Lanib

Lenvatinib Mesylate INN

DRUG INTERNATIONAL LTD.

COMPOSITION: Lanib-4: Each capsule contains Lenvatinib 4mg as Lenvatinib Mesylate INN.
Lanib-10: Each capsule contains Lenvatinib 10mg as Lenvatinib Mesylate INN.

CLINICAL PHARMACOLOGY

Mechanism of Action: Lenvatinib is a kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib inhibits other kinases 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; platelet derived growth factor receptor alpha (PDGFR), KIT, and RET. Lenvatinib also exhibited antiproliferative activity in hepatocellular carcinoma cell lines dependent on activated FGFR signaling with a concurrent inhibition of FGF-receptor substrate 2 (FRS2) phosphorylation.In syngeneic mouse tumor models, Lenvatinib decreased tumor-associated macrophages, increased activated cytotoxic T cells, and demonstrated greater antitumor activity in combination with an anti-PD-1 monoclonal antibody compared to either treatment alone.The combination of Lenvatinib and Everolimus showed increased antiangiogenic and antitumor activity as demonstrated by decreases in human endothelial cell proliferation, tube formation, and VEGF signaling in vitro, and by decreases in tumor volume in mouse xenograft models of human renal cell cancer that were greater than those with either drug alone.

Pharmacokinetics: Absorption The time to peak plasma concentration (Tmax) typically occurred from 1 to 4 hours post-dose. Food Effect: Administration with a high fat meal (approximately 900 calories of which approximately 55% were from fat, 15% from protein, and 30% from carbohydrates) did not affect the extent of absorption, but decreased the rate of absorption and delayed the median Tmax from 2 hours to 4 hours.

Distribution In vitro binding of Lenvatinib to human plasma proteins ranged from 98% to 99% at concentrations of 0.3 to 30 µg/mL. The blood-to-plasma concentration ratio ranged from 0.59 to 0.61 at concentrations of 0.1 to 10 µg/mL in vitro.

Elimination : The terminal elimination half-life of Lenvatinib was approximately 28 hours. Metabolism: The main metabolic pathways for Lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes. Excretion: Ten days after a single administration of radiolabeled Lenvatinib, approximately 64% and 25% of the radiolabel were eliminated in the feces and urine, respectively.

INDICATIONS

Differentiated Thyroid Cancer : Lenvatinib is indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC).

Renal Cell Carcinoma : Lenvatinib is indicated in combination with everolimus for the treatment of patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy.

Hepatocellular Carcinoma : Lenvatinib is indicated for the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC).

Endometrial Carcinoma : Lenvatinib, in combination with Pembrolizumab, is indicated 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. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

DOSAGE AND ADMINISTRATION : Important Dosage Information

- The dose reduction is needed for certain patients with renal or hepatic impairment.
- Lenvatinib should be taken 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.

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.

Lenvatinib should be taken orally once daily until disease progression or until unacceptable toxicity.

Recommended Dosage for Endometrial Carcinoma : The recommended dosage of Lenvatinib is 20 mg orally once daily, in combination with Pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks, until unacceptable toxicity or disease progression. Refer to the Pembrolizumab prescribing information for recommended Pembrolizumab dosing information.

Dosage Modifications for Adverse Reactions : Recommendations for Lenvatinib dose interruption, reduction and discontinuation for adverse reactions are listed in Table 1. Table 2 lists the recommended dosage reductions of Lenvatinib for adverse reactions.

Table 1. Recommended Dosage Modifications for Lenvatinib for Adverse Reactions

Adverse Reaction	Severity a	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.
Gastrointestinal 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.
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 Lenvatinibfor 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 every other day	Discontinue

When administering Lenvatinib in combination with Everolimus for the treatment of renal cell carcinoma, reduce the Lenvatinib dose first and then the Everolimus dose for adverse reactions of both Lenvatinib and Everolimus. Refer to the Everolimus prescribing information for additional dose modification information.

When administering Lenvatinib in combination with Pembrolizumab for the treatment of endometrial carcinoma, interrupt one or both drugs or dose reduce Lenvatinib as appropriate. No dose reductions are recommended for Pembrolizumab. Withhold or discontinue Pembrolizumab in accordance with the instructions in the Pembrolizumab prescribing information.

