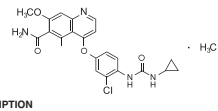
LENVATIZ 4/10
Lenvatinib Capsules 4mg /10 mg

Rx only
COMPOSITION
LENVATIZ 4
Lenvatinib Capsules 4 mg
Each Capsule contains
Lenvatinib mesylate
equivalent to Lenvatinib 4 mg
Excipients q.s.
Colours: Approved colors used in capsule shell.

LENVATIZ 10
Lenvatinib Capsules 10 mg
Each Capsule contains
Lenvatinib mesylate
equivalent to Lenvatinib 10 mg
Excipients q.s.
Colours: Approved colors used in capsule shell.



DESCRIPTION
LENVATIZ, a kinase inhibitor, is the mesylate salt of Lenvatinib. Its chemical name is 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate. The molecular formula is $C_{21}H_{19}ClN_4O_4 \cdot CH_4O_3S$, and the molecular weight of the mesylate salt is 522.96.
Lenvatinib is a white to pale reddish yellow powder. It is slightly soluble in water and practically insoluble in ethanol (dehydrated). The dissociation constant (pKa value) of LENVATIZ is 5.05 at 25°C. The partition coefficient (log P value) is 3.30.
Each 4 mg or 10 mg capsules of Lenvatinib, equivalent to 4.90 mg or 12.25 mg of Lenvatinib mesylate. Following are inactive ingredients: Calcium Carbonate, Mannitol, Microcrystalline Cellulose, Hydroxypropyl Cellulose, Hydroxypropyl Cellulose; and Talc. The hypromellose capsule shell contains titanium dioxide, ferric oxide yellow, and ferric oxide red. The printing ink contains shellac, black iron oxide, potassium hydroxide, and propylene glycol.

CLINICAL PHARMACOLOGY
Mechanism of Action: LENVATIZ 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). LENVATIZ 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. The combination of LENVATIZ 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 LENVATIZ 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 LENVATIZ, 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 LENVATIZ once daily, the maximum LENVATIZ 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 LENVATIZ to human plasma proteins ranged from 98% to 99% (0.3 – 30 µg/mL). In vitro, the LENVATIZ blood-to-plasma concentration ratio ranged from 0.589 to 0.609 (0.1 – 10 µg/mL).
Based on in vitro data, LENVATIZ 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 LENVATIZ was approximately 28 hours.
Metabolism: CYP3A is one of the main metabolic enzymes of LENVATIZ. The main metabolic pathways for LENVATIZ in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes.
Excretion: Ten days after a single administration of radiolabeled LENVATIZ to 6 patients with solid tumors, approximately 64% and 25% of the radiolabel were eliminated in the feces and urine, respectively.
Specific Populations:
Renal Impairment: The pharmacokinetics of LENVATIZ 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 LENVATIZ, the AUC0-inf for subjects with renal impairment were similar compared to those for healthy subjects.
Hepatic Impairment: The pharmacokinetics of LENVATIZ following a single 10 mg dose of LENVATIZ 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 LENVATIZ for subjects with mild, moderate, and severe hepatic impairment were 119%, 107%, and 180%, respectively.
Effects of Age, Sex, and Race: Based on a population PK analysis, weight, age, sex, and race did not have a significant effect on apparent clearance (CL/F) of LENVATIZ.

DOSAGE AND ADMINISTRATION
Recommended Dose for DTC: The recommended daily dose of LENVATIZ is 24 mg (two 10 mg capsules and one 4 mg capsule) orally taken once daily with or without food. Continue LENVATIZ until disease progression or until unacceptable toxicity. Take LENVATIZ 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 Dose for RCC: The recommended daily dose of LENVATIZ is 18 mg (one 10 mg capsule and two 4 mg capsules) in combination with 5 mg everolimus orally taken once daily with or without food. Continue LENVATIZ plus everolimus until disease progression or until unacceptable toxicity. Take LENVATIZ and everolimus 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.
Administration Instructions: LENVATIZ 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.

