinib were detectable in the plasma of breast fed pups suggesting the drug was excreted in the milk of rats (plasma levels in pups were 49 to 59% of maternal plasma levels). Aside from slight delays in eye opening and vaginal opening, there were no adverse effects on pre/postnatal development in rats at ≤ 0.3 mg/kg/day. However, exposures were subclinical. Therefore, no firm conclusions regarding effects on postnatal development can be drawn from the absence of findings in this study. A higher dose of 1 to 2 mg/kg/day could have been administered in the study based on a pilot study, which showed no maternal or offspring effects at 1 mg/kg/day. As delayed development, effects on bone development and teeth abnormalities were observed in juvenile rats treated directly with cabozantinib (see *Paediatric use*) and a significant amount of the drug is excreted into milk, mothers receiving cabozantinib should not breast feed.

[34] Ferrara N et al., *Vascular endothelial growth factor is essential for corpus luteum angiogenesis.* Nat Med 1998: 4; 336-40

[35] Dvorak, H.F. (2002). Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in tumour angiogenesis and a potential target for diagnosis and therapy. Journal of Clinical Oncology 20 (21): 4386-4380.

[36] Bladt, F., D. Riethmacher, S. Isenmann, A. Aguzzi and C. Birchmeier. (1995) Essential role for the c-met receptor in the migration of myogenic precursor cells into the limb bud. Nature 376: 768–771

Pregnancy classification

The sponsor has proposed Pregnancy Category D[37]. This is appropriate since both the pharmacological characteristics and the results of the developmental toxicity studies are consistent with the view that cabozantinib may be expected to cause an increased incidence of human fetal malformations or irreversible damage.

Phototoxicity

Cabozantinib was not phototoxic in a Neutral Red Uptake assay with Balb/c 3T3 fibroblasts.

Metabolites

The repeat-dose toxicity of the main human metabolite, EXEL1644, was assessed in mice (4 weeks) and rats (2 weeks) using the subcutaneous (SC) route of administration. The route of administration is considered appropriate as the compound would reach the systemic circulation intact, which may not have been the case if the compound were provided to the animals orally. Maximum exposures achieved were 6 to 15 times the estimated AUC for EXEL1644 in patients. Aside from reduced body weight gain in treated mice (but not rats), there were no signs of systemic toxicity in treated rodents with EXEL1644. The toxicity of this metabolite is considered to have been adequately assessed.

EXEL1646 is also a major metabolite in human circulation and is found in human plasma at 43% of the parent drug based on AUC. Since very low levels of this metabolite (< 10% of parent drug) were detected in animal species (mouse, rat and dog) used in the toxicity studies, the toxicity of this metabolite has not been adequately assessed in animal studies.

Impurities

One impurity has not been toxicologically qualified. A process impurity is mutagenic and should be controlled so that the daily intake would be ≤ 10 µg, the staged threshold of toxicological concern (TTC) for 10 years of therapy.

Paediatric use

Cabozantinib is not proposed for paediatric use. Nonetheless, the sponsor submitted a number of juvenile animal studies. In a combined pre-/postnatal and juvenile study, juveniles were dosed directly with cabozantinib from postnatal day (PND) 12. Two additional juvenile rat studies assessed dosing from ages 12 and 21 days (corresponding to infants ≤ 2 years of age).[38] Exposures to cabozantinib appeared similar in juvenile and adult rats at equivalent doses.

In general, findings in juvenile animals were similar to those seen in adult rats (at similar doses/exposures) with target organs being the liver, kidney, skin, teeth, bone, GI tract, reproductive organs, haematopoietic/lymphoreticular system and endocrine system. Retarded development may be attributed to the anti-proliferative and anti-angiogenic action of cabozantinib. The most notable findings relevant to a paediatric group include:

- Deaths occurred in juvenile rats dosed with 2 mg/kg/day cabozantinib from PND 12 but not in rats dosed from PND 21 in animals in the pre/postnatal study

[37] Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
[38] Baldrick, P. (2010) Juvenile animal testing in drug development — Is it useful? *Reg. Toxicol. Pharmacol.* **57:** 291–299.

- Delayed maturation of the male and female reproductive systems
- Effects on bone development (decreased bone mineral density and bone mineral content)
- Effects on teeth (abnormal, discoloured)
- Haematological effects appeared more pronounced in juveniles than adults. This is likely more pronounced with cabozantinib than other VEGFR inhibitors due to combined VEGFR and MET inhibition with this drug.

Nonclinical summary

• The submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of anticancer pharmaceuticals.[12] The overall quality of the dossier was reasonable with all pivotal safety studies conducted under GLP conditions.

- Cabozantinib was a multiple receptor kinase inhibitor, inhibiting VEGFR2, MET, Flt1, Flt4, RET, KIT, Flt3, TIE-2, Axl, TrkB, FMS, ROS1 and RSE (TYRO3) at clinically-relevant concentrations. None of the 4 major human metabolites of cabozantinib are expected to contribute to efficacy. Cabozantinib demonstrated anti-tumour efficacy in a number of mouse xenograft models of cancer. There were no efficacy studies in animal models of advanced renal cell carcinoma.
- Off-target effects are not predicted with cabozantinib use.
- Dedicated safety pharmacology studies assessed effects on the cardiovascular, respiratory and central nervous systems. Based on in vitro studies and in vivo studies in dogs, cabozantinib is not predicted to prolong the QTc interval during clinical use. Based on findings in animal studies CNS and respiratory effects are not predicted during clinical use.
- The rate of oral absorption was reasonably rapid in mice, rats, dogs, monkeys and humans with variable oral bioavailability in animals, dependent on formulation. The ratio of each of the four major human metabolites to the parent was lower in animal species than in human subjects. Protein binding by cabozantinib was very high in the plasma of mice, rats and humans. Drug related material was distributed widely in rats with relatively high exposures were seen in the adrenal and Harderian glands and the uveal tract in the eye. There was minimal penetration of the blood-brain barrier. CYP3A4 had a significant role in the metabolism of cabozantinib in vitro. Excretion of cabozantinib and/or its metabolites was predominantly via the faeces in rats, dogs and humans. Biliary excretion was demonstrated in both of the laboratory animal species.
- Inducers/inhibitors of CYP3A and MRP2 may alter cabozantinib exposures. Cabozantinib is not expected to affect exposures to co-administered drugs by interactions with CYP450 enzymes. Cabozantinib may alter the exposure of coadministered oral drugs that are substrates for MRP2 or coadministered drugs (by any route) that are substrates for P glycoprotein.
- Cabozantinib had a moderate order of acute oral toxicity in rats and a low order of oral toxicity in dogs.
- Repeat-dose toxicity studies by the oral route were conducted in mice (4 weeks), rats and dogs (up to 6 months). Target organs for toxicity were similar to those seen with other VEGFR inhibitors: GI tract (necrosis, epithelial hyperplasia), adrenals (necrosis and angiectasis), bone (increased trabecular bone thickness), bone marrow (depletion, hypocellularity and/or congestion/haemorrhage, with secondary haematological effects), lymphoid tissues (necrosis, lymphoid depletion), male reproductive organs (testicular hypoplasia and hypospermatogenesis, seminiferous tubule

degeneration/atrophy), female reproductive organs (absence of corpora lutea, reduction in glandular tissue of the ovaries, uterus and mammary glands), skin (white hair coat hypopigmentation, hyperkeratosis and hyperplasia), vascular inflammation in various tissues, pancreas (zymogen depletion, necrosis), kidney (alterations in serum protein levels, an increased incidence and severity of chronic progressive nephropathy), pituitary (necrosis), teeth (broken teeth/white teeth and/or malocclusion in rats) and mineralisation in multiple tissues.

- As cabozantinib inhibits MET as well as VEGFR (unlike most registered VEGFR inhibitors), greater hepatotoxicity may be expected with concomitant use of drugs that cause any form of liver injury. A greater risk for anaemia and possibly other cytopaenias may be seen in patients receiving cabozantinib compared to other VEGFR inhibitors.
- Cabozantinib was not mutagenic in the bacterial mutation assay or clastogenic in vitro (in human lymphocytes) or in vivo (mouse micronucleus test).
- No treatment-related neoplastic findings were seen after oral dosing for 6 months to transgenic mice. There was an increased incidence of benign pheochromocytomas in the adrenal gland of rats following lifetime exposure to cabozantinib. An increased incidence of the preneoplastic lesion, adrenal hyperplasia was also seen in female rats. The tumour findings are not considered a specific concern for the proposed patient group. Pheochromacytoma is induced in rats by a variety of chemicals (including xylitol, retinol, and phenylbutazone) but is rarely seen in humans.
- Cabozantinib affected male and female fertility in treated rats. Cabozantinib crossed the placenta in rats and rabbits with embryofetal toxicity and lethality observed in both species. Significant levels of cabozantinib were detectable in the plasma of breast-fed pups suggesting the drug was excreted in the milk of rats. While limited effects were seen in breast fed pups following maternal exposure, the tested exposures were low. Delayed development, effects on bone development and teeth abnormalities were observed in juvenile rats treated directly with cabozantinib.
- Cabozantinib was not phototoxic in vitro.
- The toxicity of one major human metabolite, EXEL1646 has not been adequately assessed in animal studies, though in vitro studies revealed no clinically-relevant pharmacological activity (at multiple sites). This deficiency may not preclude approval of the drug for the proposed indication for the treatment of advanced cancer if a clear clinical benefit has been demonstrated by clinical data.

