

For any information about LENVIMA, please refer to the full SPC as approved by the Israeli MoH or contact Neopharm's Patient Safety Unit at:

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Dosing and administration guide

Therapeutic indications

LENVIMA® is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the Summary of Product Characteristics for how to report adverse reactions.

For more information, including adverse events, please refer to the Israeli MoH approved SPC.

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Posology¹

Pharmaceutical form: hard capsule



4 mg capsule:

A yellowish-red body and yellowish-red cap, approximately 14.3 mm in length, marked in black ink with “E” on the cap, and “LENV 4 mg” on the body.



10 mg capsule:

A yellow body and yellowish-red cap, approximately 14.3 mm in length, marked in black ink with “E” on the cap, and “LENV 10 mg” on the body.

The recommended daily dose of LENVIMA is 24 mg taken once daily. The daily dose is to be modified as needed according to the dose/toxicity management plan (see dose adjustment section on pages 3 and 4).

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. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Method of administration

LENVIMA is for oral use. The capsules should be taken at about the same time each day, with or without food (see section 5.2 of the Summary of Product Characteristics). The capsules should be swallowed whole with water. Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.

Dose adjustments

Management of adverse reactions may require dose interruption, adjustment, or discontinuation of LENVIMA (see section 4.4 of the Summary of Product Characteristics). Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of LENVIMA, unless intolerable to the patient despite optimal management. Severe (e.g., Grade 3) or intolerable adverse reactions require interruption of LENVIMA until resolution or improvement of the reaction, after which treatment should be resumed at a reduced dose as suggested in the table on the following page. 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).

Grades are based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).

Optimal medical management for nausea, vomiting, and diarrhoea should be initiated prior to any interruption or dose reduction of LENVIMA. Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or failure (see section 4.4 of the Summary of Product Characteristics).

Dose modifications¹

Dose modifications from recommended daily dose

Dose level	Daily dose	Number of capsules
Recommended daily dose	24 mg orally once daily	Two 10 mg capsules plus one 4 mg capsule
First dose reduction	20 mg orally once daily	Two 10 mg capsules
Second dose reduction	14 mg orally once daily	One 10 mg capsule plus one 4 mg capsule
Third dose reduction	10 mg orally once daily ^a	One 10 mg capsule

^aFurther dose reductions should be considered on an individual patient basis as limited data are available for doses below 10 mg.

Dosing for special populations¹

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 LENVIMA (see section 4.8 of the Summary of Product Characteristics). All patients other than those with severe hepatic or renal impairment (see below) should initiate treatment at the recommended 24 mg dose, following which the dose should be further adjusted on the basis of individual tolerability.

Patients with hypertension

Blood pressure should be well controlled prior to treatment with LENVIMA, and should be regularly monitored during treatment (see section 4.4 of the Summary of Product Characteristics).

Patients with hepatic or renal 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.

No adjustment of starting dose is required on the basis of renal function in patients with mild or moderate renal impairment. Patients with end-stage renal disease were not studied, therefore the use of LENVIMA in these patients is not recommended.

Dosing for special populations (cont'd)¹

Dosing for patients with hepatic or renal impairment

In patients with	Recommended starting dose
Severe (Child-Pugh C) hepatic impairment	14 mg taken once daily (One 10 mg capsule plus one 4 mg capsule)
Severe renal impairment	14 mg taken once daily (One 10 mg capsule plus one 4 mg capsule)

Further dose adjustments may be necessary based on individual tolerability.

Elderly population

No adjustment of starting dose is required on the basis of age. Limited data are available on use in patients aged ≥75 years.

Paediatric population

LENVIMA must not be used in children younger than 2 years of age because of safety concerns identified in animal studies (see section 5.3 of the Summary of Product Characteristics). The safety and efficacy of LENVIMA in children aged 2 to <18 years have not yet been established (see section 5.1 of the Summary of Product Characteristics). No data are available.

Race

No adjustment of starting dose is required on the basis of race (see section 5.2 of the Summary of Product Characteristics). Limited data are available on use in patients from ethnic origins other than Caucasian or Asian.

Special warnings and precautions for use¹

Hypertension

Hypertension has been reported in patients treated with LENVIMA, usually occurring early in the course of treatment (see section 4.8 of the Summary of Product Characteristics). Blood pressure (BP) should be well controlled prior to treatment with 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 LENVIMA. The early detection and effective management of hypertension are important to minimise the need for LENVIMA dose interruptions and reductions. Antihypertensive agents should be started as soon as elevated BP is confirmed. Blood pressure should be monitored after 1 week of treatment with LENVIMA, then every 2 weeks for the first 2 months, and monthly thereafter. 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. For patients with hypertension and proteinuria, treatment with an angiotensin-converting enzyme inhibitor or angiotensin-II receptor antagonist is preferred. **When necessary, manage hypertension as recommended in the table on the following page.**

Special warnings and precautions for use (cont'd)¹

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 LENVIMA and initiate antihypertensive therapy, if not already receiving OR Continue 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 LENVIMA 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 LENVIMA at a reduced dose (see section 4.2 of the Summary of Product Characteristics)
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue LENVIMA and institute appropriate medical management.

