Cabozantinib (Cabometyx®)

Indication

Treatment of advanced renal cell carcinoma following prior vascular endothelial growth factor (VEGF) targeted therapy.

(NICE TA463)

Treatment of previously untreated advanced renal cell carcinoma that is intermediate- or poor-risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria.

(NICE TA542)

ICD-10 codes

Codes with a prefix C64

Regimen details

Day	Drug	Dose	Route
1-28	Cabozantinib	40-60mg OD*	PO

* consider starting at 40mg OD and escalating the dose to 60mg OD if well tolerated.

Cycle frequency

Every 4 weeks i.e. continuous treatment

Number of cycles

Continue until disease progression or unacceptable toxicity.

Administration

Cabozantinib is available as 20mg, 40mg and 60mg tablets. Tablets should be swallowed whole and not crushed. Patients should not eat for at least two hours before or one hour after administration. If a dose is missed the patient should not take it if it is less than 12 hours before the next dose is due.

Cabozantinib tablets are available as the Cabometyx® brand. Cabozantinib capsules (Cometriq®) are not bioequivalent and should not be used for this indication.

Grapefruit and grapefruit juice should be **avoided** whilst taking cabozantinib.

Pre-medication

Nil

Emetogenicity

This regimen has mild emetic potential (no routine antiemetics required)

Additional supportive medication

Loperamide if required.
Patients should be advised to apply regular moisturiser to their hands and feet throughout treatment to minimise the risk of developing PPE.

Extravasation

N/A

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+Es (including creatinine)	14 days
LFTs	14 days
Calcium	14 days
Magnesium	14 days
Thyroid function	14 days
Blood pressure	Must be controlled before initiating treatment

ECG if patient has significant cardiac history.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	Every 2 weeks for the first 8 weeks then monthly
U+E (including creatinine)	Every 2 weeks for the first 8 weeks then monthly
LFTs	Every 2 weeks for the first 8 weeks then monthly (or as clinically indicated)
Calcium	Every 2 weeks for the first 8 weeks then monthly
Magnesium	Every 2 weeks for the first 8 weeks then monthly
Thyroid function	Every 12 weeks
Blood pressure	Weekly for first cycle then prior to each cycle

Periodic urinalysis to monitor for proteinuria.
ECG if patient has significant cardiac history.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 50 x 10^9/L
Creatinine clearance (CrCl)	> 60mL/min (see advice below)
AST/ALT	< ULN
Bilirubin	< ULN

Dose modifications

If dose reductions are required the dose should be reduced as per table below:

Dose level	**Cabozantinib dose**
Full dose	60mg OD
1st dose reduction	40mg OD
2nd dose reduction	20mg OD

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L or platelets < 50 x 10^9/L discuss with consultant.

- **Renal impairment**

Cabozantinib should be used with caution in mild-moderate renal impairment (CrCl 30-60mL/min) and is not recommended for use in severe renal impairment (CrCl < 30mL/min) due to a lack of safety data.

- **Hepatic impairment**

In mild-moderate hepatic impairment the recommended dose is 40mg OD and patients should be monitored closely for adverse events. Cabozantinib is not recommended for use in severe hepatic impairment due to a lack of safety data.

- **Other toxicities**

Adverse reaction	**Cabozantinib dose**
Grade 1 and Grade 2 - tolerable	Dose adjustment is usually not required. Add supportive care as indicated.
Grade 2 - intolerable and cannot be managed with a dose reduction or supportive care	Interrupt treatment until resolves to Grade ≤1. Add supportive care as indicated. Consider re-commencing at reduced dose.
Any Grade 3	Interrupt treatment until resolves to Grade ≤1. Add supportive care as indicated. Re-commence at reduced dose.
Any Grade 4	Interrupt treatment. Institute appropriate medical care. If adverse reaction resolves to Grade ≤1, re-commence at reduced dose. If adverse reaction does not resolve, permanently discontinue treatment.

