For the Use of a Registered Medical Practitioner only

1. Generic Name & Brand Name

Lenvatinib Capsules I.P. 4 mg
Lenvonco™ 4 mg

Lenvatinib Capsules I.P. 10 mg
Lenvonco™ 10 mg

2. Qualitative and Quantitative Composition

Lenvonco™ 4 mg
Each hard gelatin capsule contains:
Lenvatinib Mesylate I.P. …….4.90 mg
Eq. to Lenvatinib.....4 mg
Excipients..... ……q.s.
Approved colours used in capsule shell.

Lenvonco™ 10 mg
Each hard gelatin capsule contains:
Lenvatinib Mesylate I.P. ……..12.25 mg
Eq. to Lenvatinib.....10mg
Excipients..... …….q.s.
Approved colours used in capsule shell.

3. Dosage Form and Strength

Refer section 1 & 2

4. Clinical Particulars

4.1 Therapeutic Indications

- For the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer
- First line treatment of patients with unresectable hepatocellular carcinoma (HCC)
- In combination with Everolimus, for the treatment of patients with advance cell carcinoma (RCC) following one prior anti-angiogenic therapy.

4.2 Posology and Method of Administration

Lenvatinib Capsule treatment should be initiated and supervised by a health care professional experienced in the use of anticancer therapies. 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. Optimal medical management (i.e. treatment or therapy) for nausea, vomiting, and diarrhoea should be initiated prior to any 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.

Posology for Differentiated Thyroid Cancer (DTC)
The recommended daily dose of Lenvatinib is 24 mg (two 10 mg capsules and one 4 mg 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 Lenvatinib therapy. Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of Lenvatinib, unless intolerable to the patient despite optimal management. Severe (e.g., Grade 3) or intolerable adverse reactions require interruption of Lenvatinib until improvement of the reaction to Grade 0-1 or baseline.

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

Table Dose modifications from recommended Lenvatinib daily dose in DTC patients[a]

Dose level	Daily dose	Number of capsules
Recommended daily dose	24 mg orally once daily	Two 10 mg plus one 4 mg capsule
First dose reduction	20 mg orally once daily	Two 10 mg capsules
Second dose reduction	14 mg orally once daily	One 10 mg plus one 4 mg capsule
Third dose reduction	10 mg orally once daily [a]	One 10 mg capsule
a: Further dose reductions should be considered on an individual patient basis as limited data are available for doses below 10 mg.		

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

Posology for Renal cell carcinoma (RCC)
The recommended dosage of lenvatinib is 18 mg in combination with 5 mg everolimus orally once daily until disease progression or until unacceptable toxicity. 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.

RCC dose reductions for Adverse Reactions
- First occurrence: Reduce to 14 mg PO qDay
- Second occurrence: Reduce to 10 mg PO qDay
- Third occurrence: Reduce to 8 mg PO qDay

Dose modification of everolimus in RCC
- Reduce lenvatinib dose first and then the everolimus dose for adverse reactions of both

lenvatinib and everolimus.

- Refer to the everolimus prescribing information for additional dose modification information.

Posology for Hepatocellular Carcinoma

- Dose based on actual body weight
- <60 kg: 8 mg PO qDay
- ≥60 kg: 12 mg PO qDay
- Continue until disease progression or until unacceptable toxicity.

HCC dose modifications for Adverse Reactions

First occurrence
<60 kg: Reduce to 4 mg PO qDay
≥60 kg: Reduce to 8 mg PO qDay
Second occurrence
<60 kg: Reduce to 4 mg PO every other day
≥60 kg: Reduce to 4 mg PO qDay
Third occurrence
<60 kg: Discontinue
≥60 kg: Reduce to 4 mg PO every other day

Special populations

Elderly population
DTC
Patients of age ≥75 years, of Asian race, with comorbidities (such as hypertension, and hepatic or renal impairment), or body weight below 60 kg appear to have reduced tolerability to lenvatinib, Other special populations). All patients other than those with severe hepatic or renal impairment (see below) should initiate treatment at the recommended 24 mg 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 com- pared to score of 5) appear to have reduced tolerability to 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 8 mg (two 4 mg capsules) for body weight < 60 kg and 12 mg (three 4 mg capsules) for body weight ≥ 60 kg, following which the dose should be further adjusted on the basis of individual tolerability.

