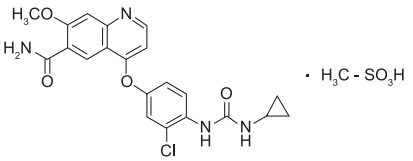
LENVUS™
(LENVATINIB)

لینوس

Capsules 4mg and 10mg

DESCRIPTION
Lenvus (Lenvatinib), 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. Its molecular formula is $C_{21}H_{19}ClN_4O_4 \cdot CH_4O_3S$, and the structural formula is:



Lenvatinib Mesylate

QUALITATIVE AND QUANTITATIVE COMPOSITION
Lenvus (Lenvatinib) is available for oral administration as:

Lenvus Capsules 4mg
Each capsule contains:
Lenvatinib Mesylate equivalent to Lenvatinib…4mg

Lenvus Capsules 10mg
Each capsule contains:
Lenvatinib Mesylate equivalent to Lenvatinib …10mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFRα, KIT, and RET. In addition, Lenvatinib had selective, direct antiproliferative activity in hepatocellular cell lines dependent on activated FGFR signalling, which is attributed to the inhibition of FGFR signalling by Lenvatinib.

Pharmacokinetics
Absorption
The time to peak plasma concentration (T_{max}) 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 T_{max} from 2 hours to 4 hours.

Distribution
Protein binding of Lenvatinib is 97% to 99%, which is independent of concentration, and is not impacted by hepatic or renal function. The blood-to-plasma concentration ratio ranged from 0.59 to 0.61 at concentrations of 0.1 to 10μg/mL in vitro.

Metabolism
The main metabolic pathways for Lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes.

Elimination
The terminal elimination half-life of Lenvatinib was approximately 28 hours. Ten days after a single administration of radiolabeled Lenvatinib, approximately 64% and 25% of the radiolabel were eliminated in the feces and urine, respectively.

Dose proportionality and accumulation
In patients with solid tumours administered single and multiple doses of Lenvatinib once daily, exposure to Lenvatinib (C_{max} and AUC) increased in direct proportion to the administered dose over the range of 3.2 to 32mg once-daily.
Lenvatinib displays minimimal accumulation at steady state. Over this range, the median accumulation index (Rac) ranged from 0.96 (20mg) to 1.54 (6.4mg). The Rac in Hepatocellular Carcinoma (HCC) subjects with mild and moderate liver impairment was similar to that reported for other solid tumours.

THERAPEUTIC INDICATIONS
Differentiated Thyroid Carcinoma (DTC)
Lenvus (Lenvatinib) as monotherapy is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).

Hepatocellular Carcinoma (HCC)
Lenvus (Lenvatinib) as monotherapy is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy.

Endometrial Carcinoma (EC)
Lenvus (Lenvatinib) in combination with pembrolizumab is indicated for the treatment of adult patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation.

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

DOSAGE AND ADMINISTRATION
Important Administration Points
Lenvus (Lenvatinib) treatment should be initiated and supervised by a healthcare professional experienced in the use of anticancer therapies.
Optimal medical management (i.e., treatment or therapy) for nausea, vomiting, and diarrhoea should be initiated prior to any Lenvus (Lenvatinib) therapy interruption or dose reduction; gastrointestinal toxicity should be actively treated in order to reduce the risk of development of renal impairment or failure.

Missed Dose
If a patient misses a dose, and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration.
Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Differentiated Thyroid Cancer (DTC)
The recommended daily dose of Lenvus (Lenvatinib) is 24mg (two 10mg capsules and one 4mg capsule) once daily. The daily dose is to be modified as needed according to the dose/toxicity management plan.

Dose adjustments and discontinuations for DTC
Management of adverse reactions may require dose interruption, adjustment, or discontinuation of Lenvus (Lenvatinib) therapy. Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of Lenvus (Lenvatinib), unless intolerable to the patient despite optimal management. Severe (e.g., Grade 3) or intolerable adverse reactions require interruption of Lenvus (Lenvatinib) until improvement of the reaction to Grade 0 to 1 or baseline.