ADVERSE REACTIONS
Differentiated Thyroid Cancer: The safety data described below are derived from Study 1 which randomized (2:1) patients with radioactive iodine-refractory differentiated thyroid cancer (RAI-refractory DTC) to LENVATIZ (n=261) or placebo (n=131). The median treatment duration was 16.1 months for Lenvatinib and 3.9 months for placebo. Among 261 patients who received LENVATIZ in Study 1, median age was 64 years, 52% were women, 80% were White, 18% were Asian, and 2% were Black; 4% identified themselves as having Hispanic or Latino ethnicity.
In Study 1, the most common adverse reactions observed in LENVATIZ - treated patients (greater than or equal to 30%) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia (PPE) syndrome, abdominal pain, and dysphonia. The most common serious adverse reactions (at least 2%) were pneumonia (4%), hypertension (3%), and dehydration (3%).
Adverse reactions led to dose reductions in 68% of patients receiving LENVATIZ and 5% of patients receiving placebo; 18% of patients discontinued LENVATIZ and 5% discontinued placebo for adverse reactions. The most common adverse reactions (at least 10%) resulting in dose reductions of LENVATIZ were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions (at least 1%) resulting in discontinuation of LENVATIZ were hypertension (1%) and asthenia (1%).

Table 1 presents the percentage of patients in Study 1 experiencing adverse reactions at a higher rate in LENVATIZ capsules-treated patients than patients receiving placebo in the double-blind phase of the DTC study.

	Lenvatinib 24 mg N=261		Placebo N=131	
Adverse Reaction	**All Grades (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Vascular Disorders				
Hypertension[a]	73	44	16	4
Hypotension	9	2	2	0
Gastrointestinal Disorders				
Diarrhea	67	9	17	0
Nausea	47	2	25	1
Stomatitis[b]	41	5	8	0
Vomiting	36	2	15	0
Abdominal pain[c]	31	2	11	1
Constipation	29	0.4	15	1
Oral pain[d]	25	1	2	0
Dry mouth	17	0.4	8	0
Dyspepsia	13	0.4	4	0
General Disorders and Administration Site Conditions				
Fatigue[e]	67	11	35	4
Edema peripheral	21	0.4	8	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/Myalgia[f]	62	5	28	3
Metabolism and Nutrition Disorders				
Weight decreased	51	13	15	1
Decreased appetite	54	7	18	1
Dehydration	9	2	2	1
Nervous System Disorders				
Headache	38	3	11	1
Dysgeusia	18	0	3	0
Dizziness	15	0.4	9	0
Renal and Urinary Disorders				
Proteinuria	34	11	3	0
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia	32	3	1	0
Rash[g]	21	0.4	3	0
Alopecia	12	0	5	0
Hyperkeratosis	7	0	2	0
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	31	1	5	0
Cough	24	0	18	0
Epistaxis	12	0	1	0
Psychiatric Disorders				
Insomnia	12	0	3	0
Infections and Infestations				
Dental and oral infections[h]	10	1	1	0
Urinary tract infection	11	1	5	0
Cardiac Disorders				
Electrocardiogram QT prolonged	9	2	2	0

a Includes hypertension, hypertensive crisis, increased blood pressure diastolic, and increased blood pressure
b Includes aphthous stomatitis, stomatitis, glossitis, mouth ulceration, and mucosal inflammation
c Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal pain
d Includes oral pain, glossodynia, and oropharyngeal pain
e Includes asthenia, fatigue, and malaise
f Includes musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia
g Includes macular rash, maculo-papular rash, generalized rash, and rash
h Includes gingivitis, oral infection, parotitis, pericoronitis, periodontitis, sialoadenitis, tooth abscess, and tooth infection

Renal Cell Carcinoma: The data described below are derived from Study 2 which randomized (1:1:1) patients with unresectable advanced or metastatic renal cell carcinoma (RCC) to LENVATIZ 18 mg + everolimus 5 mg (n=51), LENVATIZ 24 mg (n=52), or everolimus 10 mg (n=50) once daily. This data also includes patients on the dose escalation portion of the study who received LENVATIZ 18 mg + everolimus 5 mg (n=11). The median treatment duration was 8.1 months for LENVATIZ + everolimus and 4.1 months for everolimus. Among 62 patients who received LENVATIZ + everolimus in Study 2, the median age was 61 years, 71% were men, and 98% were White. The most common adverse reactions observed in the LENVATIZ + everolimus-treated group (> 30%) were, in order of decreasing frequency, 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. The most common serious adverse reactions (≥ 5%) were renal

failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%).
Adverse reactions led to dose reductions or interruption in 89% of patients receiving Lenvatinib + everolimus and 54% in patients receiving everolimus. The most common adverse reactions (≥ 5%) resulting in dose reductions in the Lenvatinib + everolimus-treated group were diarrhea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%).
Treatment discontinuation due to an adverse reaction occurred in 29% of patients in the Lenvatinib + everolimus-treated group and 12% of patients in the everolimus-treated group.