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

Patients with hypertension
Blood pressure should be well controlled prior to treatment with lenvatinib and should be regularly

monitored during treatment.

Patients with hepatic impairment

DTC
No adjustment of starting dose is required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child- Pugh B) hepatic impairment. In patients with severe (Child-Pugh C) hepatic impairment, the recommended starting dose is 14 mg taken once daily. Further dose adjustments may be necessary on the basis of individual tolerability.

HCC
In the patient populations enrolled in the HCC study no dose adjustments were required on the basis of hepatic function in those patients who had mild hepatic impairment (Child-Pugh A). The available very limited data are not sufficient to allow for a dosing recommendation for HCC patients with moderate hepatic impairment (Child-Pugh B). Close monitoring of overall safety is recommended in these patients. Lenvatinib has not been studied in patients with severe hepatic impairment (Child-Pugh C) and is not recommended for use in these patients.

RCC
No data with the combination is available in patients with hepatic impairment. No adjustment of starting dose of the combination is required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. In patients with severe (Child-Pugh C) hepatic impairment, the recommended starting dose of lenvatinib is 10 mg taken once daily in combination with the dose of everolimus recommended for patients with severe hepatic impairment in the everolimus SmPC. Further dose adjustments may be necessary on the basis of individual tolerability. The combination should be used in patients with severe hepatic impairment only if the anticipated benefit exceeds the risk.

Patients with renal impairment
DTC
No adjustment of starting dose is required on the basis of renal function in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended starting dose is 14 mg taken once daily. Further dose adjustments may be necessary based on individual tolerability. Patients with end-stage renal disease were not studied, therefore the use of lenvatinib in these patients is not recommended.

HCC
No dose adjustments are required on the basis of renal function in patients with mild or moderate renal impairment. The available data do not allow for a dosing recommendation for patients with HCC and severe renal impairment.

RCC
No adjustment of starting dose is required on the basis of renal function in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended starting dose is 10 mg of lenvatinib with 5 mg of everolimus taken once daily. Further dose adjustments

may be necessary based on individual tolerability. Patients with end-stage renal disease were not studied, therefore the use of lenvatinib in these patients is not recommended.

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

Pediatric population
Lenvatinib should not be used in children younger than 2 years of age because of safety concerns identified in animal studies. The safety and efficacy of lenvatinib in children aged 2 to <18 years have not yet been established. No data are available.

Race
No adjustment of starting dose is required on the basis of race. Limited data are available on use in patients from ethnic origins other than Caucasian or Asian.

Method of administration
Lenvatinib is for oral use. The capsules should be taken at about the same time each day, with or without food. The capsules should be swallowed whole with water. Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.

Alternatively, the Lenvatinib capsules may be added without breaking or crushing them to a tablespoon of water or apple juice in a small glass to produce a suspension. The capsules must be left in the liquid for at least 10 minutes and stirred for at least 3 minutes to dissolve the capsule shells. The suspension is to be swallowed. After drinking, the same amount of water or apple juice (one tablespoon) must be added to the glass and swirled a few times. The additional liquid must be swallowed.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 8.

4.4 Special Warnings and Precautions for Use
Hypertension: Hypertension usually observed in patients treated with Lenvatinib, usually occurring early in the course of treatment. Blood pressure should be well controlled prior to treatment with Lenvatinib and, if patients are known to be hypertensive, they should be on a stable dose of antihypertensive therapy for at least 1 week prior to treatment with Lenvatinib. The early detection and effective management of hypertension are important to minimize the need for Lenvatinib dose interruptions and reductions. Antihypertensive agents should be started as soon as elevated Blood pressure is confirmed. Blood pressure should be monitored after 1 week of treatment with Lenvatinib, then every 2 weeks for the first 2 months and monthly thereafter. When necessary, manage hypertension as recommended in below Table.