Dosage Modifications for Severe Renal Impairment : The recommended dosage of Lenvatinib for patients with DTC, RCC, or endometrial carcinoma and severe renal impairment (creatinine clearance less than 30 mL/min calculated by Cockcroft-Gault equation using actual body weight) is:

- Differentiated thyroid cancer: 14 mg orally once daily
- Renal cell carcinoma: 10 mg orally once daily
- Endometrial carcinoma: 10 mg orally once daily

Dosage Modifications for Severe Hepatic Impairment : The recommended dosage of Lenvatinib for patients with DTC, RCC, or endometrial carcinoma and severe hepatic impairment (Child-Pugh C) is:

- Differentiated thyroid cancer: 14 mg taken orally once daily
- Renal cell carcinoma: 10 mg taken orally once daily
- Endometrial carcinoma: 10 mg orally once daily

Or as directed by the registered physician.

Preparation and Administration : Lenvatinib 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.

ADVERSE 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.

CONTRAINDICATIONS : It is contraindicated in patients with known hypersensitivity to Lenvatinib or to any component of the formulation.

DRUG INTERACTIONS : 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.

PRECAUTIONS : Hypertension Hypertension occurred in 73% of patients in SELECT (DTC) receiving Lenvatinib 24 mg orally once daily and in 45% of patients in REFLECT (HCC) receiving Lenvatinib 8 mg or 12 mg orally once daily. The median time to onset of new or worsening hypertension was 16 days in SELECT and 26 days in REFLECT. Grade 3 hypertension occurred in 44% of patients in SELECT and in 24% in REFLECT. Grade 4 hypertension occurred <1% in SELECT and Grade 4 hypertension was not reported in REFLECT.

In patients receiving Lenvatinib 18 mg orally once daily with Everolimus in Study 205 (RCC), hypertension was reported in 42% of patients and the median time to onset of new or worsening hypertension was 35 days. Grade 3 hypertension occurred in 13% of patients. Systolic blood pressure ≥160 mmHg occurred in 29% of patients and diastolic blood pressure ≥100 mmHg occurred in 21%. Serious complications of poorly controlled hypertension have been reported. Control blood pressure prior to initiating Lenvatinib. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at a reduced dose when hypertension is controlled or permanently discontinue Lenvatinib based on severity.

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. Monitor patients with HCC closely for signs of hepatic failure, including hepatic encephalopathy. Withhold and resume at a reduced dose upon recovery or permanently discontinue Lenvatinib based on severity.

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. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Withhold and resume at reduced dose of Lenvatinib upon recovery based on severity.

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.

Reversible Posterior Leukoencephalopathy Syndrome : Across clinical studies of 1823 patients who received Lenvatinib as a single agent, 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. Serious tumor related bleeds, including fatal hemorrhagic events, occurred in patients treated with Lenvatinib in clinical trials and in the post-marketing setting. In post-marketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than in other tumor types. The safety and effectiveness of Lenvatinib in patients with ATC have not been demonstrated in clinical trials.

Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (e.g. carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue Lenvatinib based on the severity.

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). In those patients with a normal or low TSH at baseline, an elevation of TSH was observed post baseline in 70% of patients receiving Lenvatinib in REFLECT and 60% of patients receiving Lenvatinib with Everolimus in Study 205. Monitor thyroid function prior to initiating Lenvatinib and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

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.

Pediatric Use: The safety and effectiveness in pediatric patients have not been established.

Use in Pregnancy: Based on the mechanism of action, Lenvatinib can cause embryo-fetal harm when administered to a pregnant female. Pregnant women should be advised of the potential risk to a fetus. Females of reproductive potential should be advised to use effective contraception during treatment with Lenvatinib and for at least 30 days after the last dose.

Use in Lactation: It is not known whether Lenvatinib is present in human milk. Because of the potential for serious adverse reactions in breastfed infants, women should be advised to discontinue breastfeeding during treatment with Lenvatinib and for at least 1 week after the last dose.

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

PHARMACEUTICAL INFORMATION :

Storage: Store below 30^{O} C in a dry place. Protect from light. Keep out of the reach of children.
Packing: Lanib-4: Each container contains 30 capsules in a box.
Lanib-10: Each container contains 30 capsules in a box.