40500346

Lenvatinib Capsules I.P.

Lenvat®

लेनवाट

1. GENERIC NAME

Lenvatinib Capsules I.P.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lenvat 4
Each capsule contains:
Lenvatinib mesylate
equivalent to lenvatinib I.P. 4 mg
Approved colours used in capsule shell

Lenvat 10
Each capsule contains:
Lenvatinib mesylate
equivalent to lenvatinib I.P. 10 mg
Approved colours used in capsule shell

3. DOSAGE FORM AND STRENGTH

Dosage form: HPMC Capsules

Strength: 4 mg & 10 mg

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

- For the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine refractory differentiated thyroid cancer

4.2 Posology and Method of Administration

LENVAT treatment should be initiated and supervised by a health care professional experienced in the use of anticancer therapies.

Optimal medical management (i.e. treatment or therapy) for nausea, vomiting and diarrhea should be initiated prior to any Lenvatinib therapy interruption or dose reduction; gastrointestinal toxicity should be actively treated in order to reduce the risk of development of renal impairment or failure.

LENVAT should be taken once daily, with or without food, at the same time each day. 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.

4.2.1 Recommended Dosage for Differentiated Thyroid Cancer (DTC)

The recommended dosage of LENVAT is 24 mg orally once daily until disease progression or until unacceptable toxicity.

4.2.2 Dose Adjustments and Discontinuations for DTC

Management of adverse reactions may require dose interruption, adjustment or discontinuation of Lenvatinib therapy. Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of Lenvatinib, unless intolerable to the patient despite optimal management. Severe (e.g., Grade 3) or intolerable adverse reactions require interruption of Lenvatinib until improvement of the reaction to Grade 0-1 or baseline.

For Lenvatinib related toxicities, upon resolution/improvement of an adverse reaction to Grade 0-1 or baseline, treatment should be resumed at a reduced dose of Lenvatinib as suggested below.

Dose modifications from recommended Lenvatinib daily dose in DTC patients		
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

[a] 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).

4.2.3 Adverse reactions requiring dose modification of Lenvatinib in DTC

Adverse reaction	**Severity**	**Action**	**Dose reduce and resume Lenvatinib**
Hypertension	Grade 3 (despite optimal antihypertensive therapy)	Interrupt	Resolves to Grade 0, 1 or 2
	Grade 4	Discontinue	Do not resume
Proteinuria	≥ 2 g/24 hours	Interrupt	Resolves to less than 2 g/24 hours
Nephrotic syndrome	----------	Discontinue	Do not resume
Renal impairment or failure	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline
	Grade 4*	Discontinue	Do not resume
Cardiac dysfunction	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline
	Grade 4	Discontinue	Do not resume
PRES/RPLS	Any grade	Interrupt	Consider resuming at reduced dose if resolves to Grade 0-1
Hepatotoxicity	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline
	Grade 4*	Discontinue	Do not resume
Arterial thromboembolisms	Any grade	Discontinue	Do not resume
Hemorrhage	Grade 3	Interrupt	Resolves to Grade 0-1
	Grade 4	Discontinue	Do not resume
GI perforation or fistula	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline
	Grade 4	Discontinue	Do not resume
Non-GI fistula	Grade 4	Discontinue	Do not resume
QT interval prolongation	>500 ms	Interrupt	Resolves to <480 ms or baseline
Diarrhea	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline
	Grade 4 (despite medical management)	Discontinue	Do not resume

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

4.2.4 Preparation and Administration

LENVAT capsules can be swallowed whole or dissolved in a small glass of liquid. To dissolve in liquid, put capsules into 1 tablespoon of water or apple juice without breaking or crushing the capsules. Leave the capsules in the water or apple juice for at least 10 minutes. Stir for at least 3 minutes. After drinking the mixture, add 1 tablespoon of water or apple juice to the glass, swirl the contents a few times and swallow the water or apple juice.