Table recommended management of hypertension

Blood Pressure (BP) level	Recommended action

Systolic BP ≥140 mmHg up to <160 mmHg or diastolic BP ≥90 mmHg up to <100 mmHg	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 ≥160 mmHg or diastolic BP ≥100 mmHg despite optimal antihypertensive therapy	1. Withhold Lenvatinib 2. When systolic BP ≤150 mmHg, diastolic BP ≤95 mmHg, 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)	Urgent intervention is indicated. Discontinue Lenvatinib and institute appropriate medical management.

Aneurysms and artery dissections: The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating Lenvatinib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Proteinuria: Proteinuria is observed in patients treated with Lenvatinib, usually occurring early in the course of treatment. Urine protein should be monitored regularly. If urine dipstick proteinuria ≥2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary. Cases of nephrotic syndrome have been reported in patients using Lenvatinib. Lenvatinib should be discontinued in the event of nephrotic syndrome.

Hepatotoxicity: Liver-related adverse reactions most commonly reported in patients treated with Lenvatinib included increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and blood bilirubin. Hepatic failure and acute hepatitis (<1%) observed in patients with DTC treated with Lenvatinib. Hepatic failure cases are observed in patients with progressive metastatic liver metastases disease. Close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment. Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary.

In HCC patients treated with Lenvatinib in the REFLECT trial, liver-related adverse reactions including hepatic encephalopathy and hepatic failure (including fatal reactions) were reported at a higher frequency compared to patients treated with sorafenib. Patients with worse hepatic impairment and/or greater liver tumor burden at baseline had a higher risk of developing hepatic encephalopathy and hepatic failure. Hepatic encephalopathy also occurred more frequently in patients aged 75 years and older. Approximately half of the events of hepatic failure and one third of the events of the hepatic encephalopathy were reported in patients with disease progression.
Data in HCC patients with moderate hepatic impairment (Child-Pugh B) are very limited and there are currently no data available in HCC patients with severe hepatic impairment (Child-Pugh C). Since lenvatinib is mainly eliminated by hepatic metabolism, an increase in exposure in patients with moderate to severe hepatic impairment is expected.

Close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment. Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. Patients with HCC should be monitored for worsening liver function including hepatic encephalopathy. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary.

Renal failure and impairment: Renal impairment and renal failure are observed in patients treated with Lenvatinib. The primary risk factor identified was dehydration and/or hypovolemia due to gastrointestinal toxicity. Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or renal failure. Dose interruptions, adjustments, or discontinuation may be necessary. If patients have severe renal impairment, the initial dose of Lenvatinib should be adjusted.

Diarrhoea: Prompt medical management of diarrhoea should be instituted in order to prevent dehydration. Lenvatinib should be discontinued in the event of persistence of Grade 4 diarrhoea despite medical management.

Cardiac dysfunction: Patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or discontinuation may be necessary.
Posterior reversible encephalopathy syndrome (PRES)/ Reversible posterior leukoencephalopathy syndrome (RPLS): PRES, also known as RPLS, has been observed in patients treated with. PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control blood pressure. In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary.

Arterial thromboembolisms: Arterial thromboembolisms (cerebrovascular accident, transient ischaemic attack, and myocardial infarction) have been observed in patients treated with Lenvatinib. Lenvatinib has not been studied in patients who have had an arterial thromboembolism within the previous 6 months, and therefore should be used with caution in such patients. A treatment decision should be made based upon an assessment of the individual patient's benefit/risk. Lenvatinib should be discontinued following an arterial thrombotic event.