Nonclinical conclusions and recommendation

- The pharmacology studies generally support the use of cabozantinib as an anticancer agent. No specific comments can be made regarding support for the proposed indication and dose.
- The combined animal safety studies revealed the toxicity profile of cabozantinib was similar to that seen with other VEGFR inhibitors. Additional toxicities that may be seen with cabozantinib compared to currently-registered VEGFR inhibitors include:
  - More significant hepatotoxicity may be seen with concomitant use of drugs that cause any form of liver injury
  - A greater risk for anaemia and possibly other cytopaenia.

- One impurity has not been toxicologically qualified. As a minimum requirement, an in silico mutagenicity analysis should be conducted as recommended in the relevant ICH guideline.[39] A process impurity is mutagenic and should be controlled so that the daily intake would be ≤ 10 µg, the staged threshold of toxicological concern (TTC) for 10 years of therapy.
- The toxicity of one major human metabolite, EXEL1646 has not been adequately assessed in animal studies. However, further investigation of the toxicity of the metabolite may be outweighed by a clear clinical benefit for the treatment of advanced cancer (serious and life threatening malignancies).
- Amendments to the draft PI were recommended to the Delegate but these are beyond the scope of this AusPAR.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The clinical rationale for development was not summarised in the sponsor's Clinical overview. The sponsor states in their covering letter that there remains an unmet medical need for new treatments for advanced RCC that show benefit in terms of progression free survival (PFS) and/or overall survival (OS) beyond that of existing therapies.

Contents of the clinical dossier

Scope of the clinical dossier

The dossier includes a full clinical development program of pharmacology, efficacy and safety studies.

The clinical submission contained:

- Ten clinical pharmacology studies providing pharmacokinetic and safety pharmacology data.
- A single population safety analysis and one pivotal efficacy safety study.
- Also included are two studies that are evaluable for safety only.

Paediatric data

No paediatric data has been submitted this is acceptable given the proposed indication.

Good clinical practice

The sponsor has provided a statement that the studies complied with ICH guidelines for Good Clinical Practice (GCP).

[39] ICH M7: Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk.

Pharmacokinetics

Studies providing pharmacokinetic data are listed in Table 7 below.

Table 7: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID
PK in healthy adults	General PK Single dose	XL-184-020
	Mass Balance	XL184-012
	Bioequivalence † Single dose	XL184-016 XL184-010
	Multi-dose	No studies
	Food effect	XL184-004
PK in special populations	Target population § Single dose	No studies
	Multi-dose	XL-184-001 XL-184-308
	Hepatic impairment	XL-184-003
	Renal impairment	XL184-017
	Neonates/infants/children/adolescents	Not applicable
	Elderly	XL184-308 PopPK 001
	Other special population (MTC)	XL184-001
Genetic/gender related PK	Males versus females	XL184-308 PopPK 001
	Other genetic variable	XL184-308 PopPK 001
PK interactions	Rifampicin	XL184-006
	Ketoconazole	XL184-007
	Esomeprazole	XL184-018
Population PK analyses	Healthy subjects	XL184-308 PopPK 001
	Target population	XL184-308 PopPK 001

† Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's conclusions on pharmacokinetics

The pharmacokinetics of cabozantinib has been adequately characterised. The proposed formulation for marketing (tablet dose form) leads to higher exposure, currently no other dose form exists in Australia.

Cabozantinib is highly protein bound and the primary route of metabolism is hepatic. It is anticipated that impaired hepatic function will increase plasma levels of cabozantinib and this was confirmed in a clinical study. The PI recommends a lower starting does (40 mg versus 60 mg) in these patients with instruction to adjust the dose as needed. Further the PI states that the safety and efficacy in severe hepatic impairment has not been established and this is acceptable.

Although mild or moderate renal impairment has negligible impact on the PK the PI contains instruction to use cabozantinib with caution in such patients and does not recommend its use in patients with severe renal impairment and this would seem prudent.

The PK data are adequately reflected in the PI.

Pharmacodynamics

Studies providing pharmacodynamic data

No pharmacodynamic studies in health subjects or subjects with RCC have been submitted.

Evaluator's conclusions on pharmacodynamics

No pharmacodynamic data derived from healthy volunteers or subjects with RCC have been submitted. The PD of cabozantinib was derived form in vitro and murine models and is described in the nonclinical dossier. Given the mechanism of action and what is already know about TKIs this is acceptable.

Dosage selection for the pivotal studies

Phase II dose finding studies

No formal dose finding studies have submitted. Study XL184-001 investigated the maximum tolerated dose of cabozantinib and was determined to be 140 mg once per day.

Phase III pivotal studies investigating more than one dose regimen

Study XL184-308 was the pivotal study for this application. The initial starting dose was 60 mg once per day. Dose adjustments were allowed for tolerability and are summarised in Table 8.

Table 8: Study XL184-308 Cabozantinib dose reductions in the pivotal study

	Cabozantinib N = 331
Subjects treated, n (%)	331 (100.0)
Subjects with any dose reduction resulting from AE[a], n (%)	198 (59.8)
Received dose level, n(%)[b]	
Assigned dose level (60 mg)	331 (100.0)
First dose-level reduction (40 mg) resulting from AE	192 (58.0)
Second dose-level reduction (20 mg) resulting from AE	64 (19.3)
Lowest dose level received (excluding dose interruptions)[b], n (%)	
Assigned dose level (60 mg)	133 (40.2)
First-level dose reduction (40 mg) resulting from AE	132 (39.9)
Second-level dose reduction (20 mg) resulting from AE	65 (19.6)
Last dose level received (excluding dose interruptions), n (%)	
60 mg	142 (42.9)
40 mg	132 (39.9)
20 mg	56 (16.9)
Other dose level > 0[c]	1 (0.3)
Last dose level received (including dose interruptions), n (%)	
60 mg	98 (29.6)
40 mg	97 (29.3)
20 mg	45 (13.6)
0 mg	91 (27.5)
Other dose level > 0	0
Median (range) time (days) on treatment at:[d]	
More than 0 mg	
Assigned dose level (60 mg)	73.0 (3, 560)
First dose-level reduction (40 mg), resulting from AE	83.5 (1, 472)
Second dose-level reduction (20 mg), resulting from AE	117.0 (2, 426)
0 mg	6.0 (1, 148)
Median (range) time to first dose reduction resulting from AE (days)[d,e]	55.0 (10, 355)
Median (range) time to second dose reduction resulting from AE (days)[d,e]	93.0 (29, 317)

AE, adverse event
[a] Each subject is only counted once even though multiple dose reductions may have occurred.
[b] Includes dosing records for which the prior interval ended due to 'AE' or 'Treatment resumed/re-escalated.' Excludes dosing records for which the prior interval ended due to 'Subject noncompliance other than AE' or 'Site error' or 'Other.'
[c] Subject 1253-3505 was to take cabozantinib at a dose of 20 mg every other day (shown as 10 mg qd in the CRFs).
[d] Time on treatment = sum of total days subject actually received the specified dose level; all subjects who received treatment at that dose level are included. Dose interruptions are excluded from calculations for nonzero doses.
[e] Dosing records were excluded where the dose was zero or was higher than the most recent prior nonzero dose. Time to dose reduction is the arithmetic median among subjects with a dose reduction (or with a second dose reduction) from first dose until first (or second) dose reduction.

Dose reductions occurred for 70% of subjects and equal proportions of patients were taking the 60 mg dose and 40 mg dose at the data cut-off.

Evaluator's conclusions on dose finding for the pivotal studies

No formal dose finding has been undertaken. The 60 mg dose was carried forward into the pivotal study. At the data cut-off point an equal proportion of patients were receiving the 40 mg and 60 mg doses. This would indicate that the lowest effective dose may not have been established. The prescribing information contains sufficient information about dose adjustment based on tolerability.

Efficacy

Studies providing efficacy data

The following study was submitted in support of the proposed indication for treatment of RCC:

- Study XL184-308: A Phase III, Randomised, Controlled Study of Cabozantinib (XL184) versus Everolimus in Subjects with Metastatic Renal Cell Carcinoma that has Progressed after Prior VEGFR Tyrosine Kinase Inhibitor Therapy.

Evaluator's conclusions on efficacy

The efficacy presented demonstrates improvement in both overall survival (OS) and progression free survival (PFS) in subjects with advanced RCC that had previously received VEGFR-TKI therapy who are treated with cabozantinib. The results for PFS and

OS are supported by an improvement in objective response rate (ORR) in terms of tumour burden.