4.3 Contraindications

LENVAT is contraindicated in patients with known hypersensitivity to Lenvatinib or any other excipients of LENVAT.

4.4 Special Warnings and Precautions for Use

4.4.1 Hypertension

Hypertension has been reported in patients treated with Lenvatinib, usually occurring early in the course of treatment. Blood pressure (BP) 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 minimize the need for Lenvatinib dose interruptions and reductions. Antihypertensive agents should be started as soon as elevated BP is confirmed. BP should be monitored after 1 week of treatment with Lenvatinib, 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 an antihypertensive medicinal product, 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 the below table.

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 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

4.4.2 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.

4.4.3 Proteinuria

Proteinuria has been reported in patients treated with Lenvatinib, usually occurring early in the course of treatment. Urine protein should be monitored regularly. If urine dipstick proteinuria ≥2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary. Cases of nephrotic syndrome have been reported in patients using Lenvatinib. Lenvatinib should be discontinued in the event of nephrotic syndrome.

4.4.4 Hepatotoxicity

In DTC, liver-related adverse reactions most commonly reported in patients treated with Lenvatinib included 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.

Close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment. 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.

4.4.5 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.

4.4.6 Diarrhea

Diarrhea has been reported frequently in patients treated with Lenvatinib, usually occurring early in the course of treatment. Prompt medical management of diarrhea should be instituted in order to prevent dehydration. Lenvatinib should be discontinued in the event of persistence of Grade 4 diarrhea despite medical management.

4.4.7 Cardiac dysfunction

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

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

PRES, also known as RPLS, has been reported in patients treated with Lenvatinib (<1%). 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. In patients with signs or symptoms of PRES, dose interruptions, adjustments or discontinuation may be necessary.

4.4.9 Arterial thromboembolisms

Arterial thromboembolisms (cerebrovascular accident, transient ischemic attack and myocardial infarction) have been reported in patients treated with Lenvatinib. Lenvatinib 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 should be discontinued following an arterial thrombotic event.

4.4.10 Women of childbearing potential

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.

4.4.11 Hemorrhage

Serious tumor related bleeds, including fatal hemorrhagic events have occurred in clinical trials and have been reported in post-marketing experience. In post-marketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than in DTC or other tumor types. The degree of tumor invasion/infiltration of major blood vessels (e.g. carotid artery) should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following Lenvatinib therapy. Some cases of bleeding have occurred secondarily to tumor shrinkage and fistula formation, e.g. tracheo-esophageal fistulae. Cases of fatal intracranial hemorrhage have been reported in some patients with or without brain metastases. Bleeding in sites other than the brain (e.g. trachea, intra-abdominal, lung) has also been reported.

In the case of bleeding, dose interruptions, adjustments or discontinuation may be required.

4.4.12 Gastrointestinal perforation and fistula formation

Gastrointestinal perforation or fistulae have been reported in patients treated with Lenvatinib. 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.

4.4.13 Non-gastrointestinal fistula

Patients may be at increased risk for the development of fistulae when treated with Lenvatinib. Cases of fistula formation or enlargement that involve areas of the body other than stomach or intestines were observed in clinical trials and in post-marketing experience (e.g. tracheal, tracheo-esophageal, esophageal, cutaneous, female genital tract fistulae). In addition, pneumothorax has been reported with and without clear evidence of a bronchopleural fistula. Some reports of fistula and pneumothorax occurred in association with tumor regression or necrosis. Prior surgery and radiotherapy may be contributing risk factors. Lung metastases may also increase the risk of pneumothorax. Lenvatinib should not be started in patients with fistula to avoid worsening and Lenvatinib should be permanently discontinued in patients with esophageal or tracheobronchial tract involvement and any Grade 4 fistula; limited information is available on the use of dose interruption or reduction in management of other events, but worsening was observed in some cases and caution should be taken. Lenvatinib may adversely affect the wound healing process as for other agents of the same class.

