Levat

Lenvatinib INN

Jenphar Bangladesh | جنفار بنغلاديش

Composition:
Levat 4 Capsule: Each capsule contains Lenvatinib Mesylate INN equivalent to Lenvatinib 4 mg.
Levat 10 Capsule: Each capsule contains Lenvatinib Mesylate INN equivalent to Lenvatinib 10 mg.

Pharmacology:
Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib also inhibits other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET.

Indications:
Levat is a kinase inhibitor that is indicated-:
• Hepatocellular Carcinoma (HCC): As a first-line treatment of patients with unresectable Hepatocellular Carcinoma (HCC).
• Differentiated Thyroid Cancer (DTC): Single agent for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC).
• Advanced Renal Cell Carcinoma (RCC):
In combination with Pembrolizumab, for the first line treatment of adult patients with advanced RCC
In combination with Everolimus, for the treatment of patients with advanced RCC following one prior anti-angiogenic therapy.
• Advanced Endometrial Carcinoma: In combination with Pembrolizumab, for the treatment of patients with advanced Endometrial Carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.

Dosage And Administration:
• Recommended dosage (HCC): 12 mg orally, once daily (for adults weighing >60 Kg). 8 mg orally, once daily for adults weighing <60 Kg)
• Recommended dosage (DTC): 24 mg orally, once daily.
• Recommended dosage (RCC):
  • 20 mg orally once daily with Pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks.
  • 18 mg Lenvatinib + 5 mg Everolimus, orally, once daily
• Recommended dosage (Endometrial Carcinoma): 20 mg orally once daily with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks.

Administration Instructions:
Lenvatinib capsules should be swallowed whole. Alternatively, the capsules can be dissolved in a small glass of liquid. Measure 1 tablespoon of water or apple juice and put the capsules into the liquid without breaking or crushing them. Leave the capsules in the liquid for at least 10 minutes. Stir for at least 3 minutes. Drink the mixture. After drinking, add the same amount (1 tablespoon) of water or apple juice to the glass. Swirl the contents a few times and swallow the additional liquid.

Dosage Modifications for Adverse Reactions

Table 1. Recommended Dosage Modifications for Lenvatinib for Adverse Reactions

Adverse Reaction	Severity	Dosage Modifications for Lenvatinib
Hypertension	Grade 3	• Withhold for Grade 3 that persists despite optimal antihypertensive therapy. • Resume at reduced dose when hypertension is controlled at less than or equal to Grade 2.
	Grade 4	• Permanently discontinue.
Cardiac Dysfunction	Grade 3	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at a reduced dose or discontinue depending on the severity and persistence of adverse reaction.
	Grade 4	• Permanently discontinue.
Arterial Thromboembolic Event	Any Grade	• Permanently discontinue.
Hepatotoxicity	Grade 3 or 4	• Withhold until improves to Grade 0 to 1 or baseline. • Either resume at a reduced dose or discontinue depending on severity and persistence of hepatotoxicity. •Permanently discontinue for hepatic failure.
Renal Failure or Impairment	Grade 3 or 4	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at a reduced dose or discontinue depending on severity and persistence of renal impairment.
Proteinuria	2 g or greater proteinuria in 24 hours	• Withhold until less than or equal to 2 grams of proteinuria per 24 hours. • Resume at a reduced dose. • Permanently discontinue for nephrotic syndrome.
Gastrointestinl Perforation	Any Grade	• Permanently discontinue.
Fistula Formation	Grade 3 or 4	• Permanently discontinue.
QT Prolongation	Greater than 500 ms or greater than 60 ms increase from baseline	• Withhold until improves to less than or equal to 480 ms or baseline. • Resume at a reduced dose.
Reversible Posterior Leukoencephalopathy Syndrome	Any Grade	• Withhold until fully resolved. • Resume at a reduced dose or discontinue depending on severity and persistence of neurologic symptoms.
Other Adverse Reactions	Persistent or intolerable Grade 2 or 3 adverse reaction Grade 4 laboratory abnormality	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at reduced dose.
	Grade 4 adverse reaction	• Permanently discontinue

Table 2: Recommended Dosage Reductions of Lenvatinib for Adverse Reactions

Indication	First Dosage Reduction To	Second Dosage Reduction To	Third Dosage Reduction To
DTC	20 mg once daily	14 mg once daily	10 mg once daily
RCC	14 mg once daily	10 mg once daily	8 mg once daily
Endometrial Carcinoma	14 mg once daily	10 mg once daily	8 mg once daily
HCC			
Actual weight 60 kg or greater	8 mg once daily	4 mg once daily	4 mg every other day
Actual weight less than 60 kg	4 mg once daily	4 mg once daily	Discontinue

Dosage Modifications for Severe Renal & Hepatic Impairment
For patients with severe renal impairment (creatinine clearance less than 30 mL/min) & for patients with severe hepatic impairment (Child-Pugh C), the recommended dosage of Lenvatinib is-
• Differentiated thyroid cancer: 14 mg orally once daily
• Renal cell carcinoma: 10 mg orally once daily
• Endometrial carcinoma: 10 mg orally once daily

Contraindications:
Hypersensitivity to the active substance or to any of the excipients.