Safety

Studies providing safety data

Pivotal and/or main efficacy studies

The main study providing safety data was Study XL184-308.

Routine safety evaluations included physical examination, vital signs, performance status, 12-lead ECG, haematology, serum chemistries, lipid tests, coagulation tests, urine tests, serum pregnancy tests (in females of childbearing potential), and thyroid function tests. Subjects also reported, and were asked to describe any adverse events (AEs) experienced through 30 days after the date of the decision to permanently discontinue study treatment.

At each scheduled or unscheduled study visit, evaluations of AEs were performed after informed consent and through 30 days after the last dose of study treatment. An AE was defined as any untoward medical occurrence in a patient or clinical investigation subject who was enrolled in the study and who may have been administered an investigational product, regardless of whether or not the event was assessed as related to the study treatment.

Overall safety was monitored by an independent monitoring committee that was independent of the study sponsor and the investigators.

The Safety Population was defined as all subjects who had received any amount of study treatment.

Studies with evaluable safety data including dose finding and pharmacology studies

Study XL184-008 was a Phase I drug-drug interaction study of the effects of XL184 (cabozantinib) on the pharmacokinetics of a single oral dose of rosiglitazone in subjects with solid tumours.

Studies evaluable for safety only

Study XL184-306

This study was a Phase III, randomised, double-blind, controlled study of cabozantinib versus prednisone plus mitoxantrone plus prednisone in men with previously treated symptomatic castration resistant prostate cancer.

The study was conducted in men with previously treated metastatic CRPC with bone-dominant disease who had experienced disease progression while on docetaxel-containing chemotherapy and either abiraterone or enzalutamide.

Subjects had to have documented pain from bone metastases requiring opioid narcotics. During a 7 day Run-In Stage, subjects had to meet stringent pain (average daily worst pain score ≥ 4 and ≤ 8 on the Brief Pain Inventory (BPI) scale of increasing pain from 0 to 10) and narcotic use criteria to be eligible for the study.

Subjects received study treatment as long as they continued to experience clinical benefit, as determined by the investigator. Reasons for discontinuation of treatment included, among others, an unacceptable toxicity or the need for non-protocol systemic anticancer therapy (including the use of bone-targeted radiopharmaceuticals). Crossover between protocol treatment arms was not allowed.

Clinic visits occurred at minimum every 3 weeks through treatment discontinuation with extended follow-up to assess survival status and to document receipt of subsequent anticancer therapy. Routine safety evaluations included assessments of AEs, vital signs, laboratory tests, and concomitant medications. New or worsening AEs were collected at study visits, over the phone, or by spontaneous subject report from informed consent through 30 days after the date of the decision to discontinue study treatment.

The study was terminated early due the lack of survival benefit seen in a second study.

Study XL184-307

This study was a Phase III randomised, double blind, controlled study of cabozantinib (XL184) versus prednisone in metastatic castration resistant prostate cancer patients who have received prior docetaxel and prior abiraterone or enzalutamide.

Subjects in this study were male and ≥ 18 years of age with a documented histological or cytological diagnosis of prostate cancer and evidence of its metastasis to bone (as determined by a bone scan). Subjects were to have received prior docetaxel (with a minimum cumulative dose of 225 mg) and either abiraterone or enzalutamide with evidence of investigator assessed prostate cancer progression on each agent independently. If a subject had an AE related to a prior treatment, the AE was to have resolved to baseline or Common Terminology Criteria for Adverse Events (CTCAE) version 4 ≤ Grade 1. Subjects without prior orchiectomy must have been taking luteinizing hormone-releasing hormone (LHRH) analogue therapy at baseline and concomitantly throughout the study. In addition, subjects were to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, a serum testosterone level of < 50 ng/dL (< 1.75 nmol/L), and adequate organ and marrow function as determined by clinical laboratory tests.

Eligible subjects were randomised 2:1 to the cabozantinib and prednisone treatment arms, respectively. Randomisation was stratified by the following factors: prior treatment with cabazitaxel (yes/no), baseline pain severity (self-assessed worst pain score recalled over the prior 24 hours (BPI Item 3 scale of 0 to 10) of < 4 versus ≥ 4), and ECOG performance status (0 or 1 versus 2).

Based on treatment assignment, subjects received either, oral cabozantinib (60 mg, once daily (qd)) plus prednisone matched placebo (twice daily [bid]) or oral prednisone (5 mg, bid) plus cabozantinib-matched placebo (qd).

Clinic visits occurred at minimum every 3 weeks after treatment was initiated through Week 12 and then every 6 weeks thereafter. Routine safety evaluations included assessments of AEs, vital signs, laboratory tests, and concomitant medications. New or worsening AEs were collected at study visits, over the phone, or by spontaneous subject report from informed consent through 30 days after the date of the decision to discontinue study treatment.

The study did not meet its primary endpoint of OS. Active subjects were required to discontinue study treatment and revert to standard of care thereby limiting the overall exposure to treatment on the study.

Patient exposure

Cabozantinib has been evaluated in two randomized, double-blind, controlled, Phase III studies in subjects with metastatic castrate-resistant prostate cancer (CRPC) (Study XL184-307 and Study XL184-306). In both studies, subjects were administered the same dose and formulation as received by RCC subjects in StudyXL184-308 (60 mg tablets qd).

Table 9: Clinical studies providing safety data

Study (Phase)	Study Report	Proposed Role of Study in Application		Number of Subjects	
		Efficacy	Safety	Experimental Arm	Comparator Arm
XL184-308[a] (METEOR) (Phase 3)	Full CSR, Primary analysis[a]	√	√	Cabozantinib 60 mg: 331 RCC (safety)	Everolimus: 322 RCC (safety)
XL184-008 (Phase 1)	Full CSR, Primary analysis	√	√	Cabozantinib 140 mg: 25 RCC (safety)	-
XL184-306 (COMET-2) (Phase 3)	Full CSR, Primary analysis	-	√	Cabozantinib 60 mg: 60 CRPC (safety)	Mitoxantrone + Prednisone[b]: 57 CRPC (safety)
XL184-307 (COMET-1) (Phase 3)	Full CSR, Primary analysis	-	√	Cabozantinib 60 mg: 681 CRPC (safety)	Prednisone[b]: 342 CRPC (safety)

CRPC, castration-resistant prostate cancer; CSR, clinical study report; RCC, renal cell carcinoma
Cabozantinib dose expressed as the freebase equivalent weight.
[a] A total of 658 subjects with advanced metastatic RCC were randomly assigned 1:1 to one treatment arm. The prespecified Primary Endpoint Intent-to-Treat (PITT) population consisted of the first 375 randomized subjects (187 cabozantinib, 188 everolimus) for the primary endpoint analysis of progression-free survival

As the studied indication was CRPC the patient population differed in that it was an older population with metastatic disease and had received docetaxel, abiraterone or enzalutamide prior to entry.

Study XL184-004 was a Phase I study to evaluate the PK of cabozantinib when administered with rosiglitazone.

Table 10: Study XL184-308 Study drug exposure to cabozantinib as of data-cut-off

Tumor Type:	RCC	
Study:	XL184-308[a] Cabozantinib (N = 331)	XL184-308[a] Everolimus (N = 322)
Duration of exposure (weeks)[b]		
N	331	322
Mean (SD)	33.11 (16.838)	23.94 (17.085)
Median	32.14	18.93
Min, max	1.1, 89.3	0.9, 82.1

RCC, renal cell carcinoma; Max, maximum; Min, minimum; SD, standard deviation.
[a] The study drug exposure presented for Study XL184-308 is limited to that available at the time of the primary analysis of PFS; subjects continued to receive study treatment in both treatment arms after that point.
[b] Duration of exposure = (Date of decision to discontinue treatment – Date of first dose + 1)/7.0

The mean duration of exposure (as of data cut-off 22 May 2015) was 33 weeks for cabozantinib and 22 weeks for everolimus.

