Lenvaxen

Lenvatinib 4 mg & 10 mg

Everest

COMPOSITION

LENVAXEN 4 capsules: Each capsule contains Lenvatinib Mesylate INN equivalent to Lenvatinib 4 mg.

LENVAXEN 10 capsules: Each capsule contains Lenvatinib Mesylate INN equivalent to Lenvatinib 10 mg.

INDICATIONS AND USAGE

Lenvatinib is indicated as monotherapy 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). Lenvatinib is indicated as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy.

DOSAGE AND ADMINISTRATION

Recommended Dosage for Differentiated Thyroid Cancer (DTC)

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

Recommended Dosage for Renal Cell Carcinoma (RCC)

The recommended dosage of lenvatinib is 18 mg in combination with 5 mg everolimus orally once daily until disease progression or until unacceptable toxicity.

Refer to everolimus prescribing information for recommended everolimus dosing information.

Recommended Dosage for Hepatocellular Carcinoma (HCC)

The recommended dosage of lenvatinib is based on actual body weight, 12 mg for patients greater than or equal to 60 kg or 8 mg for patients less than 60 kg. Take lenvatinib orally once daily until disease progression or until unacceptable toxicity.

Reduce the dose for certain patients with renal or hepatic impairment. Take lenvatinib once daily, with or without food, at the same time each day. If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration.

DOSAGE MODIFICATION

Management of some 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. Details for monitoring, dose adjustment and discontinuation are provided in Table 1 & 2.

Table 1 Dose modifications from recommended lenvatinib daily dose in DTC patients[a]

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

Table 2 Dose modifications from recommended lenvatinib daily dose in HCC patients

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

Elderly population

DTC

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. All patients other than those with severe hepatic or renal impairment should initiate treatment at the recommended 24 mg dose, following which the dose should be further adjusted on the basis of individual tolerability.

HCC

Patients ≥75 years, of white race or female sex or those with worse baseline hepatic impairment (Child-Pugh A score of 6 compared to score of 5) appear to have reduced tolerability to lenvatinib.

HCC patients other than those with moderate and severe hepatic impairment or severe renal impairment should initiate treatment at the recommended starting dose of 8 mg (two 4 mg capsules) for body weight < 60 kg and 12 mg (three 4 mg capsules) for body weight ≥ 60 kg, 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 lenvatinib and should be regularly monitored during treatment.

Patients with hepatic impairment

DTC

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. In patients with severe (Child-Pugh C) hepatic impairment, the recommended starting dose is 14 mg taken once daily. Further dose adjustments may be necessary on the basis of individual tolerability.

HCC

In the patient populations enrolled in the HCC study no dose adjustments were required on the basis of hepatic function in those patients who had mild hepatic impairment (Child-Pugh A). The available very limited data are not sufficient to allow for a dosing recommendation for HCC patients with moderate hepatic impairment (Child-Pugh B). Close monitoring of overall safety is recommended in these patients. Lenvatinib has not been studied in patients with severe hepatic imparement (Child-Pugh C) and is not recommended for use in these patients.

Patients with renal impairment

DTC

No adjustment of starting dose is required on the basis of renal function in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended starting dose is 14 mg taken once daily. Further dose adjustments may be necessary based on individual tolerability. Patients with end-stage renal disease were not studied, therefore the use of lenvatinib in these patients is not recommended.

HCC

No dose adjustments are required on the basis of renal function in patients with mild or moderate renal impairment. The available data do not allow for a dosing recommendation for patients with HCC and severe renal impairment.

CONTRAINDICATION

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

WARNINGS AND PRECAUTIONS

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 minimise 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.

Cardiac Dysfunction

Serious and fatal cardiac dysfunction can occur with lenvatinib. Across clinical trials in 799 patients with DTC, RCC or HCC, Grade 3 or higher cardiac dysfunction (including cardiomyopathy, left or right ventricular dysfunction, congestive heart failure, cardiac failure, ventricular hypokinesia, or decrease in left or right ventricular ejection fraction of more than 20% from baseline) occurred in 3% of lenvatinib-treated patients. Monitor patients for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at a reduced dose upon recovery or permanently discontinue lenvatinib based on severity.