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

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

WARNINGS AND PRECAUTIONS
Hypertension: In Study 1 in DTC, hypertension was reported in 73% of LENVATIZ -treated patients and 16% of patients in the placebo group. The median time to onset of new or worsening hypertension was 16 days for LENVATIZ -treated patients. The incidence of Grade 3 hypertension was 44% as compared to 4% for placebo, and the incidence of Grade 4 hypertension was less than 1% in LENVATIZ -treated patients and none in the placebo group.
In Study 2 in RCC, hypertension was reported in 42% of patients in the Lenvatinib + everolimus-treated group and 10% of patients in the everolimus-treated group. The median time to onset of new or worsening hypertension was 35 days for Lenvatinib + everolimus-treated patients. The incidence of Grade 3 hypertension was 13% in the Lenvatinib + everolimus-treated group as compared to 2% in the everolimus-treated group. Systolic blood pressure ≥ 160mmHg occurred in 29% and 21% of patients had a diastolic blood pressure ≥100 in the Lenvatinib + everolimus-treated group.
Control blood pressure prior to treatment with LENVATIZ. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment with LENVATIZ. Withhold LENVATIZ for Grade 3 hypertension despite optimal antihypertensive therapy; resume at a reduced dose when hypertension is controlled at less than or equal to Grade 2. Discontinue LENVATIZ for life-threatening hypertension
Cardiac Dysfunction: In Study 1 in DTC, cardiac dysfunction, defined as decreased left or right ventricular function, cardiac failure, or pulmonary edema, was reported in 7% of Lenvatinib -treated patients (2% Grade 3 or greater) and 2% (no Grade 3 or greater) of patients in the placebo group. The majority of these cases in Lenvatinib -treated patients (14 of 17 cases) were based on findings of decreased ejection fraction as assessed by echocardiography. Six of 261 (2%) of patients in the Lenvatinib arm in Study 1 had greater than 20% reduction in ejection fraction as measured by echocardiography compared to no patients who received placebo.
In Study 2 in RCC, decreased ejection fraction and cardiac failure were reported in 10% of patients in the Lenvatinib + everolimus-treated group and 6% of patients in the everolimus-treated group. Grade 3 events occurred in 3% of Lenvatinib+ everolimus-treated patients and 2% of everolimus-treated patients. In the Lenvatinib + everolimus-treated group there were two patients with a Grade 2 to 4 decrease in LVEF as assessed by MUGA.
Monitor patients for clinical symptoms or signs of cardiac decompensation. Withhold LENVATIZ for development of Grade 3 cardiac dysfunction until improved to Grade 0 or 1 or baseline. Either resume at a reduced dose or discontinue LENVATIZ depending on the severity and persistence of cardiac dysfunction. Discontinue Lenvatinib for Grade 4 cardiac dysfunction.
Arterial Thromboembolic Events: In study 1 in DTC, arterial thromboembolic events were reported in 5% of Lenvatinib-treated patients and 2% of patients in the placebo group. The incidence of arterial thromboembolic events of grade 3 or greater was 3% in Lenvatinib-treated patients and 1% in the placebo group. In study 2 in RCC, 2% of patients in the Lenvatinib + everolimus-treated group and 6% of patients in the everolimus-treated group had arterial thromboembolic events reported. The incidence of arterial thromboembolic events of grade 3 or greater was 2% with Lenvatinib + everolimus-treated patients and 4% in the everolimus-treated group. Discontinue LENVATIZ following an arterial thrombotic event. The safety of resuming LENVATIZ after an arterial thromboembolic event has not been established and LENVATIZ has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.
Hepatotoxicity: Across clinical studies in which 1160 patients received LENVATIZ monotherapy, hepatic failure (including fatal events) was reported in 3 patients and acute hepatitis was reported in 1 patient. In study 1 in DTC, 4% of Lenvatinib-treated patients experienced an increase in alanine aminotransferase (ALT) and 5% experienced an increase in aspartate aminotransferase (AST) that was grade 3 or greater. No patients in the placebo group experienced grade 3 or greater increases in ALT or AST. The incidence of alt and ast elevation was similar in study 2 in rcc. In study 2, 3% of Lenvatinib + everolimus-treated patients experienced an increase in ALT and 3% experienced an increase in AST that was grade 3 or greater. Two percent of patients in the everolimus-treated group experienced an increase in alt and none experienced an increase in AST that was grade 3 or greater.