Warnings and Precautions:
Hypertension: Control blood pressure prior to treatment with Lenvatinib. Withhold Lenvatinib for Grade 3 hypertension despite optimal antihypertensive therapy. Discontinue for life-threatening hypertension.
Cardiac Failure: Monitor for clinical symptoms or signs of cardiac decompensation. Withhold Lenvatinib for Grade 3 cardiac dysfunction. Discontinue for Grade 4 cardiac dysfunction.
Arterial Thromboembolic Events: Discontinue Lenvatinib following an arterial thromboembolic event.
Hepatotoxicity: Monitor liver function tests before initiation of Lenvatinib and periodically
throughout treatment. Withhold Lenvatinib for Grade 3 or greater liver impairment. Discontinue for hepatic failure.
Proteinuria: Monitor for proteinuria before initiation of, and periodically throughout, treatment with Lenvatinib. Withhold Lenvatinib for 2 grams of proteinuria for 24 hours. Discontinue for nephrotic syndrome.
Diarrhea: May be severe and recurrent. Use standard anti-diarrheal therapy. Withhold Lenvatinib for Grade 3 and discontinue for Grade 4 diarrhea.
Renal Failure and Impairment: Withhold Lenvatinib for Grade 3 or 4 renal failure/impairment.
Gastrointestinal Perforation and Fistula Formation: Discontinue Lenvatinib in patients who develop gastrointestinal perforation or life threatening fistula.
Hypocalcemia: Monitor blood calcium levels at least monthly and replace calcium as necessary.
Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Withhold Lenvatinib for RPLS until fully resolved.
Hemorrhagic Events: Withhold Lenvatinib for Grade 3 hemorrhage. Discontinue for Grade 4 hemorrhage.
Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction: Monitor TSH levels monthly and use thyroid replacement medication as needed.
Embryo fetal Toxicity: Can cause fetal harm. Considering potential risk to a fetus, use of effective contraception.

Adverse Reactions:
In HCC, the most common adverse reactions (≥20%) were hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic events, hypothyroidism, and nausea. The most common serious adverse reactions (≥2%) were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%).

In DTC, the most common adverse reactions (incidence greater than or equal to 30%) for Lenvatinib are hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, and dysphonia.

In RCC, The most common adverse reactions (incidence ≥20%) for Lenvatinib and Pembrolizumab are fatigue, diarrhea, musculoskeletal pain, hypothyroidism, hypertension, stomatitis, decreased appetite, rash, nausea, decreased weight, dysphonia, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, hemorrhagic events, vomiting, constipation, hepatotoxicity, headache, and acute kidney injury.

The most common adverse reactions (greater than 30%) for Lenvatinib + Everolimus are diarrhea, fatigue, arthralgia/myalgia, decreased appetite, vomiting, nausea, stomatitis/oral inflammation, hypertension, peripheral edema, cough, abdominal pain, dyspnea, rash, weight decreased, hemorrhagic events, and proteinuria.

In EC, the most common adverse reactions (incidence ≥20%) for Lenvatinib and Pembrolizumab are hypothyroidism, hypertension, fatigue, diarrhea, musculoskeletal disorders, nausea, decreased appetite, vomiting, stomatitis, decreased weight, abdominal pain, urinary tract infection, proteinuria, constipation, headache, hemorrhagic events, palmar-plantar erythrodysesthesia, dysphonia, and rash.

Special Populations:
Pregnancy: Lenvatinib can cause fetal harm when administered to pregnant woman.
Lactation: Risk Summary: It is not known whether Lenvatinib is present in human milk. Because of the potential for serious adverse reactions in nursing infants from Lenvatinib, advise women to discontinue breastfeeding during treatment with Lenvatinib.
Use in children and adolescent: The safety and effectiveness of Lenvatinib in pediatric patients have not been established.
Geriatric Use: Conclusions are limited due to the small sample size, but there appeared to be no overall differences in safety or effectiveness between subjects and younger subjects.

Drug Interactions:
Effect of Other Drugs on Lenvatinib
No dose adjustment of Lenvatinib is recommended when co-administered with CYP3A, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP) inhibitors and CYP3A and P-gp inducers.

Overdosage:
Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable. Death due to multi organ dysfunction occurred in a patient who received a single dose of Lenvatinib 120 mg orally.

Storage Condition:
Store in dry place below 30° C, protect from light. Keep out of the reach of children.

Packing:
Levat 4 Capsule: Each box contains 30 capsules and one packet silica gel in a sealed HDPE container.
Levat 10 Capsule: Each box contains 30 capsules and one packet silica gel in a sealed HDPE container.

Manufactured by:
Jenphar Bangladesh Ltd.
Sreepur, Gazipur, Bangladesh.

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