LENVATINIB compassionate use (Lenvima®)

For the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine

Drug/Dosage: **Lenvatinib** initiate at 24mg po once daily, as continuous therapy

Administration: Lenvatinib is available as 10mg and 4 mg capsules, brand name Lenvima®.
Swallow whole with water, with or without food.

Frequency: continue for as long as there is clinical benefit, or unacceptable toxicity.

Main Toxicities: hypertension; proteinuria; diarrhoea; nausea; stomatitis; PPE; dysphonia; headache

Anti- emetics: mildly emetogenic (avoid domperidone)

Regular: Investigations:		
	FBC	every 4 weeks
	LFTs	every 4 weeks
	U&Es	every 4 weeks
	Blood pressure	after 1 week, then every 2 weeks for the first 2 months, then monthly
	Proteinuria	baseline, after 1 month, then as indicated
	QT interval	baseline, after 1 month, then periodically as indicated
	Thyroid function	baseline, then periodically as indicated

Comments: Ensure patient has a supply of loperamide and metoclopramide.

Patients should be advised to apply moisturiser to their hands and feet regularly throughout treatment, and to minimise activities that put pressure on feet or hands if they start to develop sore hands or feet. Recommended moisturisers are Udderly Smooth or urea-containing moisturisers eg Eucerin.

There is no data available regarding interactions with lenvatinib.

Lenvatinib has been shown to prolong the QT interval, so use with caution in patients taking other medicines that lead to QT prolongation (e.g. amiodarone, quinidine, sotalol, chloroquine, clarithromycin), and those with electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia. When using lenvatinib in these patients, periodic ECG, plus monitoring of magnesium and calcium should be considered.

Dose Modifications Management of adverse reactions may require dose interruption, dose reduction, or discontinuation of lenvatinib therapy.
Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of lenvatinib, unless intolerable to the patient despite optimal management.
Severe (e.g. Grade 3) or intolerable adverse reactions require interruption of lenvatinib until improvement of the reaction to Grade 0-1 or baseline.
For lenvatinib related toxicities (see below), upon resolution/improvement of an adverse reaction to Grade 0-1 or baseline, treatment should be resumed at a reduced dose of lenvatinib.

Reason for Update: N/A	Approved by Consultant: Dr S Whitaker
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Supersedes: None	Date: 3.5.17
Prepared by: S Taylor	Checked by: C Tucker

Dose modifications from recommended lenvatinib daily dose

Dose level	Daily dose
Recommended daily dose	24 mg orally once daily
First dose reduction	20 mg orally once daily
Second dose reduction	14 mg orally once daily
Third dose reduction	10 mg orally once daily[a]

[a:] Further dose reductions should be considered on an individual patient basis as limited data are available for doses below 10 mg.

Treatment should be discontinued in case of life-threatening reactions (e.g., Grade 4) with the exception of laboratory abnormality judged to be non-life-threatening, in which case they should be managed as severe reaction (e.g. Grade 3).

Adverse reactions requiring dose modification of lenvatinib			
Adverse reaction	**Severity**	**Action**	**When to resume lenvatinib at next step dose reduction**
Hypertension	Grade 3 (despite optimal antihypertensive therapy)	Interrupt	Resolves to Grade 0, 1 or 2. See detailed guidance below
	Grade 4	Discontinue	Do not resume
Proteinuria	≥ 2 gm / 24 hours	Interrupt	Resolves to less than 2 gm / 24 hours.
Nephrotic syndrome	-------	Discontinue	Do not resume
Renal impairment or failure	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume
Cardiac dysfunction	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume
PRES/RPLS	Any grade	Interrupt	Consider resuming at reduced dose if resolves to Grade 0-1.
Hepatotoxicity	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume
Arterial thromboembolisms	Any grade	Discontinue	Do not resume
Haemorrhage	Grade 3	Interrupt	Resolves to Grade 0-1.
	Grade 4	Discontinue	Do not resume
GI perforation or fistula	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume
Non-GI fistula	Grade 4	Discontinue	Do not resume
QT prolongation	>500 ms	Interrupt	Resolves to <480 ms or baseline
Diarrhoea	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4 (despite medical management)	Discontinue	Do not resume

*Grade 4 laboratory abnormalities judged to be non-life-threatening, may be managed as severe reactions (e.g., Grade 3)

Hypertension: Blood pressure (BP) should be well controlled prior to starting. If patients are known to be hypertensive, they should be on a stable dose of antihypertensive therapy for at least 1 week prior to starting.
The early detection and effective management of hypertension are important to minimise the need for lenvatinib dose interruptions and reductions. Antihypertensive agents should be started as soon as elevated BP is confirmed.
BP should be monitored after 1 week of treatment with lenvatinib, then every 2 weeks for the first 2 months, and monthly thereafter.
The choice of antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice.

Recommended management of hypertension

Blood Pressure (BP) level	**Recommended action**
Systolic BP ≥140 mmHg up to <160 mmHg or diastolic BP ≥90 mmHg up to <100 mmHg	Continue lenvatinib and initiate antihypertensive therapy, if not already receiving OR Continue lenvatinib and increase the dose of the current antihypertensive therapy or initiate additional antihypertensive therapy
Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg despite optimal antihypertensive therapy	1. Withhold lenvatinib 2. When systolic BP ≤150 mmHg, diastolic BP ≤95 mmHg, and patient has been on a stable dose of antihypertensive therapy for at least 48 hours, resume lenvatinib at a reduced dose.
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue lenvatinib and institute appropriate medical management.

Hepatic Impairment: No adjustment of starting dose is required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.
In patients with severe (Child-Pugh C) hepatic impairment, the recommended starting dose is 14 mg taken once daily.

Renal Impairment: No adjustment of starting dose is required on the basis of renal function in patients with mild or moderate renal impairment.
In patients with severe renal impairment (CrCl < 30ml/min), the recommended starting dose is 14 mg taken once daily.