Indication	**RENAL CELL:** For the treatment of metastatic disease or inoperable locally advanced renal cell carcinoma with a clear cell component in patients who have previously received at least 1 vascular endothelial growth factor (VEGF)-targeted systemic therapy for renal cancer and the patient has progressed on previous treatment or within 6 months of most recent dose of VEGF inhibitor. For treatment-naïve intermediate or poor risk metastatic or inoperable locally advanced renal cell carcinoma with a clear cell component. **HEPATOCELLULAR CARCINOMA (HCC):** For the second line of TKI treatment of locally advanced or metastatic Child-Pugh liver function class A HCC who have previously been treated with sorafenib for locally advanced or metastatic hepatocellular carcinoma. **NB: CABOMETYX® (cabozantinib) tablets and COMETRIQ® (cabozantinib) capsules are not bioequivalent and should not be used interchangeably.**
Treatment Intent	Palliative treatment
Frequency and number of cycles	Every 28 days Continue until progressive disease, unacceptable toxicity or patient choice. A formal medical review as to whether treatment with cabozantinib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Monitor FBC and U&Es at each cycle. In particular monitor potassium, calcium, phosphate, sodium & magnesium. • LFTS (ALT, AST and bilirubin) baseline and at each cycle. Closer monitoring is recommended in patients with mild or moderate hepatic impairment. • Monitor blood glucose prior to treatment and then as clinically indicated. • Prior to treatment neuts must be >/=1.5 and PLT >/= 100, otherwise d/w consultant. During treatment if neuts <1.0 and/or PLT <50 d/w consultant. • Thyroid function & urinalysis for proteinuria at baseline, then every cycle. Discontinue in the event of nephrotic syndrome. • ECG prior to treatment and then as clinically indicated. • Blood pressure should be well controlled before starting cabozantinib. If blood pressure exceeds 150/90mmHg please discuss with consultant. Blood pressure to be measured weekly for first cycle, then at every cycle. In the case of persistent hypertension despite use of anti-hypertensives, treatment should be interrupted until blood pressure is controlled, after which cabozantinib can be resumed at a reduced dose. Cabozantinib should be discontinued if hypertension is severe, persistent despite anti-hypertensive therapy and dose reduction. • Osteonecrosis of jaw (ONJ) has been observed with cabozantinib. An oral examination should be performed prior to initiation and periodically during therapy. Patients should be advised on oral hygiene practice. Cabozantinib treatment should be held at least 28 days prior to scheduled dental surgery or invasive dental procedures, if possible. Cabozantinib should be discontinued in patients who experience ONJ.