Table 11: Study XL184-308 Duration of overall exposure in the pivotal study

	Indication: RCC Study XL184-308 (N=331)	
Overall Exposure	Persons n (%)	Person time (Person Weeks)
≥ 4 weeks	329 (99.4)	10954
≥ 8 weeks	312 (94.3)	10857
≥ 12 weeks	291 (87.9)	10655
≥ 16 weeks	279 (84.3)	10491
≥ 20 weeks	245 (74.0)	9922
≥ 24 weeks	239 (72.2)	9793
≥ 28 weeks	215 (65.0)	9195
≥ 32 weeks	179 (54.1)	8122
≥ 36 weeks	128 (38.7)	6430
≥ 40 weeks	105 (31.7)	5560
≥ 44 weeks	90 (27.2)	4942
≥ 48 weeks	71 (21.5)	4072
≥ 52 weeks	53 (16.0)	3180
≥ 56 weeks	37 (11.2)	2318
≥ 60 weeks	21 (6.3)	1396
≥ 64 weeks	10 (3.0)	714
≥ 68 weeks	6 (1.8)	452
≥ 72 weeks	3 (0.9)	243
≥ 76 weeks	2 (0.6)	169
≥ 80 weeks	2 (0.6)	169
≥ 84 weeks	1 (0.3)	89
≥ 88 weeks	1 (0.3)	89
Total person time		10959

Post-marketing data

The sponsor has submitted the following post-marketing experience data taken form the Summary of Clinical Safety:

> *Cabozantinib capsules (Cometriq) were first approved by the FDA on 29 November 2012 for the treatment of patients with progressive, metastatic MTC at a dose of 140 mg qd. Cometriq was made commercially available in the United States on 24 January 2013. On 21 March 2014, cabozantinib capsules (Cometriq) at the 140 mg dose received approval through the centralised procedure by the European Commission for the treatment of adults with progressive, unresectable locally advanced or metastatic MTC.*
>
> *The post-marketing patient population through 22 May 2015 comprised 1149 total patients exposed including approximately 1083 in the US, 42 in the EU (marketed and named patient use, and 24 from other countries.*
>
> *Through 22 May 2015, patients in the US marketed setting have received cabozantinib for treatment of thyroid cancer (n=453) as well as malignancies other than the approved indication, including prostate cancer (n=184), renal cancer (n=183), hepatocellular cancer (n=19), and lung cancer (n=61). In the EU, patients have thus far received marketed drug for MTC (n=11), pheochromocytoma (n=1), and HCC[40] (n=1). Cumulatively, 587 serious adverse reactions have been reported in the post-marketing setting though 22 May 2015. No new safety findings bearing on the known overall safety profile of cabozantinib were identified.*

[40] AusPAR clarification: HCC=Hepatocellular carcinoma

Through 22 May 2015, 75 post-marketing serious adverse reactions for 49 cases were received in subjects who received Cometriq off-label for the indication of renal cancer (including RCC and malignant neoplasm of the renal pelvis). With the exception of unknown cause of death (death [n=11]), pneumonia (n=4), dehydration (n=3), rectal haemorrhage (n=3), hypertension (n=2), hypotension (n=2), vomiting (n=2) and pain in extremity (n=2), the occurrence of any individual serious adverse reaction was limited to one event. After the 22 May 2015 cut-off, one unconfirmed case of posterior reversible encephalopathy syndrome (PRES; also called RPLS) was reported by a non-study physician via the post-marketing process for a subject who was enrolled in Study XL184-308. The report was not contemporaneous with the event (made > 1 year afterwards) and there was inconsistent information in the report regarding the date of the event relative to study treatment. The patient also had confounding factors including receipt of a prior VEGFR-TKI and radiation for brain metastases. There is no evidence of imaging supporting the diagnosis of RPLS, and the event was not confirmed by the study investigator. Additional follow-up is ongoing.

The evaluator concluded that very limited post-marketing data have been provided and should be supplemented by the most recent available data.

Evaluator's conclusions on safety

Overall the safety profile for cabozantinib was consistent across the clinical studies submitted by the sponsor.

All subjects who received cabozantinib experienced at least one AE. The most frequent AEs of any severity were diarrhoea, PPES, nausea, fatigue, decreased appetite.

Dose reductions and interruptions were frequent and are necessary to ameliorate AEs. Most AEs requiring dose modification or interruption occurred early on commencing cabozantinib treatment (median time to first reduction 55-days and first dose interruption 38-days) and patients will require close supervision during the first 8-weeks of treatment this is covered in the PI under precautions but for clarity is probably best placed under dosage and administration.

The incidence of AEs in the cabozantinib was 97% in patients who received cabozantinib in the pivotal study versus 91% for those who had received everolimus.

The safety analysis did not include an analysis of subjects with renal or hepatic impairment however PK studies in subjects with these conditions were included. The prescribing information adequately covers these patient groups.

Data from the pivotal study (in mRCC) and the two supporting studies (in previously treated metastatic CRPC with bone-dominant disease who had experienced disease progression while on docetaxel-containing chemotherapy and either abiraterone or enzalutamide) indicate that cabozantinib is associated with an increase in hepatic transaminases. In the mCRPC studies, there were four cases which met Hy's Law criteria, but have been attributed to disease progression due to confounding factors (hepatic metastasis). In three of these cases there was a clear temporal association between discontinuation of cabozantinib and improvement in hepatic function. Other TKIs are associated with hepatic dysfunction. Monitoring of hepatic function should be included in the prescribing information particularly in patients with known intra-hepatic metastasis.

The majority of deaths were due to disease progression and this could be anticipated given the nature of the clinical study populations; there was no clear indication that deaths were related to a single AE (such as cardiac arrhythmia).

The overall safety profile of cabozantinib is consistent with that of VEGFR TKIs.

First round benefit-risk assessment

Table 12: First round assessment of benefit

Indication	
Benefits	**Strengths and Uncertainties**
A statistically significant difference between the treatment arms favouring cabozantinib was seen for the primary endpoint PFS. The HR adjusted for stratification factors was 0.59 ($p < 0.001$). The Kaplan-Meier estimates for median duration of PFS were 7.4 months in the cabozantinib arm versus 3.8 months in the everolimus arm, a difference of 3.6 months favouring cabozantinib this is considered clinically significant. At the data cut-off for the first interim analysis of OS, May 2015, a trend for improved overall survival for cabozantinib treated subjects was observed, 0.68 (95% CI: 0.51, 0.90; stratified log rank p-value = 0.006). The magnitude of this response was approximately an additional five months of survival which can be considered clinically meaningful. A second, unplanned, interim analysis was undertaken to provide OS data for at least 12-months that demonstrated a similar the HR adjusted for stratification factors was 0.67 (95% CI: 0.53, 0.83; stratified log rank p-value = 0.0003). The Kaplan-Meier estimates of median duration of OS were 21.4 months in the cabozantinib arm and 16.5 months in the everolimus arm, 4.9 month difference the result is consistent with that seen for the first planned analysis of OS. A single pivotal study is submitted in this application, the degree of statistical significance for the results of the primary endpoint, PFS ($p < 0.001$) is in line with that which would expected for an application that includes a single pivotal study (that is stronger than $p < 0.05$). The number of subjects who received non-protocol anticancer therapy was higher in those who had received everolimus as part of the study compared to those who had received cabozantinib. The secondary endpoint ORR was supportive of the results seen for PFS and OS. A statistically significant benefit was seen. The ORR was 17% for subjects who received cabozantinib and 3% for subjects who received everolimus. A reduction in tumour size from baseline was greater for subjects that had received cabozantinib compared to those who had received everolimus, 75% versus 48%	The proposed starting dose of 60 mg is poorly tolerated and by the end of the pivotal study approximately equal proportion of subjects were receiving 60 mg and 40 mg. There is uncertainty with regard the lowest effective dose. Screening for cerebral or bony metastasis that was not present only occurred at study entry. Subsequent imaging for metastasis only occurred based on the investigator's assessment of clinical symptoms. As this was an open label study there is a potential for bias comment on the steps taken (if any) to eliminate bias with regard to the need for imaging/bone scans (as appropriate) for these subjects should be provided. The second analysis undertaken to provide OS data for at least 12-months was unplanned the relevance needs to be considered uncertain. Mature OS data is pending and the final analysis should be provided as soon as practical.

Indication	
Benefits	**Strengths and Uncertainties**
respectively.	

First round assessment of risks

Table 13: First round assessment of risk

Risks	Strengths and Uncertainties
All subjects that received cabozantinib experienced at least one AE. TAEs were experienced by 97% of subjects that received cabozantinib versus 91% of those that received everolimus. Serious AEs reported for ≥1.5% of subjects in the cabozantinib arm by decreasing frequency were, abdominal pain, pleural effusion, diarrhoea, nausea, anaemia, back pain, dyspnoea, fatigue, pneumonia, pulmonary embolism, vomiting, and pain. 68 % of subjects experience grade 3 or 4 AEs. Serious (grade ≥3) AEs associated with cabozantinib included: Haemorrhage (2.1% versus 1.6 % with everolimus). Gastrointestinal perforation and/or fistula (1.2% versus 0% everolimus). Hypertension (15% versus 7.1%everolimus). Diarrhoea (11% versus 2% everolimus). Palmer-plantar erythrodysesthesia syndrome (42% versus 6% everolimus). A low rate of significant increase in liver transaminases was seen for subjects that received cabozantinib that improved when cabozantinib was stopped particularly in subjects with hepatic metastasis. QT prolongation was consistently observed across studies for subjects that received cabozantinib. The risk of VTE was higher in subjects that received cabozantinib compared to those that received everolimus.	The safety profile of subjects with hepatic or renal impairment or those with pre-existing cardiovascular disease has not been analysed. Reversible posterior leukoencephalopathy syndrome has also been reported with cabozantinib but the significance of this is unestablished.