Women of childbearing potential: Women of childbearing potential must use highly effective contraception while taking Lenvatinib and for one month after stopping treatment. It is currently unknown if Lenvatinib increases the risk of thromboembolic events when combined with oral contraceptives.

Haemorrhage: Serious tumor related bleeds; including fatal haemorrhagic events have been reported in post-marketing experience based on literature. The degree of tumor invasion/infiltration of major blood vessels (e.g. carotid artery) should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following
Lenvatinib therapy. Some cases of bleeding have occurred secondarily to tumor shrinkage and fistula formation, e.g. tracheoesophageal fistula. Screening for and subsequent treatment of

esophageal varices in patients with liver cirrhosis should be performed as per standard of care before starting treatment with Lenvatinib. In the case of bleeding, dose interruptions, adjustments, or discontinuation may be required.

Gastrointestinal perforation and fistula formation: In most cases, gastrointestinal perforation and fistulae occurred in patients with risk factors such as prior surgery or radiotherapy. In the case of a gastrointestinal perforation or fistula, dose interruptions, adjustments, or discontinuation may be necessary.

Non-Gastrointestinal fistula: Patients may be at increased risk for the development of fistulae when treated with Lenvatinib. In addition, literature showed that, pneumothorax has been reported with and without clear evidence of a bronchopleural fistula. Some reports of fistula and pneumothorax occurred in association with tumor regression or necrosis. Prior surgery and radiotherapy may be contributing risk factors. Lung metastases may also increase the risk of pneumothorax. Lenvatinib should not be started in patients with fistula to avoid worsening and Lenvatinib should be permanently discontinued in patients with oesophageal or tracheobronchial tract involvement and any Grade 4 fistula. Limited information is available on the use of dose interruption or reduction in management of other events, but worsening was observed in some cases and caution should be taken. Lenvatinib may adversely affect the wound healing process as for other agents of the same class.

QT interval prolongation: Electrocardiograms should be monitored at baseline and periodically during treatment in all patients with particular attention to those with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, and those taking medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics. Lenvatinib should be withheld in the event of development of QT interval prolongation greater than 500 ms. Lenvatinib should be resumed at a reduced dose when QTc prolongation is resolved to < 480 ms or baseline.

Electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia increase the risk of QT prolongation; therefore, electrolyte abnormalities should be monitored and corrected in all patients before starting treatment. Electrolytes (magnesium, potassium and calcium) should be monitored periodically during treatment. Blood calcium levels should be monitored at least monthly and calcium should be replaced as necessary during lenvatinib treatment. Lenvatinib dose should be interrupted or dose adjusted as necessary depending on severity, presence of ECG changes, and persistence of hypocalcaemia.

Impairment of thyroid stimulating hormone suppression/ Thyroid dysfunction: Thyroid function should be monitored before initiation of, and periodically throughout, treatment with Lenvatinib. Hypothyroidism should be treated according to standard medical practice to maintain euthyroid state. Lenvatinib impairs exogenous thyroid suppression. Thyroid stimulating hormone (TSH) levels should be monitored on a regular basis and thyroid hormone administration should be adjusted to reach appropriate TSH levels, according to the patient's therapeutic target.

Wound Healing Complications: No formal studies of the effect of Lenvatinib on wound healing have been conducted. Impaired wound healing has been reported in patients receiving Lenvatinib. Temporary interruption of Lenvatinib should be considered in patients undergoing major surgical

procedures. There is limited clinical experience regarding the timing of reinitiation of Lenvatinib following a major surgical procedure. Therefore, the decision to resume Lenvatinib following a major surgical procedure should be based on clinical judgment of adequate wound healing.

Special populations: 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. There are no data on the use of Lenvatinib immediately following sorafenib or other anticancer treatments and there may be a potential risk for additive toxicities unless there is an adequate washout period between treatments. The minimal washout period in clinical trials was 4 weeks.

4.5 Drug Interaction

Chemotherapeutic agents: Concomitant administration of lenvatinib, carboplatin, and paclitaxel has no significant impact on the pharmacokinetics of any of these 3 substances.