For Lenvus (Lenvatinib) related toxicities (see Table below), upon resolution/improvement of an adverse reaction to Grade 0 to 1 or baseline, treatment should be resumed at a reduced dose of Lenvus (Lenvatinib) as suggested in table 1 below.

Table 1: Dose modifications from recommended Lenvus (Lenvatinib) daily dose in DTC patients[a]

Dose level	Daily dose	Number of capsules
Recommended daily dose	24mg orally once daily	Two 10mg capsules plus one 4mg capsule
First dose reduction	20mg orally once daily	Two 10mg capsules
Second dose reduction	14mg orally once daily	One 10mg capsule plus one 4mg capsule
Third dose reduction	10mg orally once daily[a]	One 10mg capsule

[a]: Further dose reductions should be considered on an individual patient basis as limited data are available for doses below 10mg.

Treatment should be discontinued in case of life-threatening reactions (e.g., Grade 4) with the exception of laboratory abnormalities judged to be non-life-threatening, in which case they should be managed as severe reactions (e.g., Grade 3).

Hepatocellular Carcinoma (HCC)
The recommended daily dose of Lenvus (Lenvatinib) is 8mg (two 4mg capsules) once daily for patients with a body weight of < 60kg and 12mg (three 4mg capsules) once daily for patients with a body weight of ≥ 60kg. Dose adjustments are based only on toxicities observed and not on body weight changes during treatment. The daily dose is to be modified, as needed, according to the dose/toxicity management plan.

Dose adjustments and Discontinuation for HCC
Management of some adverse reactions may require dose interruption, adjustment, or discontinuation of Lenvus (Lenvatinib) therapy. Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of Lenvus (Lenvatinib), unless intolerable to the patient despite optimal management. For Lenvatinib-related toxicities. Details for monitoring, dose adjustment and discontinuation are provided in table 2 below.

Table 2 : Dose modifications from recommended Lenvatinib daily dose in HCC patients

Starting Dose		≥60kg BW 12mg (three 4mg capsules orally once daily)	<60 kg BW 8mg (two 4mg capsules orally once daily)
Persistent and Intolerable Grade 2 or Grade 3 Toxicities [a]			
Adverse Reaction	**Modification**	**Adjusted Dose[b] (≥60 kg BW)**	**Adjusted Dose[b] (<60kg BW)**
First occurrence	Interrupt until resolved to Grade 0-1 or baseline[d]	8mg (two 4mg capsules) orally once daily	4mg (one 4mg capsule) orally once daily
Second occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline[d]	4mg (one 4mg capsule) orally once daily	4mg (one 4mg capsule) orally every other day
Third occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baselined	4mg (one 4mg capsule) orally every other day	Discontinue
Life-threatening toxicities (Grade 4): Discontinue[e]			

a. Initiate medical management for nausea, vomiting, or diarrhoea prior to interruption or dose reduction.
b. Reduce dose in succession based on the previous dose level (12mg, 8mg, 4mg or 4mg every other day).
c. Haematologic toxicity or proteinuria: no dose adjustment required for first occurrence.
d. For haematologic toxicity, dosing can restart when resolved to Grade 2; proteinuria, resume when resolves to less than 2g/24 hours.
e. Excluding laboratory abnormalities judged to be nonlife- threatening, which should be managed as Grade 3.

Endometrial Carcinoma (EC)
The recommended dosage of Lenvus (Lenvatinib) is 20mg orally once daily, in combination with pembrolizumab either 200mg every 3 weeks or 400mg every 6 weeks, administered as an intravenous infusion over 30 minutes, until unacceptable toxicity or disease progression.

Dose adjustments and Discontinuation for EC
For Lenvus (Lenvatinib)-related toxicities see table 3 below. When administering Lenvus (Lenvatinib) in combination with pembrolizumab, interrupt, dose reduce, or discontinue Lenvus (Lenvatinib) as appropriate. Withhold or discontinue pembrolizumab in accordance with the instructions in the SmPC for pembrolizumab. No dose reductions are recommended for pembrolizumab.