Arterial Thromboembolic Events

Among patients receiving lenvatinib or lenvatinib with everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in Study 205 (RCC), 2% of patients in REFLECT (HCC) and 5% of patients in SELECT (DTC). Grade 3 to 5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials. Permanently discontinue lenvatinib following an arterial thrombotic event. The safety of resuming lenvatinib after an arterial thromboembolic event has not been established and lenvatinib has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

Hepatotoxicity

Across clinical studies enrolling 1327 lenvatinib-treated patients with malignancies other than HCC, serious hepatic adverse reactions occurred in 1.4% of patients. Fatal events, including hepatic failure, acute hepatitis and hepatorenal syndrome, occurred in 0.5% of patients. In REFLECT (HCC), hepatic encephalopathy (including hepatic encephalopathy, encephalopathy, metabolic encephalopathy, and hepatic coma) occurred in 8% of lenvatinib-treated patients and 3% of sorafenib-treated patients. Grade 3 to 5 hepatic encephalopathy occurred in 5% of lenvatinib-treated patients and 2% of sorafenib-treated patients. Grade 3 to 5 hepatic failure occurred in 3% of lenvatinib-treated patients and 3% of sorafenib-treated patients. Two percent of patients discontinued lenvatinib and 0.2% discontinued sorafenib due to hepatic encephalopathy and 1% of patients discontinued lenvatinib or sorafenib due to hepatic failure. Monitor liver function prior to initiating lenvatinib, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment.

Renal Failure or Impairment

Serious including fatal renal failure or impairment can occur with lenvatinib. Renal impairment occurred in 14% of patients receiving lenvatinib in SELECT (DTC) and in 7% of patients receiving lenvatinib in REFLECT (HCC). Grade 3 to 5 renal failure or impairment occurred in 3% (DTC) and 2% (HCC) of patients, including 1 fatality in each study. In Study 205 (RCC), renal impairment or renal failure occurred in 18% of patients receiving lenvatinib with everolimus, including Grade 3 in 10% of patients. Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at a reduced dose upon recovery or permanently discontinue lenvatinib for renal failure or impairment based on severity.

Proteinuria

Proteinuria occurred in 34% of lenvatinib-treated patients in SELECT (DTC) and in 26% of lenvatinib-treated patients in REFLECT (HCC). Grade 3 proteinuria occurred in 11% and 6% in SELECT and REFLECT, respectively. In Study 205 (RCC), proteinuria occurred in 31% of patients receiving lenvatinib with everolimus and 14% of patients receiving everolimus. Grade 3 proteinuria occurred in 8% of patients receiving lenvatinib with everolimus compared to 2% of patients receiving everolimus. Monitor for proteinuria prior to initiating lenvatinib and periodically during treatment. If urine dipstick proteinuria greater than or equal to 2+ is detected, obtain a 24-hour urine protein. Withhold and resume at a reduced dose upon recovery or permanently discontinue lenvatinib based on severity.

Diarrhea

Of the 737 patients treated with lenvatinib in SELECT (DTC) and REFLECT (HCC), diarrhea occurred in 49% of patients, including Grade 3 in 6%. In Study 205 (RCC), diarrhea occurred in 81% of patients receiving lenvatinib with everolimus, including Grade 3 in 19%. Diarrhea was the most frequent cause of dose interruption/reduction and diarrhea recurred despite dose reduction. Promptly initiate management of diarrhea. Withhold and resume at a reduced dose upon recovery or permanently discontinue lenvatinib based on severity.

Fistula Formation and Gastrointestinal Perforation

Of 799 patients treated with lenvatinib or lenvatinib with everolimus in select (DTC), Study 205 (RCC) and REFLECT (HCC), fistula or gastrointestinal perforation occurred in 2%. Permanently discontinue lenvatinib in patients who develop gastrointestinal perforation of any severity or Grade 3 or 4 fistula.