4.4.14 QT interval prolongation

QT/QTc interval prolongation has been reported at a higher incidence in patients treated with Lenvatinib than in patients treated with placebo. Electrocardiograms should be monitored at baseline and periodically during treatment in all patients with particular attention to 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. Lenvatinib should be withheld in the event of development of QT interval prolongation greater than 500 ms. Lenvatinib should be resumed at a reduced dose when QTc prolongation is resolved to < 480 ms or baseline.

Electrolyte disturbances such as hypokalemia, hypocalcemia or hypomagnesemia increase the risk of QT prolongation; therefore, electrolyte abnormalities should be monitored and corrected in all patients before starting treatment. Electrolytes (magnesium, potassium and calcium) should be monitored periodically 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 hypocalcemia.

4.4.15 Impairment of thyroid stimulating hormone suppression/ Thyroid dysfunction

Hypothyroidism has been reported in patients treated with Lenvatinib. Thyroid function should be monitored before initiation of and periodically throughout, treatment with Lenvatinib. Hypothyroidism should be treated according to standard medical practice to maintain euthyroid state.

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.

4.4.16 Wound Healing Complications

No formal studies of the effect of Lenvatinib on wound healing have been conducted. Impaired wound healing has been reported in patients receiving Lenvatinib. Temporary interruption of Lenvatinib should be considered in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of Lenvatinib following a major surgical procedure. Therefore, the decision to resume Lenvatinib following a major surgical procedure should be based on clinical judgment of adequate wound healing.

4.4.17 Osteonecrosis of the jaw (ONJ)

Cases of ONJ have been reported in patients treated with Lenvatinib. 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 is used either simultaneously or sequentially with antiresorptive therapy and/or other angiogenesis inhibitors.

Invasive dental procedures are an identified risk factor. Prior to treatment with Lenvatinib, a dental examination and appropriate preventive dentistry should be considered. In patients who have previously received or are receiving intravenous bisphosphonates, invasive dental procedures should be avoided if possible.

4.4.18 Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal reproduction studies, Lenvatinib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of Lenvatinib during organogenesis at doses below the recommended clinical doses resulted in embryotoxicity, fetotoxicity and teratogenicity in rats and rabbits.

4.5 Drug Interactions

4.5.1 Drugs That Prolong the QT Interval

Lenvatinib has been reported to prolong the QT/QTc interval. Avoid coadministration of Lenvatinib with medicinal products with a known potential to prolong the QT/QTc interval.

4.6 Use in Special Populations

4.6.1 Pregnancy

Risk Summary

Based on its mechanism of action and data from animal reproduction studies, Lenvatinib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended human doses resulted in embryotoxicity, fetotoxicity and teratogenicity in rats and rabbits (see Data). There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryofetal development study, daily oral administration of Lenvatinib mesylate at doses ≥0.3 mg/kg [approximately 0.14 times the recommended clinical dose of 24 mg based on body surface area (BSA)] to pregnant rats during organogenesis resulted in dose-related decreases in mean fetal body weight, delayed fetal ossifications and dose-related increases in fetal external (parietal edema and tail abnormalities), visceral and skeletal anomalies. Greater than 80% postimplantation loss was observed at 1.0 mg/kg/day (approximately 0.5 times the recommended clinical dose of 24 mg based on BSA).

Daily oral administration of Lenvatinib mesylate to pregnant rabbits during organogenesis resulted in fetal external (short tail), visceral (retroesophageal subclavian artery) and skeletal anomalies at doses greater than or equal to 0.03 mg/kg (approximately 0.03 times the recommended clinical dose of 24 mg based on BSA). At the 0.03 mg/kg dose, increased post-implantation loss, including 1 fetal death, was also observed. Lenvatinib was abortifacient in rabbits, resulting in late abortions in approximately one-third of the rabbits treated at a dose level of 0.5 mg/kg/day (approximately 0.5 times the recommended clinical dose of 24 mg based on BSA).