Effect of Lenvatinib on other medicinal products: A clinical drug-drug interaction (DDI) study in cancer patients showed that plasma concentrations of midazolam (a sensitive CYP3A and Pgp substrate) were not altered in the presence of Lenvatinib. No significant drug-drug interaction is therefore expected between Lenvatinib and other CYP3A4/Pgp substrates.

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.

4.6 Use in Special Population

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.

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.

Lactation: 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.

Fertility: Effects in humans are unknown.

4.7 Effects on Ability to Drive and Use Machines

Lenvatinib has a 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.

4.8 Undesirable Effects

Most frequently observed adverse reactions	Hypertension, diarrhoea, decreased appetite, decreased weight, fatigue, nausea, proteinuria, stomatitis, vomiting, dysphonia, headache, and palmar-plantar erythrodysaesthesia syndrome (PPE). Hypertension and proteinuria tend to occur early during Lenvatinib treatment. The majority of Grade 3 to 4 adverse reactions occurred during the first 6 months of treatment except for diarrhoea, which occurred throughout treatment, and weight loss, which tended to be cumulative over time.
Serious adverse reactions	Renal failure and impairment, arterial thromboembolisms, cardiac failure, intracranial tumor haemorrhage, PRES / RPLS, hepatic failure, and arterial thrombo embolisms (cerebro vascular accident), transient ischemic attack, and myocardial infarction.
Adverse reactions that most commonly led to dose reductions were hypertension, proteinuria, diarrhoea, fatigue, PPE, decreased weight, and decreased appetite. Adverse reactions that most commonly led to discontinuation of lenvatinib were proteinuria, asthenia, hypertension, cerebrovascular accident, diarrhoea, and pulmonary embolism.	

4.9 Overdose

The highest doses studied clinically based on literature were 32 mg and 40 mg per day. Accidental medication errors resulting in single doses of 40 to 48 mg have occurred in clinical trials. The most frequently observed adverse drug reactions at these doses were hypertension, nausea, diarrhoea, fatigue, stomatitis, proteinuria, headache, and aggravation of PPE. 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.

Symptoms and 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.

5. Pharmacological Properties

5.1 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 FGFR 1, 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 signaling, which is attributed to the inhibition of FGFR signaling by Lenvatinib.

5.2 Pharmacodynamic Properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors,
ATC code: L01XE29
Lenvatinib is a multikinase inhibitor which has shown mainly antiangiogenic properties in vitro and in vivo, and direct inhibition of tumor growth was also observed in in vitro models.

5.3 Pharmacokinetic Properties

Absorption: Lenvatinib is rapidly absorbed after oral administration with t_{max} typically observed from 1 to 4 hours post dose. Food does not affect the extent of absorption,but slows the rate of absorption. When administered with food, peak plasma concentrations are delayed by 2 hours. Absolute bioavailability has not been determined in humans; however, data from a mass-balance study suggest that it is in the order of 85%. Lenvatinib exhibited good oral bioavailability in dogs (70.4%) and monkeys (78.4%).

Distribution: *In vitro*, binding of Lenvatinib to human plasma proteins is high and ranged from 98% to 99% (0.3 - 30 µg/mL, mesylate). This binding was mainly to albumin with minor binding to α1-acid glycoprotein and γ-globulin. *In vitro*, the Lenvatinib blood-to-plasma concentration ratio ranged from 0.589 to 0.608 (0.1 – 10 µg/mL, mesylate).

Lenvatinib is a substrate for P-gp and BCRP. Lenvatinib is not a substrate for OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE2-K or the bile salt export pump BSEP.
In patients, the median apparent volume of distribution (Vz/F) of the first dose ranged from 50.5 L to 92 L and was generally consistent across the dose groups from 3.2 mg to 32 mg. The analogous median apparent volume of distribution at steady-state (Vz/Fss) was also generally consistent and ranged from 43.2 L to 121 L.

