Lenvatinib- DTC Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine.	C73	00295a	CDS

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 is taken once daily continuously until disease progression or unacceptable toxicity develops.

Drug	Dose	Route	Diluent & Rate	Cycle
Lenvatinib	24mg daily	PO		Continuous therapy
The capsules should be taken at about the same time each day, with or without food. The capsules should be swallowed whole with water				
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.				
Lenvatinib is available as 10mg and 4mg capsules.				

ELIGIBILTY:

- Indication as above
- ECOG status 0-2
- Measurable, pathologically confirmed differentiated thyroid cancer, evidence of iodine-131–refractory disease
  - at least one measurable lesion without iodine uptake on any iodine-131 scan,
  - at least one measurable lesion that had progressed according to the RECIST criteria within 12 months after iodine-131 therapy despite iodine-131 avidity at the time of treatment,
  - or cumulative activity of iodine-131 that was >600 mCi), and independently reviewed radiologic evidence of progression within the previous 13 months.
- May have received none or one prior treatment regimen with a tyrosine kinase inhibitor
- Adequate haematological, renal and liver status
- Thyroid hormone suppression therapy with thyroid stimulating hormone (TSH) level ≤ 0.50mIU/L

EXCLUSIONS:

- Hypersensitivity to lenvatinib or any of the excipients.
- Uncontrolled hypertension
- Breast-feeding
- Proteinuria ≥1g/24 hours or significant cardiovascular or gastrointestinal dysfunction.

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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, 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.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Patients of age ≥75 years, of Asian race, with comorbidities (such as hypertension, and hepatic or renal impairment), or body weight below 60 kg appear to have reduced tolerability to lenvatinib
- Management of suspected adverse drug reactions may require dose interruption, adjustment or discontinuation of lenvatinib therapy.
- Optimal medical management for nausea, vomiting and diarrhoea should be initiated prior to any interruption or dose reduction of lenvatinib.
- Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or failure.
- Table 1 shows the dose modifications for lenvatinib

Table 1: Dose modification table for lenvatinib therapy

Dose level	Daily Dose
Recommended daily dose	24mg orally once daily
First dose reduction	20mg orally once daily
Second dose reduction	14mg orally once daily
Third dose reduction	10mg orally once daily*
*Further dose reductions should be considered on an individual patient basis as limited data are available for doses below 10mg	

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Renal and hepatic impairment

Table 2: Dose modification of lenvatinib in renal and hepatic impairment

Renal impairment:		Hepatic Impairment	
Mild	No adjustment of starting dose required	Mild Child Pugh A	No dose adjustment is required
Moderate		Moderate Child Pugh B	
Severe	14mg once daily	Severe (Child Pugh C)	14mg once daily
Further dose adjustments may be required on the basis of individual tolerability. Patients with end-stage renal disease were not studied, therefore the use of lenvatinib in these patients is not recommended		Further dose adjustments may be required on the basis of individual tolerability	

Management of adverse events:

Table 3: Management of treatment with lenvatinib 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 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 ≤95mmHg, 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.

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Table 4: Dose modification schedule based on adverse events

Adverse Reaction	Severity	Recommended dose modification
Proteinuria	≥ 2 gm/24 hours (urine dipstick)	Interrupt until resolved to < 2gm/24 hours
Nephrotic syndrome		Discontinue
Renal impairment or failure	Grade 3	Interrupt until resolved Resolves to Grade 0-1 or baseline
	Grade 4*	Discontinue
Cardiac dysfunction	Grade 3	Interrupt until resolved to to Grade 0-1 or baseline
	Grade 4	Discontinue
PRES/RPLS	Any grade	Interrupt Consider resuming at reduced dose if resolves to Grade 0-1.
Hepatotoxicity	Grade 3	Interrupt until resolved to to Grade 0-1 or baseline
	Grade 4*	Discontinue
Arterial thromboembolism	Any grade	Discontinue
Haemorrhage	Grade 3	Interrupt until resolved to to Grade 0-1
	Grade 4	Discontinue
GI perforation or fistula	Grade 3 Grade 4	Interrupt until resolved to Grade 0-1 or baseline Discontinue
Non-GI fistula	Grade 4	Discontinue
QT interval prolongation	>500ms	Interrupt until resolved to 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)

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SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate **(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 and for one month after stopping treatment. It is currently unknown if lenvatinib 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.

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **Hypertension:** Hypertension has been reported in patients treated with lenvatinib, usually occurring early in the course of treatment. Blood pressure should be well controlled prior to treatment with lenvatinib 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. 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 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, 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. 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 should be adjusted (Ref Table 2).
- **Cardiac Failure:** Patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or discontinuation may be necessary.
- **Posterior reversible encephalopathy syndrome (PRES) / Reversible posterior leucoencephalopathy syndrome (RPLS):** In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary.

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- **Hepatotoxicity**: Liver-related adverse reactions most commonly reported in patients treated with lenvatinib 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. 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 should be adjusted
- **Haemorrhage:** Serious cases of haemorrhage have been reported in patients treated with lenvatinib. 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 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 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, 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 treatment. Lenvatinib 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 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. Temporary interruption of lenvatinib should be considered in patients undergoing major surgical procedures. The decision to resume lenvatinib following a major surgical procedure should be based on clinical judgment of adequate wound healing.
- **Hepatitis B Reactivation**: All 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 for the entire duration of chemotherapy and for six months afterwards (Refer to local policy). Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring,

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management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to stopping chemotherapy.

DRUG INTERACTIONS:

- It is currently unknown whether lenvatinib 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.

ATC CODE:

Lenvatinib - L01XE29

REFERENCES:

1. Schlumberger M, Tahara M et al. Lenvatinib versus Placebo in Radioiodine Refractory Thyroid Cancer. New Engl J Med 2015;372(7):621-630
2. LENVIMA® Summary of Product Characteristics Accessed October 2019 Available at: https://www.medicines.org.uk/emc/product/6840/smpc
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V1 2018. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp%20antiemetic%20classification%20document%20v1%202018.pdf

Version	Date	Amendment	Approved By
1	12/01/2016	Initial Draft	Dr Liam Grogan
2	15/03/2017	Presentation of dosing in renal and hepatic impairment in tabular form. Updated dose modification schedule for adverse events	Prof Maccon Keane
3	12/02/2019	Updated regimen title. Updated baseline and regular testing required as per SmPC and emetogenic potential. Updated adverse effects /regimen specific complications as per SPC update	Prof Maccon Keane
4	07/10/2019	Updated adverse effects/regimen specific complications as per SmPC update on aneurysms and artery dissections Updated Hepatitis B reactivation management recommendations	Prof maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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