4.6.2 Lactation

Risk Summary

It is not known whether Lenvatinib is present in human milk; however, Lenvatinib and its metabolites are excreted in rat milk at concentrations higher than those in maternal plasma (see Data). Because of the potential for serious adverse reactions in breastfed infants, advise women to discontinue breastfeeding during treatment with Lenvatinib and for at least 1 week after the last dose.

Data

Animal Data

Following administration of radiolabeled Lenvatinib to lactating Sprague Dawley rats, Lenvatinib-related radioactivity was approximately 2 times higher [based on area under the curve (AUC)] in milk compared to maternal plasma.

4.6.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of Lenvatinib.

Contraception

Based on its mechanism of action, Lenvatinib can cause fetal harm when administered to a pregnant woman

Females

Advise females of reproductive potential to use effective contraception during treatment with Lenvatinib and for at least 30 days after the last dose.

Infertility

Lenvatinib may impair fertility in males and females of reproductive potential

4.6.4 Pediatric Use

The safety and effectiveness of Lenvatinib in pediatric patients have not been established.

Juvenile Animal Data

Daily oral administration of Lenvatinib mesylate to juvenile rats for 8 weeks starting on postnatal day 21 (approximately equal to a human pediatric age of 2 years) resulted in growth retardation (decreased body weight gain, decreased food consumption and decreases in the width and/or length of the femur and tibia) and secondary delays in physical development and reproductive organ immaturity at doses greater than or equal to 2 mg/kg (approximately 1.2 to 5 times the human exposure based on AUC at the recommended clinical dose of 24 mg). Decreased length of the femur and tibia persisted following 4 weeks of recovery. In general, the toxicologic profile of Lenvatinib was similar between juvenile and adult rats, though toxicities including broken teeth at all dose levels and mortality at the 10 mg/kg/day dose level (attributed to primary duodenal lesions) occurred at earlier treatment time-points in juvenile rats.

4.6.5 Geriatric Use

No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

4.6.6 Hepatic Impairment

No dose adjustment is recommended for patients with DTC and mild or moderate hepatic impairment (Child-Pugh A or B). Lenvatinib concentrations may increase in patients with DTC and severe hepatic impairment (Child-Pugh C). Reduce the dose of Lenvatinib for patients with DTC and severe hepatic impairment.

4.6.7 Renal Impairment

No dose adjustment is recommended for patients with mild (CLcr 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment. Lenvatinib concentrations may increase in patients with DTC and severe (CLcr 15-29 mL/min) renal impairment. Reduce the dose of Lenvatinib for patients with DTC and severe renal impairment. Lenvatinib has not been studied in patients with end stage renal disease.

4.7 Effects on Ability to Drive and Use Machines

Lenvatinib has minor influence on the ability to drive and use machines, due to undesirable effects such as fatigue and dizziness. Patients who experience these symptoms should use caution when driving or operating machines.

