Systemic Anti Cancer Treatment Protocol

CABOZANTINIB (Cabometyx) in Renal Cell Carcinoma

PROCTOCOL REF: MPHACABCA
(Version No: 1.3)

Approved for use in:

The protocol has been temporarily amended – please see the Oral SACT Operational Changes during Covid-19. Amendments may include less frequent blood monitoring, telephone SACT assessments and longer durations of treatment being dispensed.

Cabozantinib is indicated for the treatment of advanced renal cell carcinoma (RCC) in:

a) treatment-naïve, intermediate or poor risk patient
b) patients who have previously been treated for advanced RCC

Blueteq registration required

Dosage:

Drug	Daily dosage	Route	Schedule
Cabometyx tablets	60 mg once daily	Oral	Daily, until disease progression.

Cabometyx (cabozantinib) tablets and Cometriq (cabozantinib) capsules are not bioequivalent and should **not** be used interchangeably.

Supportive Treatments:

- Metoclopramide 10mg TDS prn
- Loperamide 2mg prn as indicated

Administration/directions:

The tablets should be swallowed whole and not crushed. Patients should be instructed to not eat anything for at least 2 hours before and for 1 hour after taking cabozantinib. If a dose is missed, it should not be taken if it is less than 12 hours before the next dose would be due.

Interactions with other medicinal products

Concomitant medicinal products that are strong inhibitors of CYP3A4 should be used with caution, and chronic use of concomitant medicinal products that are strong inducers of CYP3A4 should be avoided (see SPC for more information).

P-glycoprotein substrates

Cabozantinib was an inhibitor of P-gp may increase plasma concentrations of substrates of P-gp (e.g. fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan).

Prolongation of QT interval

Use with caution in patients with a history of QT interval prolongation, patients who are taking anti-arrhythmics, or those with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using cabozantinib, periodic monitoring with on-treatment ECGs and electrolytes (serum calcium, potassium, and magnesium) should be considered.

Additional information

No dose adjustment is indicated when gastric pH modifying agents (i.e. PPIs, H2 receptor antagonists, and antacids) are co-administered with cabozantinib.

Cabozantinib's effect on contraceptive steroids is unknown and their effectiveness cannot be guaranteed.

Review all other medications for potential drug-drug interactions

Principle of Dose Modifications and management of Toxicities:

Recommended management of adverse reactions	
Grade 1 and Grade 2 adverse reactions which are tolerable and easily managed	Supportive care as indicated, dose adjustment is usually not required.
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 non relevant 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 non relevant laboratory abnormalities)	Interrupt treatment. Appropriate medical care. If adverse reaction resolves to Grade ≤1, re-initiate at a reduced dose. If adverse reaction does not resolve, permanently discontinue treatment

Please refer to the 'Oral TKI toxicity decision aid' on the extranet.

Cabozantinib dose level	New Dose
1st dose reduction	40mg
2nd dose reduction	20mg

Hepatic impairment
Mild or moderate hepatic impairment the recommended dose is 40 mg once daily. Patients should be monitored for adverse events and dose adjustment or treatment interruption should be considered as needed. Not recommended for patients with severe hepatic impairment as safety and efficacy have not been established in this population.

Renal impairment
Used with caution in patients with mild or moderate renal impairment. Not recommended for use in patients with severe renal impairment.

Hypertension	Hypertension is a known class effect of this drug and patients should be monitored closely and treated as appropriate. The choice of antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice.There is no firm data on optimal management of hypertension induced by blockade of VEGF signalling and as such treatment according to national guidelines for essential hypertension is recommended. Thiazide diuretics, beta-blockers, ACE inhibitors, angiotensin receptor blockers and dihydropyridine calcium channel antagonists (amlodipine and felodipine) are all reasonable first line agents depending on the patient's co-morbidities. Decision should not be based on single elevated BP reading and should be based on repeated evidence of elevation to eliminate possible contribution from 'white coat syndrome'. Patient should be advised to involve their GP for regular monitoring and if necessary treatment. Serial home BP monitoring can provide additional useful information. *Systolic 140-150 mmHg or Diastolic <90 mmHg:* -Continue treatment but need to monitor blood pressure closely and follow relevant steps as necessary. *Systolic 150-160mmHg or Diastolic 90-100mmgh:* -Continue treatment at same dose. -Repeat BP at GP, treatment needed if remained elevated or higher. -Continue with vigilant BP monitoring until BP <140/90mmHg. *Systolic 160-180 mmHg or diastolic 100-110 mmHg (at least 2 readings 30 minutes apart):* -Continue treatment at same dose -Instigate BP treatment, to be reviewed at GP within 5 days. -Continue with vigilant BP monitoring until BP <140/90mmHg. *Severe hypertension (>200mmHg systolic or >110mmHg diastolic)* Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment at reduced dose may be resumed once hypertension is appropriately controlled. Consider referral to cardiologist if refractory cases despite these steps. ****Verapamil and diltiazem should be avoided due to their inhibition of CYP3A4 enzymes.** NICE Clinical Guideline NG 127- Hypertension in adults diagnosis and management: https://www.nice.org.uk/guidance/ng136