Biotransformation: *In vitro*, cytochrome P450 3A4 was demonstrated as the predominant (>80%) isoform involved in the P450-mediated metabolism of lenvatinib. However, *in vivo* data indicated that non-P450-mediated pathways contributed to a significant portion of the overall metabolism of lenvatinib. Consequently, *in vivo*, inducers and inhibitors of CYP 3A4 had a minimal effect on lenvatinib exposure. In human liver microsomes, the demethylated form of lenvatinib (M2) was identified as the main metabolite. M2' and M3', the major metabolites in human faeces, were formed from M2 and lenvatinib, respectively, by aldehyde oxidase. In plasma samples collected up to 24 hours after administration, lenvatinib constituted 97% of the radioactivity in plasma radio chromatograms while the M2 metabolite accounted for an additional 2.5%. Based on $AUC_{(0 - inf)}$, lenvatinib accounted for 60% and 64% of the total radioactivity in plasma and blood, respectively.

The main metabolic pathways in humans were identified as oxidation by aldehyde oxidase, demethylation via CYP3A4, glutathione conjugation with elimination of the O-aryl group (chlorophenyl moiety), and combinations of these pathways followed by further biotransformations (e.g., glucuronidation, hydrolysis of the glutathione moiety, degradation of the cysteine moiety, and

intramolecular rearrangement of the cysteinylglycine and cysteine conjugates with subsequent dimerisation).

In vitro transporter studies: For the following transporters, OAT1, OAT3, OATP1B1, OCT1, OCT2, and BSEP, clinically relevant inhibition was excluded based on a cutoff of $IC_{50} > 50 \times C_{max,\ unbound}$. Lenvatinib showed minimal or no inhibitory activities toward P-gp-mediated and breast cancer resistance protein (BCRP)-mediated transport activities. Similarly, no induction of P-gp mRNA expression was observed.

Lenvatinib showed minimal or no inhibitory effect on OATP1B3 and MATE2-K. Lenvatinib weakly inhibits MATE1. In human liver cytosol, lenvatinib did not inhibit aldehyde oxidase activity.

Elimination: Plasma concentrations decline bi-exponentially following C_{max}. The mean terminal exponential half-life of Lenvatinib is approximately 28 hours.
Following administration of radiolabelled Lenvatinib to 6 patients with solid tumors, approximately two-thirds and one-quarter of the radiolabel were eliminated in the faeces and urine, respectively. The M3 metabolite was the predominant analyte in excreta (~17% of the dose), followed by M2' (~11% of the dose) and M2 (~4.4 of the dose).

Special populations
Hepatic impairment: The pharmacokinetics of lenvatinib following a single 10-mg dose were evaluated in 6 subjects each with mild and moderate hepatic impairment (Child-Pugh A and Child-Pugh B, respectively). A 5-mg dose was evaluated in 6 subjects with severe hepatic impairment (Child-Pugh C). Eight healthy, demographically matched subjects served as controls and received a 10-mg dose. Lenvatinib exposure, based on dose-adjusted $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ data, was 119%, 107%, and 180% of normal for subjects with mild, moderate, and severe hepatic impairment, respectively. It has been determined that plasma protein binding in plasma from hepatically impaired subjects was similar to the respective matched healthy subjects and no concentration dependency was observed.

There are not sufficient data for HCC patients with Child-Pugh B (moderate hepatic impairment, 3 patients treated with lenvatinib in the pivotal trial) and no data available in Child Pugh C HCC patients (severe hepatic impairment). Lenvatinib is mainly eliminated via the liver and exposure might be increased in these patient populations.

The median half-life was comparable in subjects with mild, moderate, and severe hepatic impairment as well as those with normal hepatic function and ranged from 26 hours to 31 hours. The percentage of the dose of lenvatinib excreted in urine was low in all cohorts (<2.16% across treatment cohorts).