QT Interval Prolongation

In SELECT (DTC), QT/QTc interval prolongation occurred in 9% of lenvatinib-treated patients and QT interval prolongation of >500 ms occurred in 2%. In Study 205 (RCC), QTc interval increases of >60 ms occurred in 11% of patients receiving lenvatinib with everolimus and QTc interval >500 ms occurred in 6%. In REFLECT (HCC), QTc interval increases of >60 ms occurred in 8% of lenvatinib-treated patients and QTc interval >500 ms occurred in 2%. Monitor and correct electrolyte abnormalities at baseline and periodically during treatment.

Hypocalcemia

In SELECT (DTC), Grade 3 to 4 hypocalcemia occurred in 9% of patients receiving lenvatinib. In 65% of cases, hypocalcemia improved or resolved following calcium supplementation, with or without dose interruption or dose reduction. In Study 205 (RCC), Grade 3 to 4 hypocalcemia occurred in 6% of patients treated with lenvatinib with everolimus. In REFLECT (HCC), Grade 3 hypocalcemia occurred in 0.8% of lenvatinib-treated patients Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue lenvatinib depending on severity.

Lenvaxen

Lenvatinib 4 mg & 10 mg

Everest

Reversible Posterior Leukoencephalopathy Syndrome

Across clinical studies of 1823 patients who received lenvatinib as a single age, reversible posterior leukoencephalopathy syndrome (RPLS) occurred in 0.3%. Confirm the diagnosis of RPLS with magnetic resonance imaging. Withhold and resume at a reduced dose upon recovery or permanently discontinue lenvatinib depending on severity and persistence of neurologic symptoms.

Hemorrhagic Events

Serious including fatal hemorrhagic events can occur with lenvatinib. Across SELECT (DTC), Study 205 (RCC) and REFLECT (HCC), hemorrhagic events of any grade occurred in 29% of the 799 patients treated with lenvatinib as a single agent or in combination with everolimus. The most frequently reported hemorrhagic events (all grades and occurring in at least 5% of patients) were epistaxis and hematuria. In SELECT, Grade 3 to 5 hemorrhage occurred in 2% of patients receiving lenvatinib, including 1 fatal intracranial hemorrhage among 16 patients who received lenvatinib and had CNS metastases at baseline. In Study 205, Grade 3 to 5 hemorrhage occurred in 8% of patients receiving lenvatinib with everolimus, including 1 fatal cerebral hemorrhage. In REFLECT, Grade 3 to 5 hemorrhage occurred in 5% of patients receiving lenvatinib, including 7 fatal hemorrhagic events.

Impairment of Thyroid Stimulating Hormone Suppression/ Thyroid Dysfunction

Lenvatinib impairs exogenous thyroid suppression. In SELECT (DTC), 88% of all patients had a baseline thyroid stimulating hormone (TSH) level ≤0.5 mU/L. In those patients with a normal TSH at baseline, elevation of TSH level >0.5 mU/L was observed post baseline in 57% of lenvatinib-treated patients. Grade 1 or 2 hypothyroidism occurred in 24% of patients receiving lenvatinib with everolimus in Study 205 (RCC) and in 21% of patients receiving lenvatinib in REFLECT (HCC).

Wound Healing Complications

Wound healing complications, including fistula formation and wound dehiscence, can occur with lenvatinib. Withhold lenvatinib for at least 6 days prior to scheduled surgery. Resume lenvatinib after surgery based on clinical judgment of adequate wound healing. Permanently discontinue lenvatinib in patients with wound healing complications.

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. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with lenvatinib and for at least 30 days after the last dose.

SIDE EFFECTS

Hypertension, Cardiac Dysfunction, Arterial Thromboembolic Events, Hepatotoxicity, Renal Failure and Impairment Proteinuria, Diarrhea, Fistula Formation and Gastrointestinal Perforation, QT Interval Prolongation, Hypocalcemia, Reversible Posterior Leukoencephalopathy Syndrome Hemorrhagic Events, Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction, Wound Healing Complications.