Cardiovascular:
Cabozantinib should be used with caution in patients with cardiac impairment or a history of QT prolongation. Treatment should be discontinued in patients who develop an acute MI.

Surgery/dental work:
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.

Hypertension:
Blood pressure should be well controlled prior to commencing treatment. All patients must be monitored for hypertension and should be treated with anti-hypertensives as appropriate. If hypertension is persistent a dose reduction may be required. Cabozantinib should be discontinued if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of cabozantinib. In case of hypertensive crisis, cabozantinib should be discontinued.

Hepatic effects:
Abnormalities of LFTs (increases in ALT/AST and bilirubin) have been frequently observed in patients treated with cabozantinib. It is recommended to perform liver function tests (ALT, AST and bilirubin) before initiation of cabozantinib treatment and to monitor closely during treatment. For patients with worsening LFTs considered to be related to cabozantinib treatment (where no alternative cause is evident), dose reductions should be considered as per table above.

Haemorrhage:
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.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
RPLS (reversible posterior leukoencephalopathy syndrome)
GI perforation, fistula
QT interval prolongation
Thyroid dysfunction
Proteinuria, nephrotic syndrome
Arterial and venous thrombotic events
Haemorrhage
Impaired wound healing
Hepatic encephalopathy, abnormalities of LFTs

- **Frequently occurring side effects**

Myelosuppression
Epistaxis
Hypertension
Electrolyte disturbances
Diarrhoea, constipation
Nausea, vomiting
Stomatitis
PPE
Arthralgia

- **Other side effects**

Skin and hair changes
Taste disturbances
Anorexia
Fatigue
Headache
Dizziness
Tinnitus

Significant drug interactions – for full details consult product literature/ reference texts

CYP3A4 inhibitors (e.g. ketoconazole, voriconazole, itraconazole, clarithromycin, ritonavir): avoid co-administration - may increase plasma concentrations of cabozantinib.

Grapefruit and grapefruit juice: avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of cabozantinib.

Inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort): avoid co-administration - may reduce exposure to cabozantinib.

MRP 2 inhibitors (e.g. cyclosporine, efavirenz, emtricitabine): administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations.

Bile salt-sequestering agents (e.g. cholestyramine and cholestagel): may interact with cabozantinib resulting in potentially decreased exposure.

P-gp substrates (e.g. fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan): cabozantinib may have the potential to increase plasma concentrations therefore P-gp substrates should be used with caution.

Contraceptives: The effect of cabozantinib on contraceptive steroids has not been investigated. As contraceptive effect may not be guaranteed, an additional contraceptive method, such as a barrier method, is recommended.

Additional comments

Women of childbearing potential must be advised to avoid pregnancy while on cabozantinib. Female partners of male patients taking cabozantinib must also avoid pregnancy. Effective methods of contraception should be used by male and female patients and their partners during therapy, and for at least 4 months after completing therapy. Because oral contraceptives might possibly not be considered as effective methods of contraception (see above), they should be used together with another method, such as a barrier method.

References

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- Summary of Product Characteristics – Cabozantinib – Cabometyx ® (Ipsen) accessed 5 December 2018 via www.medicines.org.uk
- Choueiri TK et al. METEOR study –Cabozantinib versus everolimus in advanced renal cell carcinoma. Lancet Oncology 2016 17:917-27
- Choueiri TK et al. Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. J Clin Oncol. 2017 Feb 20;35(6):591-597

Written/reviewed by: Dr A Bahl (Consultant Oncologist UHBristol NHS Trust) Dr M Beresford (Consultant Oncologist RUH Bath NHS Trust), Dr A Challapalli (Consultant Oncologist UHBristol NHS Trust) Dr S Hilman (Consultant Oncologist UHBristol NHS Trust), Dr J Mason (Consultant Oncologist RUH Bath NHS Trust), Dr S Masson (Consultant Oncologist UHBristol NHS Trust), Dr M Sephton (Consultant Oncologist RUH Bath NHS Trust)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Clinical Network)

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