Cabozantinib (Cometriq®)

Indication	The treatment of metastatic or inoperable locally advanced medullary thyroid cancer The patient should be treatment naïve to both cabozantinib and vandetanib unless the patient has had to discontinue vandetanib within 3 months of starting vandetanib because of toxicity and there has been no disease progression whilst on vandetanib. **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 or unacceptable toxicity or patient choice Formal medical review to decide whether treatment should continue or not by the end of the first 8 weeks of treatment
Monitoring parameters pre-treatment	Investigations: • Monitor FBC, U&Es, LFTs every 2 weeks for the first 2 cycles and then prior to each cycle. In particular monitor potassium, calcium, phosphate & magnesium. 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, the cabozantinib dose should be reduced. 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). Hepatic impairment: For patients with mild to moderate hepatic impairment (Child Pugh A or B) the recommended dose is 60mg once daily. Patients should be monitored for adverse events and dose adjustment or treatment interruption should be considered as needed. See SPC for further information. Cabozantinib is not recommended for use in patients with severe hepatic impairment. Adverse reactions: • 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), and gastrointestinal (GI) events). • The most common serious adverse reactions are pneumonia, mucosal inflammation, hypocalcaemia, dysphagia, dehydration, pulmonary embolism, and hypertension. • Dose interruptions - Suspected adverse drug reactions may require treatment interruption and/or dose reduction (see table 1). When dose reduction is necessary, it is recommended to reduce to 100 mg daily, then to 60 mg daily. Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or

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	intolerable grade 2 toxicities. Dose reductions are recommended for events that, if persistent, could become serious or intolerable. • Permanently discontinue in the event of the following: Cabozantinib should be permanently discontinued if there is: development of unmanageable fistula or GI perforation, arterial thromboembolic event (eg, myocardial infarction, clinically significant arterial thromboembolic complication), serious haemorrhage or recent haemoptysis, wound healing complications, hypertensive crisis or severe hypertension despite optimal medical management, osteonecrosis of the jaw, nephrotic syndrome or reversible posterior leukoencephalopathy syndrome. • Patients should be advised to use regular emollients on their skin (particularly their hands and feet). If a dose is missed, the missed dose should not be taken if it is less than 12 hours before the next dose Drug / food interactions: Cabozantinib is a CYP3A4 substrate. Concomitant medicinal products that are strong inhibitors of CYP3A4 (e.g (e.g ketoconazole, itraconazole, clarithromycin, grapefruit juice) should be used with caution, and chronic use of concomitant medicinal products that are strong inducers of CYP3A4 (e.g (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). 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. • 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. • 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 judgement of adequate wound healing. Cabozantinib should be discontinued in patients with wound healing complications requiring medical intervention. • 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.
Reference(s)	SpC accessed online 06/03/18

NB For funding information, refer to the SACT funding spreadsheet

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Repeat every 28 days

Day	Drug	Dose	Route	Administration Details
	Cabozantinib (Cometriq®)	140mg	po	od Swallow whole, do not crush. To be taken on an empty stomach (at least 2 hours after food or 1 hour before food).
TTO	Drug	Dose	Route	Directions
	Metoclopramide	10mg	po	up to 3 times a day for 3 days, then 10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	Loperamide	2-4mg	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.

Table 1: Recommended COMETRIQ 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. 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.