DRUG INTERACTIONS

Chemotherapeutic agents

Concomitant administration of lenvatinib, carboplatin, and paclitaxel has no significant impact on the pharmacokinetics of any of these 3 substances.

Effect of Lenvatinib on other medicine

A clinical drug-drug interaction (DDI) study in cancer patients showed that plasma concentrations of midazolam (a sensitive CYP3A and Pgp substrate) were not altered in the presence of lenvatinib. No significant drug-drug interaction is therefore expected between lenvatinib and other CYP3A4/Pgp substrates.

Oral contraceptives

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.

USE IN SPECIFIC POPULATION

Women of childbearing potential

Women of childbearing potential should avoid becoming pregnant and use highly effective contraception while on treatment with lenvatinib and for at least one month after finishing treatment. 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.

Pregnancy

There are no data on the use of lenvatinib in pregnant women. Lenvatinib was embryotoxic and teratogenic when administered to rats and rabbits. Lenvatinib should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus.

Breast-feeding

It is not known whether lenvatinib is excreted in human milk. Lenvatinib and its metabolites are excreted in rat milk. A risk to newborns or infants cannot be excluded and, therefore, lenvatinib is contraindicated during breast-feeding.

Fertility

Effects in humans are unknown. However, testicular and ovarian toxicity has been observed in rats, dogs, and monkeys.

Patients with Renal Impairment

The pharmacokinetics of lenvatinib following a single 24 mg dose were evaluated in subjects with mild (CLcr 60-89 mL/min), moderate (CLcr 30-59 mL/min), or severe (CLcr <30 mL/min) renal impairment, and compared to healthy subjects. Subjects with end stage renal disease were not studied. The $AUC_{(0\text{-inf})}$ for subjects with renal impairment were similar compared to those for healthy subjects.

Patients with Hepatic Impairment

The pharmacokinetics of lenvatinib following a single 10 mg dose were evaluated in subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. The pharmacokinetics of a single 5 mg dose were evaluated in subjects with severe (Child-Pugh C) hepatic impairment. Compared to subjects with normal hepatic function, the dose-adjusted $AUC_{(0\text{-inf})}$ of lenvatinib for subjects with mild, moderate, and severe hepatic impairment were 119%, 107%, and 180%, respectively. Apparent oral clearance of lenvatinib in patients with HCC and mild hepatic impairment was similar to patients with HCC and moderate hepatic impairment.

Paediatric Population

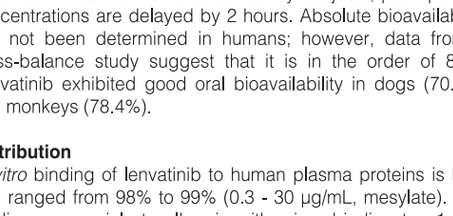
Paediatric patients have not been studied.

OVERDOSE

The highest doses of lenvatinib studied clinically were 32 mg and 40 mg per day. Accidental medication errors resulting in single doses of 40 to 48 mg have occurred in clinical trials. The most frequently observed adverse drug reactions at these doses were hypertension, nausea, diarrhoea, 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.

DESCRIPTION

Lenvatinib, 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 $C_{21}H_{19}ClN_4O_4.CH_4O_3S$, 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 & 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.

CLINICAL PHARMACOLOGY

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.

In addition, lenvatinib had selective, direct antiproliferative activity in hepatocellular cell lines dependent on activated FGFR signalling, which is attributed to the inhibition of FGFR signalling by lenvatinib.

Although not studied directly with lenvatinib, the mechanism of action (MOA) for hypertension is postulated to be mediated by the inhibition of VEGFR2 in vascular endothelial cells. Similarly, although not studied directly, the MOA for proteinuria is postulated to be mediated by downregulation of VEGFR1 and VEGFR2 in the podocytes of the glomerulus.

