Indication	For the treatment of Child-Pugh A locally advanced or metastatic hepatocellular carcinoma, as either first line systemic therapy, or following 1st line atezolizumab and bevacizumab or if sorafenib has been discontinued within 3 months of starting treatment because of unmanageable toxicity and there has been no disease progression whilst on sorafenib.
Treatment Intent	Palliative
Frequency and number of cycles	28 day cycle. Continue until progressive disease, unacceptable toxicity or patient choice. A formal medical review as to whether treatment should continue must occur by at least the end of the first 8 weeks of treatment.

Monitoring Parameters pre-treatment	• Blood pressure: must be stable prior to treatment and BP should be monitored after 1 week, then every 2 weeks for the first 2 cycles, and then prior to each cycle. See table 3 for recommended management of hypertension.
	• Monitor FBC, U&Es (in particular potassium, calcium and magnesium) and glucose prior to each cycle. Abnormalities in electrolytes should be corrected before starting treatment.
	• If neuts <1.0 or platelets <50 d/w consultant.
	• Blood calcium levels at baseline and each cycle. Calcium should be replaced as necessary. Dose adjustment or interruption maybe required if there is persistent hypocalcium.
	• Urine protein should be monitored prior to each cycle If >/=2+.
	• LFTs should be monitored before cycle 1, then every 2 weeks for the first 2 months and monthly thereafter during treatment.
	• Thyroid function should be checked prior to cycle 1 and every other cycle thereafter during treatment.
	• ECG prior to cycle 1 and then periodically. Treatment should be withheld in the event of development of QT interval prolongation greater than 500 ms. Treatment should be resumed at a reduced dose when QTc prolongation is resolved to < 480 ms or baseline.
	• ECHO: at baseline for at risk patients, then every 6/12.
	• A dental examination and appropriate preventive dentistry should be considered (see cautions below - ONJ).
	• **Hepatic impairment:** No dose adjustment required in mild impairment. Limited data in moderate impairment use with caution. Not recommended in severe impairment.
	  ○ Patients should be monitored for worsening liver function including hepatic encephalopathy. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary. See table 3.
	• **Renal impairment:** No dose adjustment required in mild to moderate impairment. No data available for the use in severe impairment (<30ml/min).
	• **Dose adjustments: Dose adjustments are based only on toxicities observed and not on body weight changes during treatment,** some adverse reactions may require dose interruption, adjustment, or discontinuation of therapy. Details for dose adjustment and discontinuation are provided in table 1. Details of dose modification following adverse reaction are provided in table 2.
	• **Cautions:**
	  ○ Patients should be monitored for clinical symptoms or signs of cardiac decompensation.

	○ Use with caution in patients who have had an arterial thromboembolism within the previous 6 months. Lenvatinib should be discontinued following an arterial thrombotic event. ○ The use of VEGF pathway inhibitors in patients with or without hypertension may promote formation of aneurysms and/or artery dissections. This risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm. ○ Lenvatinib should not be started in patients with fistula to avoid worsening and lenvatinib should be permanently discontinued in patients with oesophageal or tracheobronchial tract involvement and any Grade 4 fistula. ○ Lenvatinib may adversely affect the wound healing process as other agents of the same class. ○ Osteonecrosis of the jaw (ONJ) has been reported in patients treated with lenvatinib. Caution when lenvatinib is used either simultaneously or sequentially with antiresorptive therapy and/or other angiogenesis inhibitors. In patients who have previously received or are receiving intravenous bisphosphonates, invasive dental procedures should be avoided if possible. ○ Patients should be advised to be cautious when driving or using machines if they experience fatigue and dizziness. ○ Consider concomitant medication for interactions (see BNF / SPC) • **Missed Dose:** If a dose is missed and it cannot be taken with 12 hours of the prescribed time, treatment should resume with the next scheduled daily dose. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet.
References	SPC accessed on line 22/09/20 KMCC protocol UGI-060 v1 blueteq form accessed online

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1

Table 1 Dose modifications from recommended lenvatinib daily dose in HCC patients			
Starting Dose		**≥60 kg BW** **12 mg**	**<60 kg BW** **8 mg**
Persistent and Intolerable Grade 2 or Grade 3 Toxicities[a]			
Adverse Reaction	**Modification**	**Adjusted Dose[b]** **(≥60 kg BW)**	**Adjusted Dose[b]** **(<60 kg BW)**
First occurrence [c]	Interrupt until resolved to Grade 0-1 or baseline[d]	8 mg orally once daily	4 mg orally once daily
Second occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline[d]	4 mg orally once daily	4 mg orally every other day
Third occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline[d]	4 mg orally every other day	Discontinue
Life-threatening toxicities (Grade 4): Discontinue[e]			
a. Initiate medical management for nausea, vomiting, or diarrhoea prior to interruption or dose reduction. b. Reduce dose in succession based on the previous dose level (12 mg, 8 mg, 4 mg or 4 mg every other day). c. Haematologic toxicity or proteinuria-no dose adjustment required for first occurrence. d. For haematologic toxicity, dosing can restart when resolved to Grade 2; proteinuria, resume when resolves to less than 2g/24 hours e. Excluding laboratory abnormalities judged to be nonlife-threatening, which should be managed as Grade 3.			

Table 2

Table 2 Adverse reactions requiring dose modification of lenvatinib in HCC			
Adverse reaction	**Severity**	**Action**	**Dose reduce and resume lenvatinib**
Hypertension	Grade 3 (despite optimal antihypertensive therapy)	Interrupt	Resolves to Grade 0, 1 or 2. See detailed guidance in Table 3.
	Grade 4	Discontinue	Do not resume
Proteinuria	≥ 2 g / 24 hours	Interrupt	Resolves to less than 2 g / 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 interval 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)			

Table 3 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 (see table 1)
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue lenvatinib and institute appropriate medical management.

Repeat every 28 days

TTO	**Drug**	**Dose**	**Route**	**Directions**
	LENVATINIB	**≥60 kg** **12 mg** **<60 kg** **8 mg**	PO	Swallow whole ONCE a day with water with or without food. If a patient misses a dose, and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time. Available as 4mg and 10mg capsules.
	Metoclopramide	10mg	Take 10mg up to 3 times a day as required. Do not take for more than 5 days continuously	
	Loperamide	2mg-4mg	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 required.	