REGIMEN TITLE: Cabozantinib in Thyroid carcinoma

Indication: Medullary thyroid carcinoma
NHS England CDF criteria to be met (CDF funding approval required):
• First cycle to be prescribed by a consultant specialist specifically trained and accredited in the use of SACT
• Unresectable, locally advanced or metastatic thyroid cancer
• Progressive, symptomatic disease
• No previous treatment with a TKI or intolerant to vandetanib (i.e. patients developing serious drug toxicity within 3 months of starting vandetanib which could not be managed with a dose delay or reduction and who have also NOT progressed on vandetanib)

Patient must be able to tolerate and comply with oral dosage forms

Notes: Electrolyte imbalances (Ca, K, Mg, Phosphate) should be corrected before starting the treatment.
Existing hypertension should be well controlled before starting treatment.

Regimen details: Cabozantinib 140mg PO Once daily Continuous therapy
First dose reduction: 100mg PO Once daily
Second dose reduction: 60mg PO Once daily
Note: no other dose variations are permitted

Pack size: Available as 80mg and 20mg film-coated tablets
Three pack sizes are available with significant cost differences. Please ensure the most appropriate size is selected for the patients dose.
For the 60mg dose supply pack containing: 84 x 20mg capsules
For the 100mg dose supply the pack containing: 28 x 80mg and 28 x 20mg capsules
For the 140mg dose supply to pack containing 28 x 80mg and 84 x 20mg capsules

Administration: Capsules should be taken on an empty stomach, 1 hour before food or 2 hours after food at the same time each day.
Swallow whole with a glass of water.

If a dose is missed it should be taken immediately but only if it is more than 12 hours before the next dose is due.

Frequency: Prescribed in 4 week cycles - continued until disease progression or unacceptable toxicity

Anti-emetics: Mildly emetogenic

Supportive medication: Diarrhoea can be managed with loperamide – 2mg PRN (max. 16mg/day).
Mouthwashes according to local mouth care guidance if needed.
Regular investigations:

- LFTs Prior each cycle
- FBC Prior each cycle
- U&Es Prior each cycle
- K+, Ca, Mg, PO4- Baseline, weeks 2, 4, 8 and 12 after starting, then every 3 months
- ECG (QTc) Baseline, weeks 2, 4, 8 and 12 after starting, then every 3 months
- Blood pressure Prior each cycle
- Thyroid function Baseline, weeks 2, 4, 8 and 12 after starting, then every 3 months
- RET mutation status Record when available
- Oral examination Baseline then periodically (see non-haematological toxicities)

Comments: To be supplied to the patient for oral self-administration. Ensure that the patient has an information pack and the treatment plan.

Adequate contraception methods should be applied during and for at least 4 months after the completion of therapy.

Fertility preservation may be considered although no strong evidence exists to suggest cabozantinib has any effect on fertility.

Toxicities: QTc interval prolongation and other cardiac effects (atrial fibrillation, ventricular tachycardia, angina), posterior reversible leucoencephalopathy syndrome (RPLS), haemorrhage, osteonecrosis of the jaw, thromboembolic events, skin reactions (acne, dry skin, dermatitis, pruritis, alopecia), PPE, diarrhoea, hypertension, ALT elevations, infection, headache, hypothyroidism, decreased appetite, depression, eye disorders, GI symptoms, proteinuria, fatigue

Precautions and Dose Modifications

When dose reduction of cabozantinib is necessary due to any toxicity, the cabozantinib dose may be reduced to 100 mg daily and further to 60mg daily. (See above under pack size for the appropriate pack size to supply)

Haematological toxicity

Baseline levels

- Neutrophils ≥ 1.5 x 10^9/L
- Platelets ≥ 100 x 10^9/L 100% dose

Discuss lower than normal haematological findings and treatment doses with consultant.
Non-Haematological Toxicity

Generally dose should be withheld in any grade 3 or higher toxicity or intolerable grade 2 toxicity, and resumed with reduced dosing level after toxicity has improved to grade 1.

Toxicity is more commonly observed in patients aged 75 years and older.

QT interval change

Cabozantinib should be used with caution in patients with a history of QT prolongation, patients who are taking anti-arrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. ECG QTc interval should not be greater than 480 msec.

Serum calcitonin level should be ≥500pg/ml.

Posterior reversible encephalopathy syndrome, PRES (Reversible posterior leukoencephalopathy syndrome-RPLS)

PRES is a syndrome of subcortical vasogenic oedema diagnosed by a MRI of the brain. PRES has been observed in patients receiving carbozantinib. This syndrome should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Brain MRI should be performed in any patient presenting with seizures, confusion or altered mental status. Discontinue cabozantinib if PRES is diagnosed.

Perforations, fistulas and intraabdominal abscesses

Serious and sometimes fatal perforations, fistulas and intraabdominal abscesses have been observed with cabozantinib. Treatment should be discontinued in patients who experience a GI perforation or a GI or non-GI fistula.

Osteonecrosis of the jaw

Events of osteonecrosis of the jaw (ONJ) have 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. For invasive dental procedures, cabozantinib treatment should be held at least 28 days prior to scheduled surgery, if possible. Caution should be used in patients receiving agents associated with ONJ, such as bisphosphonates. Cabozantinib should be discontinued in patients who experience ONJ.

Diarrhoea

Stop treatment in Grade 3 diarrhoea. Re-start with a reduced dose once diarrhoea has subsided.

Hypertension

Blood pressure should be well controlled prior to initiating cabozantinib.

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-hypertensive medicinal products, consider cabozantinib dose reduction. For patients who
develop severe hypertension despite dose reduction and antihypertensives, cabozantinib should be discontinued.

**Hand-foot symptoms** Encourage regular use of moisturizers to hand and feet regularly. Advise minimizing activities that put pressure on feet or hands, as usually the pressure point areas are affected. Keeping skin cool is beneficial, avoiding extreme heat (such as strong sunlight or hot baths). Support use of non-deodorant, non-fragrance products. Consider products with anti-itch additions in pruritus, and exfoliating urea containing products in hyperkeratosis. Anti-dandruff shampoo may help in management of itchy scalp. Non-steroidal anti-inflammatory creams and analgesia may help but a 1-2 week dose interruption may be necessary for painful symptoms.

**Renal Impairment** Carbozantinib should be used with caution in renal impairment. It should be avoided in severe renal impairment.

**Hepatic Impairment** Carbozantinib is not recommended for use in patients with hepatic impairment.

**Drug interactions:**

Concurrent use of CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampicin, barbiturates, dexamethasone, St John’s Wort) can decrease carbozantinib plasma concentration and reduce efficacy.

Concurrent use of CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, grapefruit juice) can increase carbozantinib plasma concentration and increase toxicity.

Cabozantinib is an inhibitor of P-glycoprotein (P-gp) therefore it may increase plasma concentrations of P-gp substrates. Use with caution in patients taking P-gp substrates (e.g. posaconazole, fexofenadine, digoxin, dabigatran, cholchicine).

The effect of proton pump inhibitors on the gastrointestinal absorption of carbozantinib has not been determined. Carbozantinib demonstrates pH dependent solubility; therefore the co-administration of carbozantinib with proton pump inhibitors may reduce a patient’s exposure to carbozantinib. The concomitant use with these therapeutic classes is therefore not recommended.

**References:**

www.medicines.org.uk