Table 3: Adverse reactions requiring dose modification of Lenvus (Lenvatinib)

Adverse reaction	Severity Action	Action	Dose reduce and resume Lenvatinib
Hypertension	Grade 3 (despite optimal antihypertensive therapy)	Interrupt	Resolves to Grade 0, 1 or 2. See detailed guidance in Table 4
	Grade 4	Discontinue	Do not resume.
Proteinuria	≥ 2g / 24 hours	Interrupt	Resolves to less than 2g / 24 hours.
Nephrotic syndrome	-------	Discontinue	Do not resume.
Renal impairment or failure	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume.
Cardiac dysfunction	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume.
Posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (RPLS)	Any grade	Interrupt	Consider resuming at reduced dose if resolves to Grade 0-1.
Hepatotoxicity	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume.
Arterial thromboembolisms	Any grade	Discontinue	Do not resume.
Haemorrhage	Grade 3	Interrupt	Resolves to Grade 0-1.
	Grade 4	Discontinue	Do not resume.
Gastrointestinal perforation or fistula	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume.
Non-gastrointestinal fistula	Grade 4	Discontinue	Do not resume.
QT interval prolongation	>500 ms	Interrupt	Resolves to <480 ms or baseline.
Diarrhoea	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4 (despite medical management)	Discontinue	Do not resume.

*Grade 4 laboratory abnormalities judged to be non-life-threatening, may be managed as severe reactions (e.g., Grade 3).

Table 4: Recommended management of hypertension

Blood Pressure (BP) level	Recommended action
Systolic BP ≥140mmHg up to <160mmHg or diastolic BP ≥90mmHg up to <100mmHg	Continue Lenvatinib and initiate antihypertensive therapy, if not already receiving OR Continue Lenvatinib and increase the dose of the current antihypertensive therapy or initiate additional antihypertensive therapy
Systolic BP ≥160mmHg or diastolic BP ≥100mmHg despite optimal antihypertensive therapy	1. Withhold Lenvatinib 2. When systolic BP ≤150mmHg, diastolic BP ≤95mmHg, and patient has been on a stable dose of antihypertensive therapy for at least 48 hours, resume Lenvatinib at a reduced dose
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis) Systolic BP ≥160mmHg or diastolic BP ≥100mmHg despite optimal antihypertensive therapy	Urgent intervention is indicated. Discontinue Lenvatinib and institute appropriate medical management.

Special Populations
DTC
Patients of age ≥75 years, of Asian race, with comorbidities (such as hypertension, and hepatic or

renal impairment), or body weight below 60kg appear to have reduced tolerability to Lenvus (Lenvatinib). All patients other than those with severe hepatic or renal impairment should initiate treatment at the recommended 24mg dose, following which the dose should be further adjusted on the basis of individual tolerability.

HCC
Patients ≥75 years, of white race or female sex or those with worse baseline hepatic impairment (Child-Pugh A score of 6 compared to score of 5) appear to have reduced tolerability to Lenvus (Lenvatinib).

HCC patients other than those with moderate and severe hepatic impairment or severe renal impairment should initiate treatment at the recommended starting dose of 8mg (two 4mg capsules) for body weight < 60kg and 12mg (three 4mg capsules) for body weight ≥ 60kg, following which the dose should be further adjusted on the basis of individual tolerability.

Patients with Hypertension
Blood pressure should be well controlled prior to treatment with Lenvus (Lenvatinib), and should be regularly monitored during treatment.

Recommended Dose Modifications for Adverse Reactions for Lenvus (Lenvatinib) in Combination with Pembrolizumab
When administering Lenvus (Lenvatinib) in combination with pembrolizumab, modify the dosage of one or both drugs as appropriate. Refer to pembrolizumab prescribing information for additional dose modification information.