Monitor liver function before initiation of LENVATIZ, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Withhold LENVATIZ for the development of grade 3 or greater liver impairment until resolved to grade 0 to 1 or baseline. Either resume at a reduced dose or discontinue LENVATIZ depending on the severity and persistence of hepatotoxicity. Discontinue LENVATIZ for hepatic failure.
Proteinuria: In study 1 in DTC, proteinuria was reported in 34% of Lenvatinib-treated patients and 3% of patients in the placebo group. The incidence of grade 3 proteinuria in Lenvatinib-treated patients was 11% compared to none in the placebo group.
In study 2 in RCC, proteinuria was reported in 31% of patients in the Lenvatinib + everolimus-treated group and 14% of patients in the everolimus-treated group. The incidence of grade 3 proteinuria in Lenvatinib+everolimus-treated patients was 8% compared to 2% in everolimus-treated patients.
Monitor for proteinuria before initiation of, and periodically throughout treatment. If urine dipstick proteinuria greater than or equal to 2+ is detected, obtain a 24 hour urine protein. Withhold Lenvatinib for ≥2 grams of proteinuria/24 hours and resume at a reduced dose when proteinuria is <2 gm/24 hours. Discontinue LENVATIZ for nephrotic syndrome.
Renal Failure and Impairment: In study 1 in DTC, events of renal impairment were reported in 14% of Lenvatinib-treated patients compared to 2% of patients in the placebo group. The incidence of grade 3 or greater renal failure or impairment was 3% in Lenvatinib-treated patients and 1% in the placebo group. In study 2 in RCC, renal impairment was reported in 18% of Lenvatinib + everolimus-treated group and 12% in the everolimus-treated group. The incidence of grade 3 or greater renal failure or impairment was 10% in the Lenvatinib + everolimus-treated group and 2% in the everolimus-treated group. One risk factor for severe renal impairment in Lenvatinib-treated patients was dehydration/hypovolemia due to diarrhea and vomiting. Active management of diarrhea and any other gastrointestinal symptoms should be initiated for grade 1 events.
Withhold LENVATIZ for development of grade 3 or 4 renal failure/impairment until resolved to grade 0 to 1 or baseline. Either resume at a reduced dose or discontinue LENVATIZ depending on the severity and persistence of renal impairment.
Gastrointestinal Perforation and Fistula Formation: In study 1 in DTC, events of gastrointestinal perforation or fistula were reported in 2% of Lenvatinib-treated patients and 0.8% of patients in the placebo group. In study 2 in RCC, grade 3 or greater gastrointestinal perforation, abscess or fistula was reported in 2% of patients in the Lenvatinib + everolimus-treated group and no patients in the everolimus-treated group. The events resolved in all patients. Discontinue LENVATIZ in patients who develop gastrointestinal perforation or life-threatening fistula.
Hypocalcemia: In study 1 in DTC, 9% of Lenvatinib-treated patients experienced grade 3 or greater hypocalcemia compared to 2% in the placebo group. In most cases hypocalcemia responded to replacement and dose interruption/dose reduction.
In study 2 in RCC, 6% of patients in the Lenvatinib + everolimus-treated group and 2% of patients in the everolimus-treated group experienced grade 3 or greater hypocalcemia. No patients discontinued due to hypocalcemia.
Monitor blood calcium levels at least monthly and replace calcium as necessary during LENVATIZ treatment. Interrupt and adjust LENVATIZ dosing as necessary depending on severity, presence of ECG changes, and persistence of hypocalcemia.
Reversible Posterior Leukoencephalopathy Syndrome: Across clinical studies in which 1160 patients received LENVATIZ monotherapy, there were 4 reported events of reversible posterior leukoencephalopathy syndrome (RPLS). Confirm the diagnosis of RPLS with MRI. Withhold for RPLS until fully resolved. Upon resolution, resume at a reduced dose or discontinue LENVATIZ depending on the severity and persistence of neurologic symptoms.
Embryofetal Toxicity: Based on its mechanism of action and data from animal reproduction studies, LENVATIZ can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of LENVATIZ during organogenesis at doses below the recommended human dose 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 LENVATIZ and for at least 2 weeks following completion of therapy.

OVERDOSAGE
There is no specific antidote for overdose with LENVATIZ. Due to the high plasma protein binding, LENVATIZ is not expected to be dialyzable. Adverse reactions in patients receiving single doses of LENVATIZ 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
LENVATIZ 4 & 10 supplied as 30 Capsules packed in a HDPE container.

STORAGE
Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59 °F to 86°F).

SHELF LIFE
24 months

MANUFACTURED & MARKETED BY:
Tizig Pharma Private Limited
Factory: Tukucha, Nala-1, Banepa, Nepal.
Regd. Office: Maligaun-5, Kathmandu, Nepal.