First round assessment of benefit-risk balance

Advanced RCC is an incurable and all patients will experience disease progression median overall survival is around 12 months for patients with Stage 4 disease.

The primary goal of treatment is to prevent disease progression and extend overall survival.

The results of the pivotal Study XL184-308 demonstrate a statistically and clinically significant improvement in terms of PFS versus everolimus in subjects that had previously been treated with VEGF targeted therapy and not for the proposed indication, treatment of advanced RCC.

A trend to an improvement in OS was also seen for in a planned interim analysis for subjects treated with cabozantinib versus everolimus however mature data are pending.

In terms of AEs these were frequently observed but were generally managed with dose modification or interruption.

The safety profile appears to be consistent with that seen for other VEGFR-TKIs.

Cabozantinib has demonstrated benefit over an established treatment that is on the ARTG for the treatment of advanced RCC.

Overall the benefit-risk balance of cabozantinib for the treatment of advanced RCC is for the proposed indication is unfavourable but would become favourable if the changes recommend (see below) are adopted.

First round recommendation regarding authorisation

Approval of cabometyx is recommended subject to

- A modification of the indication.
- The sponsor should also commit to supply mature overall survival data to the TGA as soon as is practical and indicate a time frame for doing so. The sponsor should comment on the impact of additional spending of alpha, due to the unplanned analysis of OS, on the final results.
- Other changes to the PI should be undertaken as recommended the details of these are however beyond the scope of this AusPAR.

Second round evaluation

For details of the second round evaluation including the issues raised by the evaluator (Clinical questions), the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

The OS benefit seen in the unplanned second interim analysis of Study XL184-308 has been confirmed by the final follow-up (descriptive) OS analysis and is of a similar magnitude.

The benefit is otherwise unchanged by the second round evaluation.

Second round assessment of risks

No new safety risks have become apparent in the second round evaluation.

Modifications to the PI recommended by the first round evaluator have been made or acceptable justification given for changes that have not been made.

Second round assessment of benefit-risk balance

- Advanced RCC is incurable, all patients experience disease progression and median overall survival is around 12 months for patients with Stage 4 disease. The primary goal of treatment is to prevent disease progression and extend overall survival.
- The results of the pivotal Study XL184-308 demonstrate a statistically and clinically significant improvement in PFS and OS in subjects that had previously been treated with anti-VEGF therapy, by comparison to everolimus which is a medicine registered in Australia for the treatment of patients with advanced RCC.
- The safety profile of cabozantinib appears similar to other anti-VEGF TKIs and manageable.

Overall the benefit-risk balance of cabozantinib for the treatment of advanced RCC in the proposed indication is favourable.

Second round recommendation regarding authorisation

Approval of Cabometyx is recommended subject to negotiation of PI content with the Delegate, based on recommendations made by the second round evaluator.

VI. Pharmacovigilance findings

Risk management plan

Summary of Risk Management Plan (RMP) evaluation[41]

- The sponsor has submitted EU-RMP version 1.2 (dated 22 September 2016; data lock point (DLP) 22 May 2015) and Australian Specific Annex (ASA) version 1.0 (dated December 2016) in support of this application. In their response to the TGA's request for further information, the sponsor submitted EU-RMP version 2.0 (dated 20 April 2017; DLP 2 October 2016 and ASA version 1.1 (dated August 2017).
- The sponsor has also submitted ASA version 1.2 (Dated November 2017) in support of this application. There is no change to the EU-RMP.

[41] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below (Table 14).

Table 14: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A
Important identified risks	GI Perforation	ü	ü**	ü	–
	GI and non-GI Fistula	ü	ü**	ü	–
	Thromboembolic events	ü	ü**	ü	–
	Haemorrhage (Grade ≥ 3)	ü	ü**	ü	–
	Wound complications	ü	ü**	ü	–
	Hypertension	ü	ü**	ü	–
	Reversible posterior leukoencephalopathy syndrome (RPLS)	ü	ü**	ü	–
	Diarrhoea	ü	ü**	ü	–
	Palmar-plantar erythrodysaesthesia syndrome (PPES)	ü	ü**	ü	–
	Hypothyroidism	ü	ü**	ü	–
	Osteonecrosis	ü	ü**	ü	–
	Proteinuria	ü	ü**	ü	–
Important potential risks	QT prolongation	ü	–	ü	–
	Renal failure	ü	–	ü	–
	Hepatotoxicity	ü	–	ü	–
	Fertility impairment	ü	–	ü	–
	Embryotoxicity	ü	–	ü	–
	Medication error	ü	–	ü	–
	Carcinogenicity*	ü	–	ü	–
Missing information	Use in paediatric population	ü	–	ü	–
	Use in pregnant or lactating women	ü	–	ü	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Use in patients with cardiac impairment	ü	–	ü	–
	Use in patients with severe hepatic impairment	ü	–	ü	–
	Use in patients with severe renal impairment	ü	–	ü	–

*Carcinogenicity is now included as an Important Potential Risk in the Safety Specification and not Missing Information, based on the results of Study XL184-036, which has been completed.

**Additional planned prospective non-interventional study for CABOMETYX in Renal Cell Carcinoma to assess the risk: benefit profile with respect to all identified risks (Voluntary PASS).

- Additional pharmacovigilance activities include a nonclinical carcinogenicity rat study (Study XL184-036) and a planned prospective non-interventional study for cabometyx in RCC to assess the risk benefit profile with respect to all identified risks (Voluntary PASS).
- There are no additional risk minimisation activities.

Advice to the delegate

The following issues are recommended for consideration by the Clinical Delegate:

- The Delegate may wish to consider adding 'Diarrhoea' under Precautions in the PI as this Important Identified Risk has the potential to be severe. A similar precaution is included in the US PI, accompanied by dosing advice.

Sponsor's response

The PI has been amended with a new 'Precaution' as follows:

> *'Diarrhoea':*
>
> *'Diarrhoea has been observed with cabozantinib, and can be severe. If diarrhoea can't be managed with standard antidiarrhoeal treatment, interruption of treatment with cabozantinib should be considered. Cabozantinib should be restarted with a lower dose when diarrhoea has been resolved to Grade 1'.*

RMP evaluator comment

This has been added as per the Delegate's request.

- The CMI does not appear to contain anything regarding QT prolongation. It should be revised to include advice to patients that they should tell their doctor if they are on an antiarrhythmic medicine, have a pre-existing heart condition, or slow heart rate.

Sponsor's response

Added to CMI as recommended under 'Before you take Cabometyx – Before you start to take it'.

RMP Evaluator comment

The wording has been added as recommended and is satisfactory.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system. The suggested wording is:

- EU-RMP (version 2.0, dated 20 April 2017, data lock point 2 October 2016) with Australian Specific Annex (version 1.2, dated November 2017), and any future updates as a condition of registration.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator stated the updated version of the PI was acceptable from a chemistry and quality perspective, and recommended approval conditional on resolution of:

- Provision of updated GMP clearance certificates for some manufacturers
- The acceptability of the tradename Cabometyx compared to similar name Cosentyx (secukinumab rch injection prefilled syringe or vial, for psoriasis / psoriatic arthritis / ankylosing spondylitis)

Delegate commented that despite the similarity to 'Cosentyx' the choice of trade name Cabometyx is acceptable based on the different presentations, the different indications and the low likelihood of co-prescription (neither of the indications are common). It is also noted that this tradename has been accepted in the EU and USA.

The evaluator also noted:

- Controls for genotoxic impurities in XL184-2-1 should be reviewed if the manufacturing method is changed.
- It remains unclear that the proposed in vitro dissolution test provides useful control.

They recommended that the conditions of registration (to be negotiated) should include:

- Control malic acid used to make cabozantinib malate to the US Pharmacopeia specification.
- Set tighter limits on particle size.
- Tighten the release limit for one impurity (depending on toxicological advice).

Nonclinical

Principle conclusions from the nonclinical evaluation were that:

- The toxicology studies suggested safety of cabozantinib to be similar to that of other VEGFR inhibitors but because cabozantinib inhibits other enzymes including MET, additional toxicities may be seen such as: increased risk of hepatotoxicity with concomitant use of hepatotoxic drugs, anaemia and cytopaenia.
- Interactions with CYP3A4 and MRP2 inducers or inhibitors or substrates of p-glycoprotein or MRP2 may be possible.

