Lenvanix
Lenvatinib

COMPOSITION

Lenvanix 4 Capsule: Each capsule contains Lenvatinib Mesylate INN equivalent to Lenvatinib 4 mg.

Lenvanix 10 Capsule: Each capsule contains Lenvatinib Mesylate INN equivalent to Lenvatinib 10 mg.

THERAPEUTIC CLASS

Anti-cancer

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 FGFR1, 2, 3, and 4; the platelet derived growth factor receptor alpha (PDGFR), KIT, and RET. The combination of Lenvatinib and Everolimus showed increased antiangiogenic and antitumor activity as demonstrated by decreased human endothelial cell proliferation, tube formation, and VEGF signaling *in vitro* and tumor volume in mouse xenograft models of human renal cell cancer greater than each drug alone.

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 (T_{max}) 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 Lenvanix once daily, the maximum Lenvatinib plasma concentration (C_{max}) 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).

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.

Elimination: Plasma concentrations declined bi-exponentially following C_{max}. The terminal elimination half-life of Lenvatinib was approximately 28 hours.

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.

DOSAGE AND 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 Modification in HCC

The dose may be reduced depending on the condition of the individual patients.

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[1]	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 or 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

[1]Grade 3 despite optimal anti-hypertensive therapy

[2]Initiate prompt medical management for nausea, vomiting or diarrhea. Permanently discontinue for Grade 4 vomiting and diarrhea despite medical management

Manage other adverse reactions according to the instructions in Table 2 for DTC or Table 3 for RCC.

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[a]

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

[a]Initiate medical management for nausea, vomiting, or diarrhea prior to interruption or dose reduction of Lenvatinib
[b]Reduce dose in succession based on the previous dose level (24 mg, 20 mg, or 14 mg per day)
[c]Refers to the same or a different adverse reaction that requires dose modification

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 calculated by the Cockcroft-Gault equation) or severe hepatic impairment (Child- Pugh C)

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[a]

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

[a]Initiate medical management for nausea, vomiting, or diarrhea prior to interruption or dose reduction of Lenvatinib
[b]Reduce dose in succession based on the previous dose level (18 mg, 14 mg, 10 mg, or 8 mg per day)
[c]Refers to the same or a different adverse reaction that requires dose modification

Recommendations for Dose Modification of Everolimus in RCC

Review the Full Prescribing Information for Everolimus for recommended dose modifications. For toxicities thought to be related to Everolimus alone, discontinue, interrupt, or use alternate day dosing. For toxicities thought to be related to both Lenvatinib and Everolimus, first reduce Lenvatinib and then Everolimus.

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 (CL_{cr} less than 30 mL/min calculated by the Cockcroft-Gault equation) or severe hepatic impairment (Child-Pugh C).

In patients with severe renal or hepatic impairment, the dose is 14 mg, once daily in DTC and 10 mg once daily in RCC

USE IN SPECIFIC 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.

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.

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 lifethreatening 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.

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 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.

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.

PHARMACEUTICAL INFORMATION

Storage Conditions

Store in a cool and dry place, away from light. Keep out of the reach of children.

Presentation & Packaging

Lenvanix 4 Capsule: Each commercial box contain 30 capsules in a Pot.

Lenvanix 10 Capsule: Each commercial box contain 30 capsules in a Pot.

Manufactured By
Beacon Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

Marketed By
BEACON®
Medicare Limited
Dhaka, Bangladesh

Only for Export

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