	• Reference should be made to the UK chemotherapy board guidance on medication related osteonecrosis of the jaw: https://www.rcplondon.ac.uk/guidelines-policy/medication-related-osteonecrosis-jawguidance-oncology-multidisciplinary-team. • **Hepatic impairment:** No dose adjustment is required in mild hepatic impairment. Limited data are available in moderate impairment (Child-Pugh B) no dose recommendation available, clinician's decision to dose reduce. Patients should be monitored for adverse events and dose adjustment or treatment interruption should be considered as needed. Cabozantinib is not recommended for use in patients with severe hepatic impairment (Child-Pugh C). • **Renal impairment:** Dose adjustment is not required, but use with caution in patients with mild or moderate renal impairment. Not recommended for patients with severe renal impairment (CrCl<30ml/min). • **Management of adverse reactions and dose adjustments:** • Suspected adverse drug reactions may require treatment interruption and/or dose reduction (see table 1). • When a dose reduction is necessary, it is recommended to reduce to 40mg daily then 20mg daily. Dose interruptions are recommended for grade 3 or greater toxicities or intolerable grade 2 toxicities. • Cabozantinib should be permanently discontinued if there is: development of unmanageable fistula or GI perforation, severe hemorrhage, arterial thromboembolic event (e.g., myocardial infarction, cerebral infarction), hypertensive crisis or severe hypertension despite optimal medical management, nephrotic syndrome or reversible posterior leukoencephalopathy syndrome. • **Cautions:** • Patients who have inflammatory bowel disease, have tumour infiltration in the GI tract, or have complications from prior GI surgery should be carefully evaluated before initiating cabozantinib therapy and subsequently they should be monitored closely for symptoms of perforations and fistulas including abscesses. Persistent or recurring diarrhoea while on treatment may be a risk factor for the development of anal fistula. • Patients should be monitored for signs and symptoms of hepatic encephalopathy. • Cabozantinib should be used with caution in patients who are at risk for, or who have a history of venous thromboembolism, including pulmonary embolism, and arterial thromboembolism. • Cabozantinib should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. • Severe haemorrhage, sometimes fatal, has been observed with cabozantinib. Patients who have a history of severe bleeding prior to treatment initiation should be carefully evaluated before initiating cabozantinib therapy. Cabozantinib should not be administered to patients that have or are at risk for severe haemorrhage. • Posterior reversible encephalopathy syndrome (PRES) has been observed with cabozantinib. This syndrome should be considered in any patient presenting with multiple symptoms, including seizures, headache, visual disturbances, confusion or altered mental function. Cabozantinib treatment should be discontinued in patients with PRES. • Wound complications have been observed with cabozantinib. Cabozantinib treatment should be stopped at least 28 days prior to scheduled surgery, including dental surgery, if possible. The decision to resume cabozantinib therapy after surgery should be based on clinical judgment of adequate wound healing. Cabozantinib should be discontinued in patients with wound healing complications requiring medical intervention. • Patients should be advised to use regular emollients on their skin (particularly their hands and feet).

	• **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:** Cabozantinib is a CYP3A4 substrate. Concomitant medicinal products that are **strong inhibitors** of CYP3A4 (e.g. ketoconazole, itraconazole, clarithromycin, grapefruit juice) should be used with caution, and concomitant use of **strong inducers** of CYP3A4 (e.g. rifampicin, dexamethasone, phenytoin, and carbamazepine) should be avoided. Concomitant use of MRP2 inhibitors (e.g. cyclosporine, efavirenz, emtricitabine) may increase cabozantinib plasma concentrations. Cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan). Because of high plasma protein binding levels of cabozatinib interaction with warfarin is possible, monitor INR. Caution should be used in patients receiving agents associated with ONJ, such as bisphosphonates. • **Missed dose**: If a dose is missed, the missed dose should not be taken if it is less than 12 hours before the next dose. • **Driving and operating machinery:** Fatigue and weakness have been associated with cabozantinib, patients should be advised to be cautious when driving or operating machines. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet.
References	SPC accessed online 14.11.2022 Blueteq form and CDF list V1.238 accessed online 14.11.2022 KMCC Protocol RCC-007 V2

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1: Recommended dose modifications for adverse reactions

Adverse reaction and severity	**Treatment modification**
Grade 1 and grade 2 adverse reactions which are tolerable and easily managed	Dose adjustment is usually not required. Add supportive care as indicated.
Grade 2 adverse reactions which are intolerable and cannot be managed with a dose reduction or supportive care	Interrupt treatment until the adverse reaction resolves to grade ≤1. Add supportive care as indicated. Consider re-initiating at a reduced dose.
Grade 3 adverse reactions (except clinically nonrelevant laboratory abnormalities)	Interrupt treatment until the adverse reaction resolves to grade ≤1. Add supportive care as indicated. Re-initiate at a reduced dose.
Grade 4 adverse reactions (except clinically nonrelevant laboratory abnormalities)	Interrupt treatment. Institute appropriate medical care. If adverse reaction resolves to grade ≤1, re-initiate at a reduced dose. If adverse reaction does not resolve, permanently discontinue.

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE v4)

Repeat every 28 days

TTO	Drug	Dose	Route	Directions
Day 1	**CABOZANTINIB (Cabometyx®)**	**60mg**	PO	OD Swallow whole, do not crush. To be taken on an empty stomach (do not eat anything for at least 2 hours before dose and for 1 hour after). Available as 20mg, 40mg and 60mg tablets.
	Metoclopramide	10mg	PO	10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Loperamide	2mg-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if specified.