Renal impairment: The pharmacokinetics of lenvatinib following a single 24-mg dose were evaluated in 6 subjects each with mild, moderate, and severe renal impairment, and compared with 8 healthy, demographically matched subjects. Subjects with end-stage renal disease were not studied.

Lenvatinib exposure, based on AUC0-inf data, was 101%, 90%, and 122% of normal for subjects with mild, moderate, and severe renal impairment, respectively. It has been determined that plasma protein binding in plasma from renally impaired subjects was similar to the respective matched healthy subjects and no concentration dependency was observed.

Age, sex, weight, race: Based on a population pharmacokinetic analysis of patients receiving up to 24 mg lenvatinib once daily, age, sex, weight, and race (Japanese vs. other, Caucasian vs. other) had no significant effects on clearance.
Pediatric Population: Pediatric patients have not been studied.

6. Nonclinical Properties

6.1 Animal Toxicology or Pharmacology

In the repeated-dose toxicity studies (up to 39 weeks), lenvatinib caused toxicologic changes in various organs and tissues related to the expected pharmacologic effects of lenvatinib including glomerulopathy, testicular hypocellularity, ovarian follicular atresia, gastrointestinal changes, bone changes, changes to the adrenals (rats and dogs), and arterial (arterial fibrinoid necrosis, medial degeneration, or haemorrhage) lesions in rats, dogs, and cynomolgus monkeys. Elevated transaminase levels asociated with signs of hepatotoxicity, were also observed in rats, dogs and monkeys. Reversibility of the toxicologic changes was observed at the end of a 4-week recovery period in all animal species investigated.

Genotoxicity: Lenvatinib was not genotoxic.

Carcinogenicity studies have not been conducted with lenvatinib.
Reproductive and developmental toxicity: No specific studies with lenvatinib have been conducted in animals to evaluate the effect on fertility. However, testicular (hypocellularity of the seminiferous epithelium) and ovarian changes (follicular atresia) were observed in repeated-dose toxicity studies in animals at exposures 11 to 15 times (rat) or 0.6 to 7 times (monkey) the anticipated clinical exposure (based on AUC) at the maximum tolerated human dose. These findings were reversible at the end of a 4-week recovery period.

Administration of lenvatinib during organogenesis resulted in embryolethality and teratogenicity in rats (foetal external and skeletal anomalies) at exposures below the clinical exposure (based on AUC) at the maximum tolerated human dose, and rabbits (foetal external, visceral or skeletal anomalies) based on body surface area; mg/m^2 at the maximum tolerated human dose. These findings indicate that lenvatinib has a teratogenic potential, likely related to the pharmacologic activity of lenvatinib as an antiangiogenic agent. Lenvatinib and its metabolites are excreted in rat milk.

Juvenile animal toxicity studies: Mortality was the dose-limiting toxicity in juvenile rats in which dosing was initiated on postnatal day (PND) 7 or PND21 and was observed at exposures that were respectively 125- or 12-fold lower compared with the exposure at which mortality was observed in adult rats, suggesting an increasing sensitivity to toxicity with decreasing age. Therefore, mortality may be attributed to complications related to primary duodenal lesions with possible contribution from additional toxicities in immature target organs.

The toxicity of lenvatinib was more prominent in younger rats (dosing initiated on PND7) compared with those with dosing initiated on PND21 and mortality and some toxicities were observed earlier in the juvenile rats at 10 mg/kg compared with adult rats administered the same dose level. Growth retardation, secondary delay of physical development, and lesions attributable to pharmacologic effects (incisors, femur [epiphyseal growth plate], kidneys, adrenals, and duodenum) were also observed in juvenile rats.

7. Description

Lenvatinib Capsules 4 mg
Lenvonco 4 is supplied for oral administration, as a hard gelatin capsule of Lenvatinib. Each hard gelatin capsule of Lenvonco 4 contains Lenvatinib mesylate 4.90 mg equivalent to Lenvatinib 4 mg.