4.8 Undesirable Effects

ORGAN SITE	SIDE EFFECT
	Clinically important side effects are in bold, italics
Blood and lymphatic system/ febrile neutropenia	lymphopenia (7%, severe 1%)
	thrombocytopenia (14%, severe 2%)
Cardiac	***arterial thromboembolic event*** (5%, severe 3%); includes cerebrovascular accident, transient ischemic attack, and myocardial infarction; requires treatment discontinuation
	cardiac failure (<1%)
Endocrine	hypothyroidism (5%); may require thyroid replacement therapy
	TSH increase (61%)
Gastrointestinal	emetogenic potential: low-moderate
	abdominal pain (32%, severe 2%)
	constipation (29%, severe <1%)
	diarrhea (67%, severe 9%)
	dry mouth (17%, severe <1%)
	dyspepsia (13%, severe <1%)
	flatulence (6%)
	gastrointestinal fistula (2%, severe <1%)
	gastrointestinal perforation (<1%); requires treatment discontinuation
	nausea (47%, severe 2%)
	oropharyngeal pain (25%, severe 1%)
	stomatitis (41%, severe 5%)
	vomiting (36%, severe 2%)
General disorders and administration site conditions	asthenia (25%, severe 6%)
	fatigue (43%, severe 5%)
	malaise (5%)
	peripheral edema (21%, severe <1%)
Hepatobiliary	***hepatic failure*** (severe <1%)
Infections and infestations	pneumonia (severe 4%)
	urinary tract infection (12%, severe 1%)
Investigations	ALT increase (severe 4%)
	AST increase (severe 5%)
	left ventricular ejection fraction decrease (5%)
	QT interval prolongation (8-9%, severe 2%)
	weight loss (51%, severe 13%)
Metabolism and nutrition	***anorexia*** (54%, severe 7%)
	dehydration (9%, severe 2%)
	hypoalbuminemia (10%)
	hypocalcemia (13%, severe 5%)
	hypokalemia (14%, severe 3%)
	hypomagnesemia (severe <1%)
Musculoskeletal and connective tissue	arthralgia (26%)
	back pain (18%, severe 2%)
	myalgia (19%, severe 2%)
	pain in extremity (15%, severe 1%)
Nervous system	dizziness (15%)
	dysgeusia (18%)
	headache (38%, severe 3%)
	posterior reversible encephalopathy syndrome (<1%, severe 0%); dose interruption, adjustment, or discontinuation may be necessary
Psychiatric	insomnia (12%)
Renal and urinary	***proteinuria*** (34%, severe 11%)
	renal impairment, including acute renal failure (4-14%, severe 2-3%)
Respiratory, thoracic and mediastinal	cough (24%)
	dysphonia (32%, severe 1%)
	epistaxis (12%)
Skin and subcutaneous tissue	alopecia (12%)
	palmar-plantar erythrodysesthesia syndrome (32%, severe 3%)
	rash (19%)
Vascular	***hemorrhage*** (35%, severe 2%); includes serious tumor related bleeds and fatal intracranial hemorrhagic events in patients with brain metastases
	hypertension (73%, severe 44%)
	hypotension (9%, severe 2%)
	venous thromboembolic events, including pulmonary embolism (2-5%, severe 4%)

4.9 Overdose

The highest doses of Lenvatinib studied clinically were 32 mg and 40 mg per day. The most frequently observed adverse drug reactions at these doses were hypertension, nausea, diarrhea, fatigue, stomatitis, proteinuria, headache and aggravation of PPE. There have also been reports of overdose with Lenvatinib involving single administrations of 6 to 10 times the recommended daily dose. These cases were associated with adverse reactions consistent with the known safety profile of Lenvatinib (i.e., renal and cardiac failure), or were without adverse reactions.

There is no specific antidote for overdose with Lenvatinib. In case of suspected overdose, Lenvatinib should be withheld and appropriate supportive care given as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR) and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptors FGFR1, 2, 3 and 4, the platelet derived growth factor (PDGF) receptor PDGFRα, KIT and RET. Lenvatinib's broad spectrum of antitumor activity and potent inhibition of FGFR1 differentiates it from other multi-kinase inhibitors with antiangiogenic properties.

5.2 Pharmacodynamic Properties

QT interval prolongation

A single 32-mg dose of Lenvatinib did not prolong the QT/QTc interval based on results from a thorough QT study in healthy volunteers; however, QT/QTc interval prolongation has been reported at a higher incidence in patients treated with Lenvatinib than in patients treated with placebo.

