LENVATINIB (Lenvima)

INDICATION (ICD10) C22

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)

The first line systemic therapy of Child-Pugh A locally advanced or metastatic hepatocellular carcinoma where the following criteria are met:

2. Either the patient has a confirmed histological diagnosis of hepatocellular carcinoma (HCC) or in which a biopsy is deemed to be very high risk or technically not feasible in the patient and the criteria below are also all met:

a. the decision not to biopsy has been made and documented by a specialist HCC multi-disciplinary team meeting

b. the tumour meets the non-invasive diagnostic criteria of HCC.

c. data is submitted as part of the ongoing 'Systemic Therapy Audit, previously known as the Sorafenib Audit 2'.It is expected that this option will only apply in exceptional circumstances and it should be noted that audit of non-biopsy rates will be reviewed regularly.*EASL-EORTC Clinical Practice Guidelines: Management, Journal of Hepatology 2012 vol 56 p908-943. Non-invasive criteria can only be applied to cirrhotic patients and are based on imaging techniques obtained by 4-phase multidetector CT scan or dynamic contrast-enhanced MRI. Diagnosis should be based on the identification of the typical hallmark of HCC (hypervascular in the arterial phase with washout in the portal venous or delayed phases). While one imaging technique is required for nodules beyond 1cm in diameter, a more conservative approach with 2 techniques is recommended in suboptimal settings.3. The patient has either metastatic disease or locally advanced disease that is ineligible for or failed surgical or loco-regional therapies

4. The patient has either:- not received any previous systemic therapy for hepatocellular carcinoma or- had to discontinue sorafenib within 3 months of starting sorafenib and solely because of toxicity (ie there was sorafenib toxicity which could not be managed by dose delay or dose modification) and there has been no disease progression whilst on sorafenib.

5. The patient has Child-Pugh liver function class A

6. The patient has an ECOG PS of 0 or 1.Lenvatinib is not commissioned in patients of ECOG PS of 2 or more.

7. Lenvatinib is to be used as monotherapy.

8. The prescribing clinician is aware of the differing starting doses of lenvatinib according to the patient body weight being above or below 60Kg

9. A formal medical review as to whether treatment with lenvatinib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment

10. Lenvatinib is to be continued until loss of clinical benefit or unacceptable toxicity or patient choice to stop treatment.

11. No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve).

12. Lenvatinib will be otherwise used as set out in its Summary of Product Characteristics.

REGIMEN

LENVATINIB 8mg (under 60kg*) orally once daily
LENVATINIB 12mg (60kg* or over) orally once daily
*weight at initiation of treatment

CYCLE FREQUENCY AND NUMBER OF CYCLES

Continuously until disease progression.

ADMINISTRATION

Available as 4mg capsules
Swallowed whole with water once daily with or without food

ANTI-EMETICS
Minimal risk

CONCURRENT MEDICATION REQUIRED

Lenvatinib	Diarrhoea – Loperamide required Skin – apply moisturizer to hands and feet regularly

EXTRAVASATION AND TYPE OF LINE / FILTERS
Not applicable

INVESTIGATIONS
Blood results required before SACT administration
FBC and U&E every cycle
LFTs every 2 weeks for first 2 cycles then every cycle
Neutrophils x 10^9/L ≥1.0
Platelets x 10^9/L ≥50
Creatinine every cycle
Blood pressure every cycle
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Lenvatinib	Diarrhoea –Proactive management of diarrhoea including adequate hydration combined with anti-diarrhoeal medicinal products especially within the first 6 weeks of the treatment is important and should start at first signs of diarrhoea. Prolonged QT interval Hypertension Skin – apply moisturizer to hands and feet regularly

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Lenvatinib	-

DOSE MODIFICATIONS

Non-haematological

Management of adverse reactions may require dose interruption, dose reduction, or discontinuation of lenvatinib.

Mild to moderate adverse reactions (eg Grade 1 or 2) generally do not warrant interruption, unless intolerable to the patient despite optimal management.

Permanently discontinue for any life-threatening Grade 4 toxicities, with the exception of laboratory abnormality judged to be non-life-threatening, in which case they should be managed as Grade 3.

Grade 2 intolerable or Grade 3 toxicity	**Immediate management**	**Dose adjustment if start dose 12mg**	**Dose adjustment if start dose 8mg**
1st occurrence[a]	Interrupt until resolved to G1-0 or baseline[b]	8mg od	4mg od
2nd occurrence (same reaction or new reaction)	Interrupt until resolved to G1-0 or baseline[b]	4mg od	4mg on alternate days
3rd occurrence (same reaction or new reaction)	Interrupt until resolved to G1-0 or baseline[b]	4mg on alternate days	Permanently discontinue

[a]Haematologic toxicity or proteinuria - no dose adjustment required for 1st occurrence

[b]For haematologic toxicity, dosing can restart when resolved to Grade 2; proteinuria, resume when resolves to less than 2g/24 hours

Hypertension

Grade 3 (despite optimal antihypertensive therapy)	Interrupt until resolves to Grade 0, 1 or 2.
Grade 4	Discontinue. Do not resume

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.

Proteinuria ≥2gm/24 hours	Interrupt Resolves to less than 2g/24hours
Nephrotic syndrome	Discontinue. Do not resume
Renal impairment or failure, or Hepatotoxicity Grade 3	Interrupt. Resolves to Grade 0-1 or baseline
Renal impairment or failure, or Hepatotoxicity Grade 4	Discontinue. Do not resume
Cardiac dysfunction, GI perforation or fistula Grade 3	Interrupt. Resolves to Grade 0-1 or baseline
Cardiac dysfunction, GI perforation or fistula Grade 4	Discontinue. Do not resume
Non-GI fistula Grade 4	Discontinue. Do not resume
PRES/RPLS Any grade	Interrupt. Consider resuming at reduced dose if resolves to Grade 0-1
Arterial thromboembolisms Any grade	Discontinue. Do not resume
Haemorrhage Grade 3	Interrupt. Resolves to Grade 0-1
Haemorrhage Grade 4	Discontinue. Do not resume
QT prolongation >500ms	Interrupt. Resolves to <480ms or baseline
Diarrhoea Grade 3	Interrupt. Resolves to Grade 0-1 or baseline
Diarrhoea Grade 4 (despite medical management)	Discontinue. Do not resume

Hepatic impairment
Lenvatinib
No adjustment of starting dose is required in HCC patients with mild (Child-Pugh A) hepatic impairment.
There is no dosing recommendation (or funding) for HCC patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

Renal impairment
Lenvatinib
No adjustment of starting dose is required on the basis of renal function in patients with mild or moderate renal impairment.
There is no dosing recommendation for HCC patients with CrCl <30ml/min.

REFERENCES
1. Kudo, M et al; Lancet 2018 online