Lenvatinib (Lenvima®)–HCC Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
As monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy	C22	00644a	CDS 01/05/2021

*This is for post 2012 indications only

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Lenvatinib (Lenvima®) is taken once daily continuously until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Cycle
Lenvatinib (Lenvima®)	8mg once daily for patients < 60kg 12mg once daily for patients ≥ 60kg	PO	Continuous therapy
The capsules should be taken at about the same time each day, with or without food. Lenvatinib (Lenvima®) capsules can be swallowed whole with water or administered as a suspension prepared by dispersing the whole capsule(s) in water, apple juice or milk. If administered via a feeding tube, then the suspension should be prepared using water. Place the capsule(s) corresponding to the prescribed dose (up to 5 capsules) in a small container (approximately 20mL (4 tsp) capacity) or oral syringe (20mL); do not break or crush the capsules. Add 3 mL of liquid to the container or oral syringe, wait 10 minutes for the capsule shell to disintegrate, then stir or shake the mixture for 3 minutes until the capsules are fully disintegrated. Administer the contents directly into the mouth or via feeding tube. Add an additional 2 mL of liquid to the container and administer.			
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 of administration.			

ELIGIBILITY:

- Confirmed diagnosis of unresectable HCC with any of following criteria:
  - Histologically or cytologically confirmed diagnosis of HCC
  - Clinically confirmed diagnosis of HCC according to American Association for the Study of Liver Diseases (AASLD) criteria, including cirrhosis of any aetiology or with chronic hepatitis B or C infection criteria
- Patients categorized to stage B (not applicable for TACE) or stage C based on Barcelona Clinic Liver Cancer (BCLC) staging system.
- Child-Pugh score A
- Adequate haematological and organ function
- Adequately controlled blood pressure

EXCLUSIONS:

- Hypersensitivity to lenvatinib (Lenvima®) or any of the excipients
- Imaging findings for HCC corresponding to any of the following:
  - HCC with ≥ 50% liver occupation
  - Clear invasion into the bile duct
  - Portal vein invasion at the main portal branch (Vp4)
- Prior treatment with any systemic chemotherapy for advanced/unresectable HCC. Note: Patients who have received local hepatic injection chemotherapy are eligible.
- Significant cardiovascular impairment
- Prolongation of QTc interval to > 480ms
- Gastrointestinal malabsorption or any other condition that might affect the absorption of lenvatinib (Lenvima®)
- Patients with urine protein ≥ 1g /24h

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profiles
- Coagulation, proteinuria <1g/24 hours, TSH
- Blood pressure
- ECG
- Virology screen -Hepatitis B (HBsAg, HBcoreAb) & C, HIV
  *See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:

- FBC, renal profile, coagulation, proteinuria, TSH every 28 days
- Liver profile every 2 weeks for the first 2 months and monthly thereafter during treatment*
- Calcium levels monthly
- Blood pressure should be monitored after 1 week of treatment with lenvatinib (Lenvima®), then every 2 weeks for the first 2 months, and monthly thereafter
- ECG as clinically indicated
  *See Adverse Reactions/Regimen Specific Complications for more information

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Table 1 shows the dose modifications for lenvatinib (Lenvima®)

Table 1: Dose modification from recommended lenvatinib (Lenvima®) daily dose

Starting dose		**≥60kg 12mg (three 4mg capsules orally once daily)**	**<60kg 8mg (two 4mg capsules orally once daily)**
Persistent and Intolerable Grade 2 or Grade 3 Toxicities[a]			
Adverse reaction	**Modification**	**Adjusted Dose[b] (≥60kg)**	**Adjusted Dose[b] (<60kg)**
First occurrence[c]	Interrupt until resolved to Grade 0-1 or baseline[d]	8mg (two 4mg capsules) orally once daily	4mg (one 4mg capsule) orally once daily
Second occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline[d]	4mg (one 4mg capsule) orally once daily	4mg (one 4mg capsule) orally every other day
Third occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline[d]	4mg (one 4mg capsule) 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 (12mg, 8mg, 4mg or 4mg 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.			