5.3 Pharmacokinetic Properties

Absorption	T_{max}: 1 - 4 hours; food slows the rate, but not the extent, of absorption	
Distribution	highly plasma protein bound to albumin; minor binding to α1-acid glycoprotein and ϫ-globulin	
	cross blood brain barrier?	no information found
	volume of distribution	43-121 L
	plasma protein binding	98-99%
Metabolism	major metabolism by cytochrome P450 3A4; minor metabolism by aldehyde oxidase and non-enzymatic processes	
	active metabolite	yes (degree of relative activity unknown)
	inactive metabolite	yes
Excretion	plasma concentrations decline bi-exponentially following C_{max}	
	Urine	64%
	Feces	25%
	Half life	28 hours

6. NONCLINICAL PROPERTIES

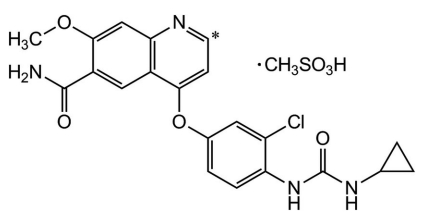
6.1 Animal Toxicology

Carcinogenicity studies have not been conducted with Lenvatinib. Lenvatinib mesylate was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay. Lenvatinib was not clastogenic in the in vitro mouse lymphoma thymidine kinase assay or the in vivo rat micronucleus assay.

No specific studies with Lenvatinib have been conducted in animals to evaluate the effect on fertility; however, results from general toxicology studies in rats, monkeys and dogs suggest there is a potential for Lenvatinib to impair fertility. Male dogs exhibited testicular hypocellularity of the seminiferous epithelium and desquamated seminiferous epithelial cells in the epididymides at Lenvatinib exposures approximately 0.02 to 0.09 times the AUC at the recommended clinical dose of 24 mg once daily. Follicular atresia of the ovaries was observed in monkeys and rats at exposures 0.2 to 0.8 times and 10 to 44 times the AUC at the recommended clinical dose of 24 mg once daily, respectively. In addition, in monkeys, a decreased incidence of menstruation was reported at Lenvatinib exposures lower than those observed in humans at the recommended clinical dose of 24 mg once daily.

7. DESCRIPTION

LENVAT, a kinase inhibitor, is the mesylate salt of Lenvatinib. Its chemical name is 4-[3chloro-4-(N'-cyclopropylureido) phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate. The molecular formula is $C_{21}H_{19}ClN_4O_4 \cdot CH_4O_3S$, and the molecular weight of the mesylate salt is 522.96. The chemical structure of lenvatinib mesylate is:



Lenvatinib mesylate is a white to pale reddish yellow powder. It is slightly soluble in water and practically insoluble in ethanol (dehydrated). The dissociation constant (pKa value) of Lenvatinib mesylate is 5.05 at 25°C. The partition coefficient (log P value) is 3.3.

LENVAT capsules for oral administration contain 4 mg or 10 mg of Lenvatinib, equivalent to 4.90 mg or 12.25 mg of Lenvatinib mesylate, respectively. The inactive ingredients are: Microcrystalline cellulose, Calcium Carbonate, Mannitol, Hydroxy propyl cellulose and Talc.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

24 Months

8.3 Packaging Information

LENVAT 4 : Blister of 10 capsules. 3 Blisters with pack insert housed in a carton.

LENVAT 10 : Blister of 10 capsules. 3 Blisters with pack insert housed in a carton.

8.4 Storage and Handling Instructions

Store protected from moisture, at a temperature not exceeding 30°C.

9. Patient Counselling Information

9.1 What is LENVAT?

LENVAT is a prescription medicine that is used to treat differentiated thyroid cancer (DTC), a type of thyroid cancer that can no longer be treated with radioactive iodine and is progressing.

It is not known if LENVAT is safe and effective in children.

9.2 Before you take LENVAT, tell your healthcare provider about all of your medical conditions, including if you:

- have high blood pressure
- have heart problems
- have a history of blood clots in your arteries (type of blood vessel), including stroke, heart attack or change in vision
- have or have had liver or kidney problems
- have a history of a tear (perforation) in your stomach or intestine or an abnormal connection between two or more body parts (fistula)
- have headaches, seizures or vision problems
- have any bleeding problems
- plan to have surgery, a dental procedure, or have had a recent surgery. You should stop taking LENVAT at least 1 week before planned surgery. See **"What are the possible side effects of LENVAT?"**
- are pregnant or plan to become pregnant. LENVAT can harm your unborn baby. **Females who are able to become pregnant**:
  - Your healthcare provider should do a pregnancy test before you start treatment with LENVAT.
  - You should use an effective method of birth control during treatment with LENVAT and for at least 30 days after the last dose of LENVAT. Talk with your healthcare provider about birth control methods you can use during this time. Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with LENVAT.
- are breastfeeding or plan to breastfeed. It is not known if LENVAT passes into your breast milk. Do not breastfeed during treatment with LENVAT and for at least 1 week after the last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