Lenvatinib Capsules 10 mg
Lenvonco 10 is supplied for oral administration, as a hard gelatin capsule of Lenvatinib. Each hard gelatin capsule of Lenvonco 4 contains Lenvatinib mesylate 12.25 mg equivalent to Lenvatinib 10 mg.

8. Pharmaceutical Particulars

8.1 Incompatibilities
Not applicable.

8.2 Shelf Life
Refer Pack

8.3 Packaging Information
Refer Pack

8.4 Storage and Handling Instruction
Refer Pack

9. Patient Counselling Information
- Patient should be advised to take Lenvatinib exactly as directed by the healthcare provider.
- Patient should be informed that Lenvatinib should be taken once every day at the same time, with or without food. In case the 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.
- In case the patient is unable to swallow the Lenvatinib capsule whole, patient should be instructed to place the Lenvatinib capsules (as per the prescribed dose) in a small glass containing water or apple juice without breaking or crushing them for at least 10 minutes. They should then stir the contents for at least 3 minutes & then drink the mixture. After drinking, the glass should be rinsed with a small amount of additional water or apple juice and swallowed.

- Patient should be advised to undergo regular blood pressure monitoring and to contact their health care provider if blood pressure is elevated as Lenvatinib can cause raised blood pressure.
- Patient should be informed that Lenvatinib can cause cardiac dysfunction and to immediately contact their healthcare provider if they experience any clinical symptoms of cardiac dysfunction like shortness of breath with activity or when lying down, fatigue and weakness, swelling in the legs, ankles and feet.
- Advise patient to seek immediate medical attention for new onset chest pain or acute neurologic symptoms consistent with myocardial infarction or stroke.
- As Lenvatinib can cause hepatic & renal impairment, patient should be informed that they will need to undergo routine laboratory tests to monitor liver function, renal function tests & urine in protein.
- Patient should be informed that Lenvatinib can cause diarrhea and should be advised to maintain adequate hydration & start antidiarrheal treatment in discussion with their healthcare provider.
- Patient should be informed that Lenvatinib can increase the risk of fistulas and gastrointestinal perforation and to seek immediate medical attention for severe abdominal pain.
- Patients who may be at risk of QTc Interval Prolongation may be required to undergo regular ECG monitoring & laboratory tests to monitor electrolytes.
- Patient should be informed that Lenvatinib can cause hypocalcemia & should undergo routine laboratory tests to monitor calcium levels, and the potential requirement for calcium supplementation.
- Patient should be informed that Lenvatinib in can cause Reversible Posterior Leukoencephalopathy Syndrome. Although it is very rare, they should be informed to contact their healthcare provider for new onset or worsening neurological function like headache, seizures, altered consciousness, and visual disturbance.
- Patient should be informed to that Lenvatinib can increase the risk of bleeding and to contact their healthcare provider for bleeding or symptoms of severe bleeding.
- Patient should be informed that Lenvatinib can increase the risk of wound healing complications. Advise patients to inform their healthcare provider of any planned surgical procedure.
- Female patient of reproductive potential should be informed of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy. Advise females of reproductive potential to use effective contraception during treatment with Lenvatinib and for at least 30 days after the last dose.
- Female patient should be advised to discontinue breastfeeding during treatment with Lenvatinib and for at least 1 week after the last dose.

10. Details of Manufacturer

Refer pack for manufacturer details.

Marketed By:
Abbott Healthcare Pvt Ltd,
Angel Space, Bldg No D4,
Gala No 1 to 6 & 11 to 16 Gr. Floor,

101 to 106 & 111 to 116, First Floor
201 to 206 & 211 to 216, 2nd Floor,
Pimplas, Bhiwandi, District Thane,
Tal: Bhiwandi – 16 (Thane Z5).

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11. Details of Permission or Licence Number
Refer pack for Permission/License details.

12. Date of Revision
Version 2.0, Dated 13/05/2024

For Product Complaints/Adverse events or Queries please write to **webmasterindia@abbott.com**