GI disorder	Diarrhoea, nausea/vomiting, abdominal pain, dyspepsia and stomatitis/oral pain are the most commonly reported gastrointestinal adverse reactions. **Diarrhoea:** Grade 1 and 2 can be managed with supportive measures at home and with the use of anti-diarrhoeal medication such as Loperamide 2mg after each stool if necessary. Treatment break or dose changes may not be required if symptoms improved to Grade 1 or less quickly with simple measures. Grades 3 and 4 will need treatment interruption until improvement to Grade 1 or less. 1 step dose reduction is required. Advise the patient to avoid any exacerbating foods and to eat small high carbohydrate meals. Also to drink plenty of water and to record the daily stool frequency. Severe presentation may need admission if also associated with any of the following: nausea/vomiting, cramping, fever, sepsis, neutropenia or dehydration. **Nausea:** cyclizine is usually satisfactory. Nausea often settles with habituation to the drug. Administration just before bedtime can help ameliorate this side-effect.
Perforations, fistulas, intra-abdominal abscesses.	Serious GI perforations and fistulas have been observed. Patients at risk should be evaluated carefully before commencing therapy.
Wound complication	Treatment should be stopped at least 28 days prior to surgery
Haemorrhage	Patients with involvement of the trachea or bronchi by tumour or history of haemoptysis prior to treatment should be carefully evaluated before commencing therapy
Thromboembolic events	Venous and arterial thromboembolisms have been observed with Cabozantinib. Discontinue in patients who develop an acute MI or clinically significant arterial complications.
Skin and tissue disorders	The patients should be advised to avoid hot water and to wear gloves when performing housework. Use simple moisturising creams to keep the skin moist and limit peeling
Cardiovascular	Use in caution in patients with history of QT interval prolongation, patients taking antiarrhythmics or relevant pre-existing cardiac disease or electrolyte disturbances. Periodic monitoring should be considered.
Endocrine, metabolism and nutrition disorders	Hypothyroidism, decreased appetite, hypocalcaemia, hypophosphataemia, hypomagnesemia hyperbilirubinemia, hypoalbumenia and dehydration. Regularly review and treat as indicated.
Osteonecrosis of the jaw	For invasive dental procedures, cabozantinib should be held at least 28 days prior to scheduled surgery, if possible.

Proteinuria	Monitor as clinically indicated during treatment. Discontinue cabozantinib in patients who develop nephrotic syndrome
Additional side effects	Immunosuppression, fatigue and muscle spasms are also common side effects. Seizures, headaches and confusion may be signs of a serious but uncommon side effect of RPLS (reversible posterior leukoencephalopathy syndrome)

Investigations and treatment plan:

Cycle	Pre	C1		C2		C3		C4	Ongoing
Week		***1***	***3***	***5***	***7****	***9***	***11-12***	***13***	→
Informed Consent	X								
Clinical Assessment	X		X		X		x		Every 12 weeks thereafter
SACT Assessment (including PS and toxicities)	x	X		X		X		X	Every cycle
FBC	X		X	X	X	X		X	Every cycle
U&E & LFTs	X		X	X	X	X		X	Every cycle
Thyroid function tests	X					X			Every 8 weeks
CT scan	X						X		Every 12 weeks
Blood pressure measurement	X	X	X	X	X	X	X	X	Every Cycle
Weight recorded	X	X	X	X	X	X	X	X	Every cycle
Height recorded	X								
Urine dipstick for protein									As clinically indicated
ECG									As clinically indicated

Week 7 assessment may not be required depending on patient progress/need

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

Please contact clinician to inform them if the patients bloods do not meet the requirements.

References:

1. Cabometyx 20mg, 40mg, 60mg 190 Bath Road, Slough, Berkshire, Available from: https://www.medicines.org.uk/emc/product/7631/smpc Accessed December 2019

2. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR study) Choueiri TK et al. Lancet Oncology 2016 17:917-27

3. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update Choueiri, Toni K. et al.European Journal of Cancer, Volume 94, 115 – 125

4. NHS England. National Drugs Fund (CDF) list. Available from https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/ Accessed: December 2018

5. NICE NG136. Available from: https://www.nice.org.uk/guidance/ng136. Accessed September 2019