Renal and Hepatic Impairment:

Table 2: Dose modification of lenvatinib (Lenvima®) in renal and hepatic impairment

Renal impairment:		**Hepatic Impairment**	
CrCl (mL/min)	**Dose**	Child Pugh A/B	No dose adjustment is needed
≥ 30	No dose adjustment is needed		
< 30	Not studied (EMA)	Child Pugh C	Not recommended (EMA)
Haemodialysis	50% of the original dose may be considered		
Renal dose modifications from Giraud et al 2023 (< 30 mL/min recommendation from EMA, SmPC), Hepatic dose modifications from Giraud et al 2023 (Child Pugh C from EMA, SmPC)			

Management of adverse events:

Table 3: Management of treatment with lenvatinib (Lenvima®) related 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 (Lenvima®) and initiate antihypertensive therapy, if not already receiving **OR** Continue lenvatinib (Lenvima®) 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 (Lenvima®) 2.When systolic BP ≤150 mmHg, diastolic BP ≤95mmHg, and patient has been on a stable dose of antihypertensive therapy for at least 48 hours, resume lenvatinib (Lenvima®) at a reduced dose (see table 1)
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue lenvatinib (Lenvima®) and institute appropriate medical management.

Table 4: Dose modification schedule based on adverse events

Adverse Reaction	Severity	Recommended dose modification
Proteinuria	≥ 2 g/24 hours (urine dipstick)	Interrupt until resolved to < 2gm/24 hours
Nephrotic syndrome		Discontinue
Renal impairment or failure	Grade 3	Interrupt until resolved to Grade 0-1 or baseline
	Grade 4*	Discontinue
Cardiac dysfunction	Grade 3	Interrupt until resolved to Grade 0-1 or baseline
	Grade 4	Discontinue
Posterior reversible encephalopathy syndrome (PRES)/ Reversible posterior leukoencephalopathy syndrome (RPLS)	Any grade	Interrupt. Consider resuming at reduced dose if resolves to Grade 0-1.
Hepatotoxicity	Grade 3	Interrupt until resolved to Grade 0-1 or baseline
	Grade 4*	Discontinue
Arterial thromboembolism	Any grade	Discontinue
Haemorrhage	Grade 3	Interrupt until resolved to Grade 0-1
	Grade 4	Discontinue

GI perforation or fistula	Grade 3	Interrupt until resolved to Grade 0-1 or baseline
	Grade 4	Discontinue
Non-GI fistula	Grade 4	Discontinue
QT interval prolongation	>500ms	Interrupt until resolved to <480ms or baseline
Diarrhoea	Grade 3	Interrupt until resolved to Grade 0-1 or baseline
	Grade 4 (despite medical management)	Discontinue

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

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Minimal to low for dose ≤12mg/day **(Refer to local policy)**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

- Anti-diarrhoeal treatment **(Refer to local policy)**
- Women of childbearing potential must use highly effective contraception while taking lenvatinib (Lenvima®) and for one month after stopping treatment. It is currently unknown if Lenvatinib (Lenvima®) increases the risk of thromboembolic events when combined with oral contraceptives.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Hypertension:** Hypertension has been reported in patients treated with lenvatinib (Lenvima®), usually occurring early in the course of treatment. Blood pressure should be well controlled prior to treatment with lenvatinib (Lenvima®) and, if patients are known to be hypertensive, they should be on a stable dose of antihypertensive therapy for at least 1 week prior to treatment with lenvatinib (Lenvima®). Serious complications of poorly controlled hypertension, including aortic dissection, have been reported. The early detection and effective management of hypertension are important to minimise the need for lenvatinib (Lenvima®) dose interruptions and reductions. Antihypertensive agents should be started as soon as elevated BP is confirmed. The choice of antihypertensive treatment should be individualized to the patient's clinical circumstances and follow standard medical practice. For previously normotensive subjects, monotherapy with one of the classes of antihypertensives should be started when elevated BP is observed. For those patients already on antihypertensive medication, the dose

of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added. When necessary, manage hypertension as recommended in Table 3.