Especially tell your healthcare provider if you are taking, or have taken, an osteoporosis medicine.

Know the medicines you take. Keep a list of your medicines to show to your healthcare provider and pharmacist when you get a new medicine.

9.3 How should I take LENVAT?

- Take LENVAT exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much LENVAT to take and when to take it. Your healthcare provider may change your dose during treatment, stop treatment for some time, or completely stop treatment with LENVAT if you have side effects.
- Take LENVAT 1 time each day at the same time, with or without food.
- If you miss a dose of LENVAT, take it as soon as you remember. If your next dose is due within 12 hours, skip the missed dose and take the next dose at your regular time.
- If you cannot swallow LENVAT capsules whole:
  - Use a medicine cup to measure about one tablespoon of water or apple juice and place into a small glass.
  - Place the LENVAT capsules into the small glass without breaking or crushing them.
  - Leave the capsules in the liquid for at least 10 minutes.
  - Stir the contents of the glass for at least 3 minutes.
  - Drink the mixture. After drinking, rinse the glass with a small amount of additional water or apple juice and swallow the liquid.
- If you take too much LENVAT, call your healthcare provider or go to the nearest hospital emergency room right away.

9.4 What are the possible side effects of LENVAT?

LENVAT may cause serious side effects, including

- **High blood pressure (hypertension):** High blood pressure is a common side effect of LENVAT and can be serious. Your blood pressure should be well controlled before you start taking LENVAT. Your healthcare provider should check your blood pressure regularly during treatment with LENVAT. If you develop blood pressure problems, your healthcare provider may prescribe medicine to treat your high blood pressure.
- **Heart problems:** LENVAT can cause serious heart problems that may lead to death. Call your healthcare provider right away if you get symptoms of heart problems, such as shortness of breath or swelling of your ankles.
- **Problem with blood clots in your blood vessels (arteries)**: Get emergency medical help right away if you get any of the following symptoms:
  - severe chest pain or pressure
  - trouble talking
  - pain in your arms, back, neck or jaw
  - sudden severe headache
  - shortness of breath
  - sudden vision changes
  - numbness or weakness on one side of your body
- **Liver problems**: LENVAT may cause liver problems that may lead to liver failure and death. Your healthcare provider will check your liver function before and during treatment with LENVAT. Tell your healthcare provider right away if you have any of the following symptoms:
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark "tea colored" urine
  - light-colored bowel movements (stools)
  - feeling drowsy, confused or loss of consciousness
- **Kidney problems**: Kidney failure, which can lead to death, has happened with LENVAT treatment. Your healthcare provider should do regular blood tests to check your kidneys.
- **Increased protein in your urine (proteinuria):** Proteinuria is a common side effect of LENVAT and can be serious. Your healthcare provider should check your urine for protein before and during your treatment with LENVAT.
- **Diarrhea:** Diarrhea is a common side effect of LENVAT and can be serious. If you get diarrhea, ask your healthcare provider about what medicines you can take to treat your diarrhea. It is important to drink more water when you get diarrhea. Tell your healthcare provider or go to the emergency room, if you are unable to drink enough liquids and your diarrhea is not able to be controlled.
- **An opening in the wall of your stomach or intestines (perforation) or an abnormal connection between two or more body parts (fistula):** Get emergency medical help right away if you have severe stomach (abdomen) pain.
- **Changes in the electrical activity of your heart called QT prolongation:** QT prolongation can cause irregular heartbeats that can be life threatening. Your healthcare provider will do blood tests before and during your treatment with LENVAT to check the levels of potassium, magnesium and calcium in your blood and may check the electrical activity of your heart with an ECG.