- The pharmacology studies generally support the use of cabozantinib as an anticancer agent.
- As justified by the sponsor, if there is a clear clinical benefit, additional toxicity characterisation of the metabolite EXEL1646 may not be conducted for the treatment of advanced cancer. Further toxicity studies should be conducted if indications for non-advanced cancers are sought in the future.
- For one impurity, the ICH guideline S9 indicates that impurities in drug substances for the treatment of advanced cancer at levels above the qualification threshold could be appropriate with adequate justification.[42] The sponsor's justification was based on clinical benefit of cabozantinib versus potential risk posed by the impurity. The sponsor's justification is partly acceptable. A repeat dose toxicity study for the impurity may not be needed if there is a clear clinical benefit of the drug (assessed by the clinical evaluator) but an in silico analysis of mutagenicity should be conducted (since cabozantinib is not genotoxic). The sponsor's statement in the response 'As the amount of the impurity [information redacted] is less than 1 mg, no further genotoxicity testing will be required regardless of other qualification threshold' is misleading. The ICH guideline M7 meant that no further genotoxicity testing is required regardless of other qualification thresholds in cases where the amount of the impurity is less than 1 mg *and* an in silico analysis and/or a bacterial mutagenicity test gave negative results'.

The Delegate commented that mutagenicity analysis of [information redacted] should be addressed with the sponsor but does not preclude registration.

Clinical

Summary of the sponsor's submitted clinical data:

- One pivotal efficacy/safety study (Study XL184-308).
- Ten clinical pharmacology studies providing pharmacokinetic (PK) and safety pharmacology data, including population data analyses.
  - One of these studies was a drug-drug interaction study on the PK of a single dose of rosiglitazone in subjects with solid tumours and included efficacy as an exploratory outcome but the number of subjects with RCC was 25 and the capsule formulation and dose was used. Therefore this study was not considered to contribute to efficacy.
- Two studies that are evaluable for safety only, conducted in metastatic castration-resistant prostate cancer patients (Studies XL184-306 and XL184-307).
- One population safety analysis.

Clinical pharmacokinetics

Absorption

- Oral administration, rapid absorption (peak in 2 to 3 hours) and multiple plasma concentration-time peaks after single oral dosing, suggesting enterohepatic circulation.
- pH dependent solubility: practically insoluble above pH 4, however , a single dose esomeprazole interaction study suggests no clinically significant effect of PPIs on absorption.

[42] ICH guideline S9: Nonclinical Evaluation for Anticancer Pharmaceuticals

- Bioavailability after multiple doses was investigated with the capsule formulation. With 140 mg daily dose, AUC was 5.4 fold higher on Day 19 than at Day 1. Steady state is reached by approximately Day 15.
- Exposure is increased with high fat meals (increased C_{max} by 39%, AUC by 56%) and dosing is therefore recommended in the fasting state.
- Exposure variability:
  - Intrasubject variability in both C_{max} and AUC approximately 30%.
  - Intersubject variability approximately 20 to 60% for AUC and 30 to 70% for C_{max}.
  - Variability was similar in healthy subjects and in cancer patients.

Distribution

- Estimated volume of distribution = 319 L.
- Highly plasma protein bound (> 99.9%), and minimally erythrocyte-associated.

Metabolism

- Primarily hepatic metabolism (CYP3A4 substrate), not expected to be affected by genetic polymorphism.

Excretion

- Mass balance study showed 54% faecal and 27% urinary excretion, and approximately 80% excreted by 48 hours post dose.

Special populations

- Impaired hepatic function: mild or moderate impairment was associated with increased exposure by 60 to 80%, severe impairment has not been studied.
- Mild and moderate impairment of renal function had minimal impact on exposure, in keeping with predominant hepatic metabolism and excretion, but caution recommended in PI regardless, and use not recommended in severe renal impairment.

Interactions

- Not expected to have a clinically relevant effect on CYP450 substrates based on rosiglitazone interaction study.
- Potential for increased exposure with coadministration of potent CYP3A4 inhibitors based on ketoconazole interaction study.
- Potential for displacement interaction with other highly protein-bound drugs (for example, warfarin, diazepam and furosemide).

Summary of population pharmacokinetic analysis

- A two-compartment model with two parallel (fast and slow) lagged first-order absorption processes adequately described the population pharmacokinetics of cabozantinib. The absorption rate constant for the faster absorption process was dose dependent.
- Minor covariates: female sex and Asian race (lower clearance - higher AUC). This was marginal in context of interindividual variability.
- The population PK (popPK) evaluator was satisfied with the quality of analyses and stated the following:

Important inferences from the exposure-response analyses would be:

- A starting dose of 60 mg daily of cabozantinib is expected to result in a greater reduction in baseline tumour size than 40 mg daily (-11.9% versus -9.1%, respectively).
- The inhibitory effect of cabozantinib therapy on tumour growth was predicted to attenuate over time, with a half-life of about 25 days. This suggests that cabozantinib therapy has its primary benefit in terms of reducing tumour size within the first 4 to 5 months of therapy, after which disease progression will become the primary determinate of tumour size.
- Subjects starting on 60 mg daily are predicted to require more dose reductions than those starting on a 40 mg daily dose, presumably because of an increased likelihood of adverse effects with the 60mg daily. Note however, that a 40 mg daily starting dose would come at the cost of reduced efficiency in terms of tumour growth inhibition.

Dose selection

Previously, using the capsule formulation, the maximum tolerated dose of cabozantinib was determined to be 140 mg once per day. No formal dose-finding studies were submitted in this application, and 60 mg daily was the starting dose in the pivotal study. Given the above conclusions of the population PK exposure-response analyses, this is considered acceptable.

Clinical efficacy

The pivotal efficacy trial design for the '*Phase III, Randomised, and Controlled Study of Cabozantinib (XL184) versus Everolimus in Subjects with Metastatic Renal Cell Carcinoma that has Progressed after Prior VEGFR Tyrosine Kinase Inhibitor Therapy'* is described Table 15 below.

This study was open-label to allow for appropriate dose reduction for adverse events.

Table 15: Study XL184-308 Design of the pivotal efficacy trial

Study XL184-308	
Patients N = 658 (ITT)	*Inclusion criteria (abbreviated)* Histologically or cytologically confirmed RCC with a clear cell component; measurable disease on RECIST 1.1. Progression or refractory to prior lines of therapy, which must include at least one VEGFR-targeting TKI. Kanrnofsky Performance Status (KPS) score at least 70%, any toxicity from prior treatment resolved or managed stably. Adequate organ and marrow function. *Exclusion criteria (abbreviated)* Prior everolimus, other specific/selective TORC1/PI3K/AKT inhibitor or prior cabozantinib. Recent therapy (including investigational, within x weeks of randomisation) with:

Study XL184-308	
	small molecule kinase inhibitor (x = 2) any type of anti-cancer antibody (x = 4) external radiotherapy to bony metastasis (x = 2) external radiotherapy to anywhere else (x = 4) systemic radionuclides (x = 6) Ongoing clinically relevant complications of radiation therapy Brain metastases or cranial epidural disease unless treated, stable for at least 3 months symptomatic and no steroids Cavitating pulmonary lesion(s) or known endobronchial disease manifestation Elevated risk of bleeding (for example, most therapeutic-dose anticoagulation, lesion invasion of major vessels) Elevated risk of GI perforation or fistula Chronic treatment with immunosuppressive medication (exception: corticosteroids if daily equivalent dose ≤10mg, or if topical/inhaled) Major surgeries, uncontrolled illnesses, QT prolongation at baseline, NY class 3 or 4 heart failure, recent history of stroke (6 months)
Intervention N = 330 (ITT)	Cabozantinib 60 mg once daily, oral tablet, fasting conditions at same time each day Dose reduction for unacceptable toxicity allowed at any time: first to 40 mg then to 20 mg
Comparator N = 328 (ITT)	Everolimus 10 mg once daily, oral tablet, fed or fasted but at same time each day Dose reduction by 50% for management of severe/intolerable adverse reactions, use following product labelling At the time of evaluation, everolimus was the most frequently used second-line therapy following a VEGFR-TKI in patients with RCC. Everolimus is therefore an appropriate choice of comparator. In November 2015, a phase III study was published showing nivolumab to be superior to everolimus in RCC that progressed after first-line antiangiogenic therapy, and it was registered by TGA in August 2016 for this usage. This trial does

Study XL184-308	
	not provide a direct comparison to nivolumab in second-line therapy after a VEGF inhibitor, but indirect comparison can be made.
Endpoints	*Primary efficacy endpoint:* Progression Free Survival (PFS) assessed by blinded independent review committee (IRC) using RECIST 1.1 in the Primary Endpoint Intention-to-treat population (PITT);[43] *Secondary efficacy endpoint:* Overall Survival (OS) Overall Response Rate (ORR): proportion of subjects for whom the best overall response at time of data cut-off was complete response (CR) or partial response (PR) as assessed by IRC using RECIST 1.1 and confirmed at least 28 days later *Additional endpoints:* Duration of response (DoR) Safety and tolerability Pharmacokinetics Change in symptoms as measured by patient-reported questionnaires: Functional Assessment of Cancer Therapy - Kidney Symptom Index (FKSI-19). EuroQol Health questionnaire instrument (EQ-5D-5L) Bone scan and serology measures including some molecular studies Proportion of subjects with post-randomisation skeletal-related events (SREs) Health care resource utilisation parameters (e.g. admissions, procedures, length of stay) *Randomisation and stratification for:* Number of prior VEGFR-targeting TKI therapies Number of Memorial Sloan-Kettering Cancer Centre RCC prognostic criteria: Karnofsky performance status score < 80% Haemoglobin < 13 g/dL (< 130 g/L) for

[43] This population was the first 375 randomised subjects, as pre-specified in the statistical analysis plan (SAP), and was used only for the primary endpoint analysis.

