Lenvakin

Lenvatinib Mesylate INN

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

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

Indications:
Lenvakin 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.

Dosage & Administration:
Recommended dose (HCC): 12 mg orally, once daily (for adults weighing >60 Kg). 8 mg orally, once daily for adults weighing <60 Kg).
Recommended dose (DTC): 24 mg orally, once daily.
Recommended dose (RCC): 18 mg Lenvatinib + 5 mg Everolimus, orally, once daily
Administration Instructions: Lenvatinib capsules should be swallowed whole. Alternatively, the capsules can be dissolved in a small glass of liquid. Measure 1 tablespoon of water or apple juice and put the capsules into the liquid without breaking or crushing them. Leave the capsules in the liquid for at least 10 minutes. Stir for at least 3 minutes. Drink the mixture. After drinking, add the same amount (1 tablespoon) of water or apple juice to the glass. Swirl the contents a few times and swallow the additional liquid.

Dose Modifications for DTC and RCC:
Table 1: Adverse Reactions Requiring Dose Modification of Lenvatinib in DTC and RCC

Adverse Reaction	CTCAE Grade	Action	Dose Reduce and Resume Lenvatinib
Hypertension	Grade 3	Hold	Resolves to Grade 0, 1, or 2
	Grade 4	Discontinue	Do Not Resume
Cardiac Dysfunction	Grade 3	Hold	Resolves to Grade 0, 1, or baseline
	Grade 4	Discontinue	Do Not Resume
Arterial Thrombotic Event	Any Grade	Discontinue	Do Not Resume
Hepatotoxicity	Grade 3 or 4	Hold or Discontinue	Consider resuming at reduced dose if resolves to Grade 0-1 or baseline
Hepatic Failure	Grade 3 or 4	Discontinue	Do Not Resume
Proteinuria	Greater than equal to 2 gm/24 hours	Hold	Resolves to less than 2 gm/24 hours
Nephrotic Syndrome	-------	Discontinue	Do Not Resume
Nausea, Vomiting, & Diarrhea[2]	Grade 3	Hold	Resolves to Grade 0, 1 or baseline
Vomiting and Diarrhea[2]	Grade 4	Discontinue	Do Not Resume
Renal Failure or Impairment	Grade 3 or 4	Hold or Discontinue	Consider resuming at reduced dose if resolves to Grade 0-1 or baseline
GI Perforation	Any Grade	Discontinue	Do Not Resume
Fistula	Grade 3 or 4	Discontinue	Do Not Resume
QTc Prolongation	Greater than 500 ms	Hold	Resolves to less than 480 ms or baseline
RPLS	Any Grade	Hold or Discontinue	Consider resuming at reduced dose if resolves to Grade 0 to 1
Hemorrhage	Grade 3	Hold	Resolves to Grade 0 to 1
	Grade 4	Discontinue	Do Not Resume

Recommendations for Dose Modifications in DTC:
Table 2: Dose Modifications for Lenvatinib for Persistent and Intolerable Grade 2 or Grade 3 Adverse Reactions or Grade 4 Laboratory Abnormalities in DTC.

Adverse Reaction	Modification	Adjusted Dose
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	20 mg (two 10 mg capsules) orally once daily
Second occurrence	Interrupt until resolved to Grade 0-1 or baseline	14 mg (one 10 mg capsules one 4 mg capsule) orally once daily
Third occurrence	Interrupt until resolved to Grade 0-1 or baseline	10 mg (one 10 mg capsule) orally once daily

Severe Renal or Hepatic Impairment in DTC:
For patients with DTC, 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.

Recommendations for Dose Modifications in RCC:
Table 3: Dose Modifications for Lenvatinib for Persistent and Intolerable Grade 2 or Grade 3 Adverse Reactions or Grade 4 Laboratory Abnormalities in RCC.

Adverse Reaction	Modification	Adjusted Dose
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	14 mg (one 10 mg capsule One 4 mg capsule) orally once daily
Second occurrence	Interrupt until resolved to Grade 0-1 or baseline	10 mg (one 10 mg capsule) orally once daily
Third occurrence	Interrupt until resolved to Grade 0-1 or baseline	8 mg (Two 4 mg capsules) orally once daily

Severe Renal or Hepatic Impairment in RCC:
For patients with RCC, the recommended dose of Lenvatinib is 10 mg taken orally once daily in patients with severe renal impairment (CLcr less than 30 mL/min. In patients with severe renal or hepatic impairment, the dose is 14 mg, once daily in DTC and 10 mg once daily in RCC

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

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

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

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

Use in Special Populations:
Pregnancy: Lenvatinib can cause fetal harm when administered to pregnant woman.
Lactation
Risk Summary: It is not known whether Lenvatinib is present in human milk. 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.
Females and Males of Reproductive Potential
Contraception: Based on its mechanism of action, Lenvatinib can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with Lenvatinib and for at least 2 weeks following completion of therapy.
Infertility
Females: Lenvatinib may result in reduced fertility in females of reproductive potential.
Males: Lenvatinib may result in damage to male reproductive tissues leading to reduced fertility of unknown duration.
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 No dose adjustment is recommended in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended dose is 14 mg in the treatment of DTC and 10 mg in the treatment of RCC, either taken orally once daily. Patients with end stage renal disease were not studied.
Hepatic Impairment No dose adjustment is recommended in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, the recommended dose is 14 mg in the treatment of DTC and 10 mg in the treatment of RCC, either taken orally once daily.

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

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 Lenvakin 120 mg orally.

Storage:
Do not store above 30° C. Protect from light. Keep out of the reach of children.

Packing:
Lenvakin 4 Capsule: Each box contains 2x7's capsules in blister pack.
Lenvakin 10 Capsule: Each box contains 2x7's capsules in blister pack.

Manufactured by:
Ziska Pharmaceuticals Ltd.
Kaliakoir, Gazipur, Bangladesh

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