Recommended Dose Modifications for Adverse Reactions for Lenvus (Lenvatinib) in Combination with Everolimus
When administering Lenvus (Lenvatinib) in combination with everolimus, withhold or reduce the Lenvus (Lenvatinib) dose first and then the everolimus dose for adverse reactions of both Lenvus (Lenvatinib) and everolimus. Refer to the everolimus prescribing information for additional dose modification information.

Dosage Modifications for Severe Renal Impairment
The recommended dosage of Lenvus (Lenvatinib) for patients with DTC, RCC, or endometrial carcinoma and severe renal impairment (creatinine clearance less than 30mL/min calculated by Cockcroft-Gault equation using actual body weight) is:
- Differentiated thyroid cancer: 14mg orally once daily
- Renal cell carcinoma: 10mg orally once daily
- Endometrial carcinoma: 10mg orally once daily

Dosage Modifications for Severe Hepatic Impairment
The recommended dosage of Lenvus (Lenvatinib) for patients with DTC, RCC, or endometrial carcinoma and severe hepatic impairment (Child-Pugh C) is:
- Differentiated thyroid cancer: 14mg taken orally once daily
- Renal cell carcinoma: 10mg taken orally once daily
- Endometrial carcinoma: 10mg orally once daily

Pediatric
The safety and efficacy of Lenvus (Lenvatinib) in children aged 2 to <18 years have not been established.

Elderly
No adjustment of starting dose is required on the basis of age. Limited data are available on use in patients aged ≥75 years.

Important Administration Points
- Lenvus (Lenvatinib) is for oral use. The capsules should be taken at about the same time each day, with or without food.
- Lenvus (Lenvatinib) capsules can be swallowed whole with water or administered as a suspension prepared by dispersing the whole capsule(s) in water, apple juice, or milk. The suspension may be administered orally or via a feeding tube. If administered via a feeding tube, then the suspension should be prepared using water.

ADVERSE REACTIONS
Very common
Urinary tract infection, thrombocytopenia, lymphopenia, leukopenia, neutropenia, hypothyroidism, increased blood thyroid stimulating hormone, hypocalcaemia, hypokalaemia, hypercholesterolaemia, hypomagnesaemia, decreased weight, decreased appetite, insomnia, dizziness, headache, dysgeusia, haemorrhage, hypertension, hypotension, dysphonia, diarrhoea, gastrointestinal and abdominal pains, vomiting, nausea, oral inflammation, oral pain, constipation, dyspepsia, dry mouth, increased lipase, increased amylase, increased blood bilirubin, hypoalbuminaemia, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood alkaline phosphatase, increased gamma-glutamyltransferase, palmar-plantar erythrodysaesthesia syndrome, rash, alopecia, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, proteinuria, increased blood creatinine, fatigue, asthenia and edema peripheral.

Uncommon
Perineal abscess, splenic infarction, adrenal insufficiency, posterior reversible encephalopathy syndrome, monoparesis, transient ischaemic attack, pneumothorax, pancreatitis, colitis, hepatocellular damage/hepatitis, osteonecrosis of the jaw, nephrotic syndrome and impaired healing.

Common
Dehydration, cerebrovascular accident, myocardial infarction, cardiac failure, prolonged electrocardiogram QT, decreased ejection fraction, pulmonary embolism, anal fistula, flatulence gastrointestinal perforation, hepatic failure, hepatic encephalopathy, abnormal hepatic function, cholecystitis, hyperkeratosis, renal failure, renal impairment, increased blood urea and malaise.

Not known
Non-gastrointestinal fistula.

Rare
Tumour lysis syndrome.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
Lenvatinib is contraindicated in patients with:
- Hypersensitivity to the active substance or to any of the excipients of the product.
- Breast-feeding.

PRECAUTIONS
Hypertension
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. 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
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
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 Hepatocellular Carcinoma (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. 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
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
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
Permanently discontinue Lenvatinib in patients who develop gastrointestinal perforation of any severity or Grade 3 or 4 fistula.