The mechanism of action for hypothyroidism is not fully elucidated.

Pharmacokinetic properties

Pharmacokinetic parameters of lenvatinib have been studied in healthy adult subjects, adult subjects with hepatic impairment, renal impairment, and solid tumours.

Absorption

Lenvatinib is rapidly absorbed after oral administration with T_{max} typically observed from 1 to 4 hours postdose. Food does not affect the extent of absorption but slows the rate of absorption. When administered with food to healthy subjects, peak plasma concentrations are delayed by 2 hours. Absolute bioavailability has not been determined in humans; however, data from a mass-balance study suggest that it is in the order of 85%. Lenvatinib exhibited good oral bioavailability in dogs (70.4%) and monkeys (78.4%).

Distribution

In vitro binding of lenvatinib to human plasma proteins is high and ranged from 98% to 99% (0.3 - 30 µg/mL, mesylate). This binding was mainly to albumin with minor binding to α1-acid glycoprotein and γ-globulin.

In vitro, the lenvatinib blood-to-plasma concentration ratio ranged from 0.589 to 0.608 (0.1 – 10 µg/mL, mesylate).

Lenvatinib is a substrate for P-gp and BCRP. Lenvatinib is not a substrate for OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE2-K or the bile salt export pump BSEP.

In patients, the median apparent volume of distribution (Vz/F) of the first dose ranged from 50.5 L to 92 L and was generally consistent across the dose groups from 3.2 mg to 32 mg. The analogous median apparent volume of distribution at steady-state (Vz/Fss) was also generally consistent and ranged from 43.2 L to 121 L.

Biotransformation

In vitro, cytochrome P450 3A4 was demonstrated as the predominant (>80%) isoform involved in the P450-mediated metabolism of lenvatinib. However, *in vivo* data indicated that non-P450-mediated pathways contributed to a significant portion of the overall metabolism of lenvatinib. Consequently, in vivo, inducers and inhibitors of CYP 3A4 had a minimal effect on lenvatinib exposure.

In human liver microsomes, the demethylated form of lenvatinib (M2) was identified as the main metabolite. M2' and M3', the major metabolites in human faeces, were formed from M2 and lenvatinib, respectively, by aldehyde oxidase.

In plasma samples collected up to 24 hours after administration, lenvatinib constituted 97% of the radioactivity in plasma radiochromatograms while the M2 metabolite accounted for an additional 2.5%. Based on $AUC_{(0-inf)}$, lenvatinib accounted for 60% and 64% of the total radioactivity in plasma and blood, respectively.

Elimination

Plasma concentrations decline bi-exponentially following C_{max}. The mean terminal exponential half-life of lenvatinib is approximately 28 hours.

Following administration of radiolabelled lenvatinib to 6 patients with solid tumours, approximately two-thirds and one-quarter of the radiolabel were eliminated in the faeces and urine, respectively. The M3 metabolite was the predominant analyte in excreta (~17% of the dose), followed by M2' (~11% of the dose) and M2 (~4.4 of the dose)

NONCLINICAL TOXICOLOGY

Carcinogenesis, mutagenesis, impairment of fertility 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.

PHARMACEUTICAL INFORMATION

Storage Conditions

Store in a cool and dry place. Do not store above 30°C. Do not take **LENVAXEN** if it is suspected of having been exposed to temperatures greater than 40° C or 104° F.

Keep **LENVAXEN** out of reach and sight of the children.
Dispended only in original container.

HOW SUPPLIED

LENVAXEN 4 capsules: Each Child-resistant HDPE container contains 30 capsules (each capsule contains Lenvatinib Mesylate INN equivalent to Lenvatinib 4 mg).

LENVAXEN 10 capsules: Each Child-resistant HDPE container contains 30 capsules (each capsule contains Lenvatinib Mesylate INN equivalent to Lenvatinib 10 mg).

Manufactured By
Everest Pharmaceuticals Ltd.
BSCIC, Kanchpur, Narayanganj, Bangladesh
www.everestpharmabd.com