Women of childbearing potential

Women of childbearing potential must use highly effective contraception while taking LENVIMA and for one month after stopping treatment (see section 4.6 of the Summary of Product Characteristics). It is currently unknown if LENVIMA increases the risk of thromboembolic events when combined with oral contraceptives.

Proteinuria

Proteinuria has been reported in patients treated with LENVIMA, usually occurring early in the course of treatment (see section 4.8 of the Summary of Product Characteristics). Urine protein should be monitored regularly. If urine dipstick proteinuria ≥2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2 of the Summary of Product Characteristics). LENVIMA should be discontinued in the event of nephrotic syndrome.

Renal failure and impairment

Renal impairment and renal failure have been reported in patients treated with LENVIMA (see section 4.8 of the Summary of Product Characteristics). 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 (see section 4.2 of the Summary of Product Characteristics).

If patients have severe renal impairment, the initial dose of LENVIMA should be adjusted (see sections 4.2 and 5.2 of the Summary of Product Characteristics).

Special warnings and precautions for use (cont'd)¹

Cardiac failure

Cardiac failure (<1%) and decreased left ventricular ejection fraction have been reported in patients treated with LENVIMA (see section 4.8 of the Summary of Product Characteristics). Patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2 of the Summary of Product Characteristics).

Posterior reversible encephalopathy syndrome / Reversible posterior leucoencephalopathy syndrome (RPLS)

Posterior reversible encephalopathy syndrome (PRES, also known as RPLS), has been reported in patients treated with LENVIMA (<1%; see section 4.8 of the Summary of Product Characteristics). PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control blood pressure (see section 4.4 of the Summary of Product Characteristics). In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2 of the Summary of Product Characteristics).

Hepatotoxicity

Liver-related adverse reactions most commonly reported in patients treated with LENVIMA included increases in alanine aminotransferase, increases in aspartate aminotransferase, and increases in blood bilirubin. Hepatic failure and acute hepatitis (<1%; see section 4.8 of the Summary of Product Characteristics) have been reported in patients treated with LENVIMA. The hepatic failure cases were generally reported in patients with progressive liver metastases. 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 (see section 4.2 of the Summary of Product Characteristics).

If patients have severe hepatic impairment, the initial dose of LENVIMA should be adjusted (see sections 4.2 and 5.2 of the Summary of Product Characteristics).

Special warnings and precautions for use (cont'd)¹

Haemorrhage

Serious cases of haemorrhage have been reported in patients treated with LENVIMA (see section 4.8 of the Summary of Product Characteristics). Cases of fatal intracranial haemorrhage have been reported in some patients with brain metastases. In the case of bleeding, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2 of the Summary of Product Characteristics).

Arterial thromboembolisms

Arterial thromboembolisms (cerebrovascular accident, transient ischaemic attack, and myocardial infarction) have been reported in patients treated with LENVIMA (see section 4.8 of the Summary of Product Characteristics). 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. LENVIMA should be discontinued following an arterial thrombotic event.

Gastrointestinal perforation and fistula formation

Gastrointestinal perforation or fistulae have been reported in patients treated with LENVIMA (see section 4.8 of the Summary of Product Characteristics). In most cases, gastrointestinal perforation and fistulae occurred 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 (see section 4.2 of the Summary of Product Characteristics).

QT interval prolongation

QT/QTc interval prolongation has been reported at a higher incidence in patients treated with LENVIMA than in patients treated with placebo (see section 4.8 of the Summary of Product Characteristics). 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 considered during treatment.

Impairment of thyroid stimulating hormone suppression

LENVIMA impairs exogenous thyroid suppression (see section 4.8 of the Summary of Product Characteristics). 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.

Special warnings and precautions for use (cont'd)¹

Special populations

Limited data are available for patients of ethnic origin other than Caucasian or Asian, and in patients aged ≥ 75 years. LENVIMA should be used with caution in such patients, given the reduced tolerability of LENVIMA in Asian and elderly patients (see section 4.8 of the Summary of Product Characteristics).

There are no data on the use of LENVIMA immediately following sorafenib or other anticancer treatments and there may be a potential risk for additive toxicities unless there is an adequate washout period between treatments. The minimal washout period in clinical trials was of 4 weeks.

Storage and handling¹

Shelf life

3 years.

Special precautions for storage

Do not store above 25°C. Store in the original blister in order to protect from moisture.

Nature and contents of container

Polyamide/Aluminium/PVC/Aluminium blisters containing 10 capsules. Each carton contains 30 capsules.

Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.

Reference: 1. LENVIMA® [Israeli MoH approved SPC].