Non-gastrointestinal fistula
Patients may be at increased risk for the development of fistulae when treated with Lenvatinib. Lenvatinib should not be started in patients with fistula to avoid worsening and Lenvatinib should be permanently discontinued in patients withoesophageal or tracheobronchial tract involvement and any Grade 4 fistula.

Tumour lysis syndrome (TLS)
Lenvatinib can cause TLS which can be fatal. Risk factors for TLS include but are not limited to high tumour burden, pre-existing renal impairment and dehydration. These patients should be monitored closely and treated as clinically indicated, and prophylactic hydration should be considered.

QT Interval Prolongation
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
Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue Lenvatinib depending on severity.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
RPLS, has been reported in patients treated with Lenvatinib. 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
The safety and effectiveness of Lenvatinib in patients with anaplastic thyroid carcinoma (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. Monitor thyroid function prior to initiating Lenvatinib and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

Impaired Wound Healing
Impaired wound healing has been reported in patients who received Lenvatinib. Withhold Lenvatinib for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Lenvatinib after resolution of wound healing complications has not been established.

Osteonecrosis of the Jaw (ONJ)
Osteonecrosis of the Jaw (ONJ) has been reported in patients receiving Lenvatinib Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease or invasive dental procedures, may increase the risk of ONJ. Perform an oral examination prior to treatment with Lenvatinib and periodically during Lenvatinib treatment. Advise patients regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on Lenvatinib treatment, particularly in patients at higher risk. Withhold Lenvatinib for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold Lenvatinib if ONJ develops and restart based on clinical judgement of adequate resolution.

Embryo-Fetal Toxicity
Lenvatinib can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Lenvatinib and for 30 days after the last dose.

Women of childbearing potential
Women of childbearing potential should avoid becoming pregnant and use highly effective contraception while on treatment with Lenvatinib and for at least one month after finishing treatment. It is currently unknown whether Lenvatinib may reduce the effectiveness of hormonal contraceptives, and therefore women using oral hormonal contraceptives should add a barrier method.

Effects on ability to drive and use machines
Lenvatinib has minor influence on the ability to drive and use machines, due to undesirable effects such as fatigue and dizziness. Patients who experience these symptoms should use caution when driving or operating machines.

Race
Limited data are available for patients of ethnic origin other than Caucasian or Asian, and in patients aged ≥75 years. Lenvatinib should be used with caution in such patients, given the reduced tolerability of Lenvatinib in Asian and elderly patients.

Pregnancy
There are no data on the use of Lenvatinib in pregnant women. Lenvatinib should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus.

Nursing Mother
It is not known whether Lenvatinib is excreted in human milk. A risk to newborns or infants cannot be excluded and, therefore, Lenvatinib is contraindicated during breast-feeding.

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.

Oral contraceptives
It is currently unknown whether Lenvatinib may reduce the effectiveness of hormonal contraceptives, and therefore women using oral hormonal contraceptives should add a barrier method.

OVERDOSAGE
The most frequently observed adverse drug reactions at 32mg and 40mg per day were hypertension, nausea, diarrhoea, fatigue, stomatitis, proteinuria, headache, and aggravation of Palmar-Plantar Erythrodysesthesia. There have also been reports of overdose with Lenvatinib involving single administrations of 6 to 10 times the recommended daily dose. These cases were associated with adverse reactions consistent with the known safety profile of Lenvatinib (i.e., renal and cardiac failure), or were without adverse reactions.

Management
There is no specific antidote for overdose with Lenvatinib. In case of suspected overdose, Lenvatinib should be withheld and appropriate supportive care given as required.

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Lenvus (Lenvatinib) Capsules 4mg are available in blister pack of 30's.
Lenvus (Lenvatinib) Capsules 10mg are available in blister pack of 30's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Laboratorio Eczane Pharma S.A.
Laprida 43, Avellaneda (1870),
Buenos Aires, Argentina.

Manufactured for:

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