Study XL184-308	
	males and < 11.5 g/dL (< 115 g/L) in females Corrected calcium > upper limit of normal

Baseline characteristics of the OS population from the published article are described in the table below (Table 16).

Table 16: Study XL184-308 Baseline characteristics of the OS population from the NEJM article

	Cabozantinib n=330	Everolimus n=328
Age, Md (range)	63 (32, 86)	62 (31, 84)
Men	77%	73%
ECOG 0 ECOG 1	68% 32%	66% 34%
MSKCC prognostic risk cat Favourable Intermediate Poor	 45% 42% 12%	 46% 41% 13%
Prior VEGFR TKI 1 2+	 71% 29%	 70% 30%
Previous systemic therapy Sunitinib Pazopanib Axitinib Sorafenib Beva Interleukin-2 Interferon alpha Nivo	 64% 44% 16% 6% 2% 6% 6% 5%	 62% 41% 17% 9% 3% 9% 7% 4%
RT	33%	33%
Nephrectomy	85%	85%

Baseline data and protocol deviations were generally balanced across arms. There was a higher rate of discontinuation in the everolimus arm; the imbalance was mainly due to disease progression. The rate of death was higher in the everolimus arm (39%) than the cabozantinib arm (34%).

Efficacy results

Outcomes based on lesion measurement are outlined in Table 17. Regarding the secondary efficacy outcome of overall survival (OS), three analyses of OS were performed:

1. The first (planned, interim) showed a trend towards favouring the cabozantinib arm but did not reach statistical significance.
2. A second (unplanned, interim) was carried out at 78% of the total required events, and was statistically significant. It is cited here as the final statistically valid OS result.
3. The per-protocol final analysis was completed and provided at the post-first round evaluation response stage.

In response to a request from the TGA, the sponsor provided the third and final analysis 'for descriptive purposes' and have made changes to the PI: adding a sentence noting the descriptive analysis, a forest plot of exploratory subgroup analyses of PFS and a table regarding health-related quality of life outcomes. This information is extraneous and should be removed so that the Australian PI has content similar to that of the European SmPC and US label.

Table 17: Study XL184-308 Results for measurable lesion based radiological efficacy outcomes: PFS, OS, ORR and DoR

	Cabozantinib	Everolimus
Primary in PITT	(n=187)	(n=188)
PFS		
Median, months [95% CI]	7.4 (5.6, 9.1)	3.8 (3.7, 5.4)
Stratified hazard ratio [95% CI]	0.59 [0.46, 0.76]	
Stratified log-rank p value	< 0.001	
Secondary in ITT	(n = 330)	(n = 328)
OS		
Median, months [95% CI]	21.4 (18.7, NE)	16.5 (14.7, 18.8)
Stratified Hazard ratio [95% CI]	0.67 [0.53, 0.83]	
Stratified log-rank p value	0.0003[44]	
ORR		
Complete response (CR), n (%)	0 (0)	0 (0)
Partial response (PR), n (%)	57 (17)	11 (3)
Stable disease (SD), n (%)	216 (65)	203 (62)
Progressive disease (PD), n (%)	41 (12)	88 (27)

[44] Adjusted critical value for rejecting the null hypothesis was p < 0.0163.

	Cabozantinib	Everolimus
Unable to evaluate, n (%)	2 (0.6)	2 (0.6)
Missing;[45], n (%)	14 (4)	24 (7)
ORR n (%) [95% CI]	57 (17) [13, 22]	11 (3) [2, 6]
Stratified CMH;[46] p value	<0.001	
Un-stratified Chi-squared p-value	<0.001	
DoR		
Median, months [95% CI]	NE [7.2, NE]	7.4 [1.9, NE]

NE = not estimable, CI = confidence interval

Additional analyses and outcomes:

- Sensitivity analyses on the primary efficacy outcome were undertaken using differing definitions of PFS and in the Intent to treat (ITT) population were consistent with the pre-specified primary efficacy outcome.
- Subgroup analyses showed consistent PFS benefit in all but two subgroups: females in Primary endpoint intent to treat (PITT) (but not ITT) and subjects with only one organ metastasis (both PITT and ITT). These subgroups were small and the findings are considered equivocal.
- Bone scan response per IRC (exploratory): a trend towards higher incidence of improvement in lesions seen on bone scan was seen with cabozantinib compared to everolimus, but the confidence intervals for this exploratory endpoint significantly overlapped.
- 'Relationship of baseline and changes in plasma biomarkers, serum bone markers, serum calcium, and circulating tumour cells (CTCs) with treatment and/or clinical outcome' was listed as an outcome of this study but results have not been submitted.
- Health care resource utilisation parameters: hospitalisation rates (37% versus 40% of subjects; 6.4 versus 10.2 days per person-year), intensive care unit (ICU) visit rates (1.2% versus 2.1% of subjects; 0.07 versus 0.32 days per person-year) and surgeries per person-year (0.90 versus 1.35) were lower in the cabozantinib arm than the everolimus arm.
- Proportion of subjects with post-randomisation skeletal related events (pathologic fractures, spinal cord compression, and surgery to bone or external radiation therapy to bone) was similar between arms.
- Change in symptoms as measured by patient-reported questionnaires: baseline scores and scores over time were not notably different.

Pharmacokinetic parameters

Table 18 describes the PK results from the pivotal study.

[45] No qualifying post-baseline assessment for overall response
[46] Cochran-Mantel-Haenszel test

Table 18: Study XL184-308 PK results from the pivotal study (cabozantinib arm only, n = 290 with analysis-eligible records)

		Concentration (ng/mL) at Scheduled Visit					
		Week 5 Day 1			Week 9 Day 1		
Nominal Dose (mg)	Statistics	Males	Females	Male & Female	Males	Females	Male & Female
60	N	244	66	310	224	66	290
	Mean	1180	1390	1230	937	987	949
	SD	587	675	611	477	611	510
	CV%	49.6	48.6	49.9	50.9	61.9	53.7
	Geo Mean[b]	ND	1160	ND	800	ND	ND
	SD (Logs)[b]	ND	0.726	ND	0.652	ND	ND
	Min	0	51.9	0	18.0	0	0
	Median	1170	1370	1200	896	925	899
	Max	3040	3360	3360	3480	2630	3480

CV%, coefficient of variation; Geo, Geometric; Max, maximum; Min, minimum; ND, not determined; SD, standard deviation; SD (Logs), standard deviation of the logs.

[a] A concentration record had to meet specific requirements to be considered analysis eligible, which included the following: 1) The sample met stability requirements, 2) The PK concentration was measured at least 14 days after the first dose of cabozantinib, (ie, ≥ Study Day 15 relative to first cabozantinib dose), 3) The PK concentration was not missing, 4) The actual visit was within 21 days of the planned visit, and 5) The PK plasma sample was associated with a planned visit (ie, was not unscheduled or taken during screening).

[b] The geometric mean and SD (Logs) could not be determined in those cases were zero values were present.

The Delegate commented that the efficacy of cabozantinib in second line treatment of RCC after an anti-VEGF therapy is considered adequately shown in this study.

Safety

Safety in the pivotal study

Treatment related AEs in the pivotal study are described in Table 19 below.

Table 19: Study XL184-308 Treatment-related adverse events reported for at least 20% of subjects in either treatment arm in the pivotal study

	Cabozantinib N=331 n (%)		Everolimus N=322 n (%)	
	Grade		Grade	
Preferred term	**All**	**3/4**	**All**	**3/4**
Diarrhoea	227 (69)	35 (11)	65 (20)	6 (1.9)
Fatigue	164 (50)	26 (7.9)	114 (35)	14 (4.3)
Nausea	145 (44)	9 (2.7)	56 (17)	1 (0.3)
Palmar-plantar erythrodysaesthesia syndrome	136 (41)	27 (8.2)	14 (4.3)	2 (0.6)
Decreased appetite	129 (39)	8 (2.4)	77 (24)	1 (0.3)
Hypertension	109 (33)	47 (14)	10 (3.1)	6 (1.9)

	Cabozantinib N=331 n (%)		Everolimus N=322 n (%)	
Weight decreased	79 (24)	5 (1.5)	26 (8.1)	0
Vomiting	75 (23)	3 (0.9)	18 (5.6)	0
Dysgeusia	72 (22)	0	27 (8.4)	0
Stomatitis	67 (20)	7 (2.1)	75 (23)	7 (2.2)
Mucosal inflammation	62 (19)	3 (0.9)	70 (22)	11 (3.4)
Rash	40 (12)	0	73 (23)	2 (0.6)
Anaemia	37 (11)	7 (2.1)	84 (26)	30 (9.3)

As stated by the clinical evaluator:

The nature of AEs experienced by subjects was different for subjects who had received cabozantinib versus those who had received everolimus. Fatigue, PPES (palmar-planter erythrodysaesthesia), dysgeusia, hypertension, stomatitis, hypothyroidism and dysphonia have been reported for, and are in the product information for, other TKIs (sorafenib, sunitinib and pazopanib).

