165mm

155mm

Hemorrhagic Events:
Withhold Lenvatinib for Grade 3 hemorrhage. Discontinue for Grade 4 hemorrhage.

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction:
Monitor TSH levels monthly and use thyroid replacement medication as needed.

Embryofetal Toxicity:
Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception.

EFFECT OF OTHER DRUGS ON LENVATINIB
No dose adjustment of LENVATINIB is recommended when co-administered with CYP3A, Pglycoprotein (P-gp), and breast cancer resistance protein (BCRP) inhibitors and CYP3A and P-gp inducers.

OVERDOSAGE
There is no specific antidote for overdose with LENVATINIB. Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable. Adverse reactions in patients receiving single doses of LENVATINIB as high as 40 mg were similar to the adverse events reported in the clinical studies at the recommended dose for DTC and RCC.

HOW SUPPLIED
LENVANIB 4mg tablet is available in Alu-Alu blister packs of 1x10's & 2x10's & 3x10's.
LENVANIB 10mg tablet is available in Alu-Alu blister packs of 1x10's & 2x10's & 3x10's.
Dosage: As directed by the physician.

Instructions: Store at 25°C, (Excursions permitted between 15°C to 30°C).
Protect from sunlight & moisture.
Keep out of the reach of children.
To be dispensed on the prescription of a registered medical practitioner only.

خوراک : ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات : دوا کو ۲۵ ڈگری سینٹی گریڈ درجہ حرارت پر رکھیں۔
(درجہ حرارت کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے)۔
دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

Kaizen Pharmaceuticals (Pvt) Ltd.

Manufactured by:
Kaizen Pharmaceuticals (Pvt.) Ltd.
E-127-129, North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

Art no. 1459

Lenvanib

(Lenvatinib Mesylate)

4mg & 10mg Capsule

لینوانِب

(لینواٹینب میسائیلیٹ)

۴ ملی گرام اور ۱۰ ملی گرام کیپسولز

Composition:

Each capsule contains:
Lenvatinib Mesylate 4.9mg Eq. to Lenvatinib 4mg

Each capsule contains:
Lenvatinib Mesylate 12.25mg Eq. to Lenvatinib 10mg

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

Pharmacodynamics:
Cardiac Electrophysiology: A single 32 mg dose (1.3 times the recommended daily dose) of Lenvatinib did not prolong the QT/QTc interval in a thorough QT study in healthy subjects. However, QT prolongation was observed in clinical studies

PHARMACOKINETICS
Absorption: After oral administration of LENVATINIB, time to peak plasma concentration (Tmax) typically occurred from 1 to 4 hours post-dose. Administration with food did not affect the extent of absorption, but decreased the rate of absorption and delayed the median Tmax from 2 hours to 4 hours. In patients with solid tumors administered single and multiple doses of LENVANIB once daily, the maximum lenvatinib plasma concentration (Cmax) and the area under the concentration- time curve (AUC) increased proportionally over the dose range of 3.2 to 32 mg with a median accumulation index of 0.96 (20 mg) to 1.54 (6.4 mg).

Distribution: In vitro binding of Lenvatinib to human plasma proteins ranged from 98% to 99% (0.3 – 30 µg/mL). In vitro, the Lenvatinib blood-to-plasma concentration ratio ranged from 0.589 to 0.608 (0.1 – 10 µg/mL).Based on in vitro data, Lenvatinib is a substrate of P-gp and BCRP but not a substrate for organic anion transporter (OAT) 1, OAT3, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, or the bile salt export pump (BSEP).

Elimination: Plasma concentrations declined bi-exponentially following Cmax. The terminal elimination half-life of lenvatinib was approximately 28 hours.
Metabolism: CYP3A is one of the main metabolic enzymes of lenvatinib. 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 to 6 patients with solid tumors, approximately 64% and 25% of the radiolabel were eliminated in the feces and urine, respectively.

INDICATIONS:
Lenvatinib is a kinase inhibitor that is indicated for: Hepatocellular Carcinoma (HCC): As first line therapy in patients with unresectable hepatocellular carcinoma. Differentiated Thyroid Cancer (DTC): Single agent for patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC. Renal Cell Cancer (RCC): Use in combination with Everolimus, for patients with advanced RCC following one prior anti-angiogenic therapy.