- **Low levels of blood calcium (hypocalcemia):** Your healthcare provider will check your blood calcium levels during treatment with LENVAT and may tell you to take a calcium supplement if your calcium levels are low.
- **A condition called Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** Call your healthcare provider right away if you get severe headache, seizures, weakness, confusion or blindness or change in vision.
- **Bleeding**: LENVAT may cause serious bleeding problems that may lead to death. Tell your healthcare provider if you have any signs or symptoms of bleeding during treatment with LENVAT, including:
  - severe and persistent nose bleeds
  - blood in your urine
  - vomiting blood
  - coughing up blood or blood clots
  - red or black (looks like tar) stools
  - heavy or new onset vaginal bleeding
- **Change in thyroid hormone levels:** Your healthcare provider should check your thyroid hormone levels before starting and every month during treatment with LENVAT.
- **Wound healing problems:** Wound healing problems have happened in some people who take LENVAT. Tell your healthcare provider if you plan to have any surgery before or during treatment with LENVAT.
  - You should stop taking LENVAT at least 1 week before planned surgery.
  - Your healthcare provider should tell you when you may start taking LENVAT again after surgery.
- **Severe jaw bone problems (osteonecrosis):** Severe jaw bone problems have happened in some people who take LENVAT. Certain risk factors such as taking a bisphosphonate medicine or the medicine denosumab, having dental disease, or an invasive dental procedure may increase your risk of getting jaw bone problems. Your healthcare provider should examine your mouth before you start and during treatment with LENVAT. Tell your dentist that you are taking LENVAT. It is important for you to practice good mouth care during treatment with LENVAT. Tell your healthcare provider right away if you get signs or symptoms of jaw bone problems during treatment with LENVAT, including jaw pain, toothache, or sores on your gums. Tell your healthcare provider if you plan to have any dental procedures before or during treatment with LENVAT. You should avoid having invasive dental procedures if possible, during treatment with LENVAT. Stopping your bisphosphonate medicine before an invasive dental procedure may help decrease your risk of getting these jaw problems.
  - You should stop taking LENVAT at least 1 week before planned dental surgery or invasive dental procedures.
  - Your healthcare provider should tell you when you may start taking LENVAT again after dental procedures.
- **The most common side effects of LENVAT in people treated for thyroid cancer include:**
- Tiredness
- Headache
- Joint and muscle pain
- Vomiting
- Decreased appetite
- Rash, redness, itching or peeling of your weight loss skin on your hands and feet
- Nausea
- Stomach (abdomen) pain
- Mouth sores
- Hoarseness

LENVAT may cause fertility problems in males and females. Talk to your healthcare provider if this is a concern for you.

9.5 How should I store LENVAT?

- Store protected from moisture, at a temperature not exceeding 30°C.

Keep LENVAT and all medicines out of the reach of children.

9.6 General information about the safe and effective use of LENVAT

- Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LENVAT for a condition for which it is not prescribed. Do not give LENVAT to other people, even if they have the same symptoms you have. It may harm them.

9.7 What are the ingredients in LENVAT?

Active Ingredient: Lenvatinib Mesylate

Inactive Ingredients: Microcrystalline cellulose, Calcium Carbonate, Mannitol, Hydroxy propyl cellulose and Talc.

10. Details of manufacturer

Made in India by:

NATCO PHARMA LIMITED

Kothur - 509 228.

Regd. Office: Natco House, Road No.2,

Banjara Hills, Hyderabad - 500 034.

®Registered Trade Mark

11. Details of permission or license number with date

M. L.: 164/MN/AP/95/F/R ; Date: 17/12/2020

12. Date of revision:

December 2022

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References

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3. http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Lenvatinib_monograph.pdf