Elevated liver enzymes were common but there were no cases that met Hy's Law criteria in the pivotal study.

Liver enzyme elevation in the cabozantinib group was approximately three times more frequent than the everolimus arm: around 15% of patients had elevated ALT/AST and the rate of events of Grade 3 or4 severity was between 1 and 2%.

Deaths in the pivotal study were most frequently due to disease progression. Adverse events that had fatal outcomes were not suggestive of any particular safety signal.

Adverse events that led to dose reductions or interruptions in the pivotal study were very common in the cabozantinib arm (60% and 70% respectively). The most frequent adverse events leading to dose reduction were diarrhoea (16%), palmar-planter erythrodysaesthesia (11%), fatigue (10%) and hypertension (7.6%). The rate of study drug discontinuation was similar between arms (10% cabozantinib and 9.6% everolimus).

The high rate of dose reductions was flagged by the evaluator as possibly representative of a failure to identify the maximal tolerated dose in the early phase studies. However, the findings of the popPK efficacy report suggest that the 60 mg dose is significantly more likely to have efficacy than the 40 mg dose, suggesting the approach of starting with the higher dose and reducing according to tolerance is preferable to beginning with the lower dose (and risking loss of efficacy). The rate of discontinuation is much lower than the rates of dose interruption/reduction, suggesting adverse events are mostly manageable with dose interruption/reduction.

Particular adverse events of interest, termed 'events to monitor,' were pre-specified based on the known safety profile of other VEGF inhibitors and an analysis of these is included in the clinical study report for the pivotal study (see Table 20 below).

Table 20: Study XL184-308 Incidence of 'Events to monitor' in both study arms

	RCC (XL184-308)					
	Cabozantinib (60 mg) N=331			Everolimus (10 mg) N=322		
	Any Grade	Grade 3/4	Grade 5	Any Grade	Grade 3/4	Grade 5
ETM	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
GI perforation	3 (0.9)	2 (0.6)	0	3 (0.9)	1 (0.3)	1 (0.3)
Fistula[a]	4 (1.2)	1 (0.3)	0	0	0	0
Abscess—all	7 (2.1)	4 (1.2)	0	6 (1.9)[b]	1 (0.3)[b]	0
Intra-abdominal and pelvic abscess	4 (1.2)	4 (1.2)	0	1 (0.3)	0	0
Haemorrhage (≥ Grade 3)	7 (2.1)[c]	5 (1.5)	2 (0.6)[d]	5 (1.6)[c,e]	5 (1.6)[e]	0
Arterial thrombotic events	3 (0.9)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Venous and mixed/unspecified thrombotic events	24 (7.3)	12 (3.6)	0	8 (2.5)[f,g]	3 (0.9)[f]	0
Wound complications	8 (2.4)	1 (0.3)	0	4 (1.2)	1 (0.3)	0
Hypertension	128 (39)	52 (16)	0	24 (7.5)	10 (3.1)	0
Osteonecrosis	2 (0.6)	1 (0.3)	0	2 (0.6)[h]	2 (0.6)	0
PPES	139 (42)	27 (8.2)	NA	19 (5.9)	3 (0.9)	NA
Proteinuria	41 (12)	8 (2.4)	NA	30 (9.3)	1 (0.3)	NA
RPLS	0	0	0	0	0	0
Diarrhoea	245 (74)	38 (11)	0	89 (28)	7 (2.2)	0
QTc prolongation	1 (0.3)	0	0	1 (0.3)	1 (0.3)	0

ETM, event to monitor; GI, gastrointestinal; MedDRA, Medical Dictionary of Regulatory Activities; NA, not applicable; PPES, palmar-plantar erythrodysaesthesia syndrome; RCC, renal cell carcinoma; RPLS, reversible posterior leukoencephalopathy syndrome.

All of the events to monitor except osteonecrosis and diarrhoea are reflected in the Precautions text in the proposed PI. Osteonecrosis is included in the adverse events table as a rare event. A precaution regarding diarrhoea is found in the US label but not the European Summary of Product Characteristics (SmPC), and the Delegate believes it should be included in the Australian PI.

Safety in supporting studies

Additional safety information for cabozantinib was submitted from two supporting studies in metastatic prostate cancer and a PK study that includes subjects with various other solid tumours including thyroid cancer. The latter used the capsule formulation that is, starting at 140 mg, and 80% of patients underwent dose reduction, due to AEs. Generally the safety profile was consistent with that of the pivotal study.

The Delegate commented that the safety of cabozantinib in second line treatment of RCC after an anti-VEGF therapy is considered adequately characterised.

Risk management plan

The RMP evaluator has made the following recommendations:

- The US PI includes 'Diarrhoea' under Warnings and Precautions and states that 'Diarrhea: May be severe. Interrupt cabometyx treatment immediately until diarrhea resolves or decreases to Grade 1. Recommend standard antidiarrheal treatments'. As this safety concern has the potential to be severe, the Delegate may wish to consider adding 'Diarrhoea' under Precautions in the PI.
- QT prolongation is listed under Precautions in the PI. However, the CMI does not appear contain anything regarding this risk or to tell the doctor if the patient is on an antiarrhythmic medicine, has a pre-existing heart condition, or slow heart rate. The sponsor should revise the CMI to include this advice.

The second round RMP evaluation also notes '*Effects on bone and teeth in paediatric patients*' should be added on the basis of nonclinical advice as an Important Potential Risk in the Safety Specification of the RMP.

The Delegate commented that diarrhoea was seen very frequently in the pivotal trial (69%), resulted in dose modification in 26%, and was Grade 3 or 4 in 11% of subjects. Diarrhoea of this severity is defined in the CTCAE criteria;[47] as at least 7 stools per day/incontinence/requiring hospitalisation/limiting self-care ADLs (Grade 3) or life-threatening/urgent intervention indicated (Grade 4). The inclusion of a Precaution regarding diarrhoea, similar to the US label, is clinically warranted due to the severity and frequency of this event. The RMP evaluator's comments regarding the CMI and QT prolongation are also agreed by the Delegate.

Risk-benefit analysis

Delegate's considerations

Clinical need

A number of therapies are currently available for advanced RCC. However, none are without toxicity and despite the improved rates of overall survival with first-line therapies in recent years, eventual progression remains a problem.

Benefit-risk balance and associated uncertainties

The pivotal study for registration reported an improvement in median PFS of 3.6 months (compared to everolimus) in patients who had at least one previous systemic therapy. The study also reported a benefit on median OS over everolimus of about 5 months. The hazard ratio for OS versus everolimus was similar to that for nivolumab (though a head to-head comparison is not available); however the toxicity profile is different. Adverse events with cabozantinib are similar to other VEGFR TKIs and are consistent with its broad scope of inhibitory activity.

In the setting of advanced RCC that progresses after initial therapy with a VEGFR TKI, the benefit-risk balance of cabozantinib use is favourable. The choice of treatment in second line RCC will involve a discussion with patients about the expected benefits and the toxicity profile. It is reasonable that cabozantinib should be included in these discussions.

Conditions of registration

Standard conditions of registration should apply.

Summary of issues

This product has been registered for this indication in Europe and the US, and there are no concerns that preclude registration in Australia at this time. Efficacy is considered supported and the safety profile is well characterised. Though there is considerable toxicity, in keeping with anti-VEGF class effects, the benefit-risk balance is positive for patients covered by the proposed indication.

[47] National Cancer Institute. Common Terminology Criteria for Adverse Events v4.0. NCI, NIH, DHHS. May 29, 2009. NIH publication # 09-7473. Accessed 18/10/2017. Available at: https://evs.nci.nih.gov/ftp1/CTCAE/

Advisory Committee Considerations

The Delegate did not refer this application to the Advisory Committee on Prescription Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of cabometyx cabozantinib 20 mg film coated tablet; cabometyx cabozantinib 40 mg film coated tablet and cabometyx cabozantinib 60 mg film coated tablet for oral administration, indicated for:

> *Cabometyx is indicated for the treatment of advanced renal cell carcinoma (RCC) in adults following prior treatment with vascular endothelial growth factor targeted therapy*

Specific conditions of registration applying to these goods

- Cabometyx (cabozantinib) is to be included in the Black Triangle Scheme. The PI and CMI for Cabometyx must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The cabozantinib EU-Risk Management Plan (EU-RMP), version 2.0, dated 20 April 2017, data lock point 2 October 2016) with Australian Specific Annex (version 1.2, dated November 2017) included with submission PM-2016-04459-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Cabometyx approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au