SPECIAL POPULATION
Pregnancy:
Lenvatinib can cause fetal harm when administered to pregnant woman.

Lactation Risk Summary:
It is not known whether Lenvatinib is present in human milk. However, Lenvatinib and its metabolites are excreted in rat milk at concentrations higher than in maternal. Because of the potential for serious adverse reactions in nursing infants from Lenvatinib, advise women to discontinue breastfeeding during treatment with Lenvatinib.

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

Geriatric Use:
Conclusions are limited due to the small sample size, but there appeared to be no overall differences in safety or effectiveness between subjects and younger subjects.

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), and severe (CLcr <30 mL/min) renal impairment, and compared to healthy subjects. Subjects with end stage renal disease were not studied. After a single 24 mg oral dose of LENVATINIB, the AUC0-inf for subjects with renal impairment were similar compared to those for healthy subjects.

Hepatic Impairment:
The pharmacokinetics of lenvatinib following a single 10 mg dose of LENVATINIB were evaluated in subjects with mild (Child Pugh A) and 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 AUC0-inf of lenvatinib for subjects with mild, moderate, and severe hepatic impairment were 119%, 107%, and 180%, respectively.

DOSAGE & ADMINISTRATION
Important Dosing Information
The recommended daily dose of LENVATINIB is 24 mg (two 10 mg capsules and one 4 mg capsule) orally taken once daily with or without food. Continue LENVATINIB until disease progression or until unacceptable toxicity occurs.
Take LENVATINIB 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.

Severe Renal or Hepatic Impairment:
The recommended dose of LENVATINIB is 14 mg taken orally once daily in patients with severe renal impairment (creatinine clearance [CLcr] less than 30 mL/min calculated by the Cockcroft-Gault equation) or severe hepatic impairment (Child-Pugh C).

ROUTE OF ADMINISTRATION
For oral administration only.

ADVERSE REACTIONS
In DTC, the most common adverse reactions (incidence greater than or equalto 30%) for Lenvatinib are hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, and dysphonia.
In RCC, the most common adverse reactions (greater than 30%) for Lenvatinib + Everolimus are diarrhea, fatigue, arthralgia/myalgia, decreased appetite, vomiting, nausea, stomatitis/oral inflammation, hypertension, peripheral edema, cough, abdominal pain, dyspnea, rash, weight decreased, hemorrhagic events, and proteinuria.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Hypertension:
Control blood pressure prior to treatment with Lenvatinib. Withhold Lenvatinib for Grade 3 hypertension despite optimal antihypertensive therapy. Discontinue for life-threatening hypertension.

Cardiac Failure:
Monitor for clinical symptoms or signs of cardiac decompensation. Withhold Lenvatinib for Grade 3 cardiac dysfunction. Discontinue for Grade 4 cardiac dysfunction.

Arterial Thromboembolic Events:
Discontinue Lenvatinib following an arterial thromboembolic event.

Hepatotoxicity:
Monitor liver function tests before initiation of Lenvatinib and periodically throughout treatment. Withhold Lenvatinib for Grade 3 or greater liver impairment. Discontinue for hepatic failure.

Proteinuria:
Monitor for proteinuria before initiation of, and periodically throughout, treatment with Lenvatinib. Withhold Lenvatinib for 2 grams of proteinuria for 24 hours. Discontinue for nephrotic syndrome.

Diarrhea:
May be severe and recurrent. Use standard anti-diarrheal therapy. Withhold Lenvatinib for Grade 3 and discontinue for Grade 4 diarrhea.

Renal Failure and Impairment:
Withhold Lenvatinib for Grade 3 or 4 renal failure/impairment.

Gastrointestinal Perforation and Fistula Formation:
Discontinue Lenvatinib in patients who develop gastrointestinal perforation or life threatening fistula

QT Interval Prolongation:
Monitor and correct electrolyte abnormalities in all patients. Withhold Lenvatinib for the development of Grade 3 or greater QT interval prolongation.

Hypocalcemia:
Monitor blood calcium levels at least monthly and replace calcium as necessary.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS):
Withhold Lenvatinib for RPLS until fully resolved.