Cabozantinib Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
The treatment of advanced renal cell carcinoma (RCC) in adults following prior VEGF targeted therapy.	C64	00518a	CDS 02/01/2019

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Drug	Dose	Route	Cycle
Cabozantinib	60mg once daily	PO Patient should not eat two hours prior or one hour after taking a dose	Continuous
Missed doses: If a patient misses a dose, the missed dose should not be taken if it is less than 12 hours before the next dose			

ELIGIBILITY:

- Indications as above
- Advanced or metastatic renal-cell carcinoma with a clear cell component
- Aged 18 years or older
- ECOG 0-2
- Patients must have received prior treatment with at least one VEGFR-targeting tyrosine kinase inhibitor
- Adequate organ and marrow function

EXCLUSIONS:

- Hypersensitivity to cabozantinib or any of the excipients
- Previous therapy with an mTOR inhibitor or cabozantinib

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal, liver and bone profile
- Blood glucose
- Urinary Protein
- Thyroid Function
- Blood Pressure
- ECG

Regular tests:

- FBC, renal, liver and bone profile monthly
- Urinary protein monthly
- Thyroid function monthly
- Blood pressure monthly
- ECG as clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Dose reductions are detailed in Table 1

Table 1: Dose reductions for cabozantinib

Dose Level	Dose
Starting Dose	60mg
First dose reduction	40mg
Second dose reduction	20mg
Third dose reduction	Discontinue

Renal and Hepatic Impairment:

Table 2: Dose modification of cabozantinib in renal and hepatic impairment

Renal Impairment	Dose	Hepatic Impairment	Dose
Mild/Moderate	Use with caution	Mild	No dose adjustment is required
		Moderate	Since only limited data are available, no dosing recommendation can be provided. Close monitoring is recommended.
Severe	Not recommended	Severe	Not recommended

Management of adverse events:

Table 3: Dose Modification of cabozantinib for Adverse Events

Adverse reactions	Recommended dose modification
Grade 1 and Grade 2 adverse reactions which are tolerable and easily managed	Dose adjustment is usually not required. Consider adding 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 cabozantinib

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal-Low (**Refer to local policy).**

PREMEDICATIONS: None

OTHER SUPPORTIVE CARE:
No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

As most events can occur early in the course of treatment, the physician should evaluate the patient closely during the first eight weeks of treatment to determine if dose modifications are warranted. Events that generally have early onset include hypocalcaemia, hypokalaemia, thrombocytopenia, hypertension, palmar-plantar erythrodysaesthesia syndrome (PPES), proteinuria, and gastrointestinal (GI) events (abdominal pain, mucosal inflammation, constipation, diarrhoea, vomiting).

- **Hypertension:** Hypertension has been observed with cabozantinib. Blood pressure should be well-controlled prior to initiating cabozantinib. During treatment with cabozantinib, all patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensives, the cabozantinib dose should be reduced. 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.

- **Perforations and fistulas:** Serious gastrointestinal (GI) perforations and fistulas, sometimes fatal, have been observed with cabozantinib. Patients who have inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, peritonitis, diverticulitis, or appendicitis), have tumour infiltration in the GI tract, or have complications from prior GI surgery (particularly when associated with delayed or incomplete healing) should be carefully evaluated before initiating cabozantinib therapy and subsequently they should be monitored closely for symptoms of perforations and fistulas including abscesses and sepsis. Persistent or recurring diarrhoea while on treatment may be a risk factor for the development of anal fistula. Cabozantinib should be discontinued in patients who experience a GI perforation or a fistula that cannot be adequately managed.
- **Thromboembolic events:** Events of venous thromboembolism, including pulmonary embolism, and events of arterial thromboembolism have been observed with cabozantinib. Cabozantinib should be used with caution in patients who are at risk for, or who have a history of, these events. Cabozantinib should be discontinued in patients who develop an acute myocardial infarction or any other clinically significant arterial thromboembolic complication.
- **Haemorrhage**: Severe haemorrhage 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.
- **Proteinuria:** Urine protein should be monitored regularly during cabozantinib treatment. Cabozantinib should be discontinued in patients who develop nephrotic syndrome.
- **Wound complications:** 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.
- **Prolongation of QT interval:** Cabozantinib should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using cabozantinib, periodic monitoring with on-treatment ECGs and electrolytes (serum calcium, potassium, and magnesium) should be considered.
- **Palmar-plantar erythrodysaesthesia syndrome** (PPES): This has been observed with cabozantinib. When PPES is severe, interruption of treatment with cabozantinib should be considered. Cabozantinib should be restarted with a lower dose when PPES has been resolved to grade 1.
- **Reversible posterior leukoencephalopathy syndrome:** Reversible Posterior Leukoencephalopathy Syndrome (RPLS), also known as Posterior Reversible Encephalopathy Syndrome (PRES), has been observed with cabozantinib.
- **Aneurysms and artery dissections:** The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating cabozantinib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.
- **Osteonecrosis of the jaw (ONJ):** ONJ has been observed with cabozantinib. An oral examination should be performed prior to initiation of cabozantinib and periodically during cabozantinib therapy. Patients should be advised regarding 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.

- **Excipient related warnings**: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take cabozantinib.

DRUG INTERACTIONS:

- 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. Selection of an alternative concomitant medicinal product with no or minimal potential to induce or inhibit CYP3A4 should be considered.
- Caution should be used in patients receiving agents associated with ONJ, such as bisphosphonates.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1 Choueiri TK, Escudier B, Powles T et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial; Lancet oncol. 2016; 17(7): 917-927

2 Choueiri TK, Escudier B, Powles T et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma New Engl J Med 2015; 373: 1814-1823

3 NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

4 Cabometyx Tablets SmPC EMA Accessed Dec 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/cabometyx-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	18/12/2018		Prof Ray McDermott
2	06/01/2021	Amended hepatic impairment dose modification, adverse effects and drug interactions	Prof. Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.