- **Aneurysms and artery dissections:** The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating lenvatinib (Lenvima®), this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.
- **Renal failure and impairment:** Renal impairment and renal failure have been reported in patients treated with lenvatinib (Lenvima®). The primary risk factor identified was dehydration and/or hypovolemia due to gastrointestinal toxicity. Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or renal failure. Dose interruptions, adjustments, or discontinuation may be necessary. If patients have severe renal impairment, the initial dose of lenvatinib (Lenvima®) should be adjusted (Ref Table 2).
- **Diarrhoea:** Diarrhoea has been reported frequently in patients treated with lenvatinib (Lenvima®) , usually occurring early in the course of treatment. Prompt medical management of diarrhoea should be instituted in order to prevent dehydration. Lenvatinib (Lenvima®) should be discontinued in the event of persistence of Grade 4 diarrhoea despite medical management.
- **Cardiac Failure:** Patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or discontinuation may be necessary.
- **PRES / RPLS:** PRES, also known as RPLS, has been reported in patients treated with lenvatinib (Lenvima®). In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary.
- **Arterial thromboembolisms:** Arterial thromboembolisms (cerebrovascular accident, transient ischaemic attack, and myocardial infarction) have been reported in patients treated with lenvatinib (Lenvima®). Lenvatinib (Lenvima®) has not been studied in patients who have had an arterial thromboembolism within the previous 6 months, and therefore should be used with caution in such patients. A treatment decision should be made based upon an assessment of the individual patient's benefit/risk. Lenvatinib (Lenvima®) should be discontinued following an arterial thrombotic event.
- **Hepatotoxicity**: Liver-related adverse reactions most commonly reported in patients treated with lenvatinib (Lenvima®) include increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and blood bilirubin. Hepatic failure and acute hepatitis (<1%) have been reported in patients with DTC treated with lenvatinib (Lenvima®). The hepatic failure cases were generally reported in patients with progressive metastatic liver metastases disease. Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary. If patients have severe hepatic impairment, the initial dose of lenvatinib (Lenvima®) should be adjusted.
- **Haemorrhage:** Serious cases of haemorrhage have been reported in patients treated with lenvatinib (Lenvima®). Cases of fatal intracranial haemorrhage have been reported in some patients with brain metastases. Screening for and subsequent treatment of oesophageal varices in patients with liver cirrhosis should be performed as per standard of care before starting treatment with lenvatinib (Lenvima®) In the case of bleeding, dose interruptions, adjustments, or discontinuation may be necessary. The degree of tumour invasion/infiltration of major blood vessels (e.g. carotid artery) should be considered because of the potential risk of severe haemorrhage associated with tumour shrinkage/necrosis following lenvatinib (Lenvima®) therapy. In the case of bleeding, dose interruptions, adjustments, or discontinuation may be

required.

- **Gastrointestinal perforation or fistula:** These have been reported in patients treated with lenvatinib (Lenvima®), mostly in patients with risk factors such as prior surgery or radiotherapy.. In the case of a gastrointestinal perforation or fistula, dose interruptions, adjustments, or discontinuation may be necessary.
- **QT Interval Prolongation**: Electrocardiograms should be monitored in all patients with a special attention for those with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, and those taking medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics. Electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia increase the risk of QT prolongation, therefore electrolyte abnormalities should be monitored and corrected in all patients before starting treatment. Periodic monitoring of ECG and electrolytes (magnesium, potassium and calcium) should be during treatment. Blood calcium levels should be monitored at least monthly and calcium should be replaced as necessary during lenvatinib (Lenvima®) treatment. Lenvatinib (Lenvima®) dose should be interrupted or dose adjusted as necessary depending on severity, presence of ECG changes, and persistence of hypocalcaemia.
- **Impairment of thyroid stimulating hormone suppression:** Lenvatinib (Lenvima®) impairs exogenous thyroid suppression. Thyroid stimulating hormone (TSH) levels should be monitored on a regular basis and thyroid hormone administration should be adjusted to reach appropriate TSH levels, according to the patient's therapeutic target.
- **Wound Healing Complications**: Impaired wound healing has been reported in patients receiving lenvatinib (Lenvima®). Temporary interruption of lenvatinib (Lenvima®) should be considered in patients undergoing major surgical procedures. The decision to resume lenvatinib (Lenvima®) following a major surgical procedure should be based on clinical judgment of adequate wound healing.
- **Osteonecrosis of the jaw (ONJ):** Cases of ONJ have been reported in patients treated with lenvatinib (Lenvima®). Some cases were reported in patients who had received prior or concomitant treatment with antiresorptive bone therapy, and/or other angiogenesis inhibitors, e.g. bevacizumab, TKI, mTOR inhibitors. Caution should therefore be exercised when lenvatinib (Lenvima®) is used either simultaneously or sequentially with antiresorptive therapy and/or other angiogenesis inhibitors.
- **Hepatitis B Reactivation**: Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy **(Refer to local infectious disease policy).** These patients should be considered for assessment by hepatology.

DRUG INTERACTIONS:

- It is currently unknown whether lenvatinib (Lenvima®) may reduce the effectiveness of hormonal contraceptives, and therefore women using oral hormonal contraceptives should add a barrier method.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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3. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
5. Lenvatinib (LENVIMA®) Summary of Product Characteristics. Last updated: 09/01/2024. Accessed January 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/lenvima-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	30/4/2021		Prof Maccon Keane
2	14/03/2024	Reviewed.Added tradename Lenvima®. Updated treatment table with administration information. Updated Emetogenic Potential. Updated renal and hepatic information in line with Giraud recommendations, 2023 and SmPC.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.