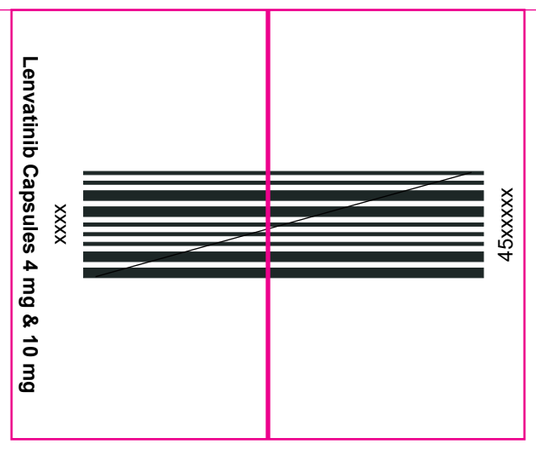
40 mm

40 mm

67 mm



Lenvatinib Hard Capsules 4 mg & 10 mg

1. Product Name

ENVA Lenvatinib Hard Capsules 4 mg

ENVA Lenvatinib Hard Capsules 10 mg

2.Name and Strength of Active Substance(s)

Lenvatinib Hard Capsules 4 mg

Each hard Capsule contains lenvatinib mesylate equivalent to 4 mg of lenvatinib.

Lenvatinib Hard Capsules 10 mg

Each hard Capsule contains lenvatinib mesylate equivalent to 10 mg of lenvatinib.

Product Description

Lenvatinib Hard Capsules 4 mg

Hard hypromellose capsule with pink opaque body and pink opaque cap imprinted with SML on the cap and 18 on the body with black ink containing off white to pale yellow granular powder.

Lenvatinib Hard Capsules 10 mg

Hard hypromellose capsule with yellow opaque body and pink opaque cap imprinted with SML on the cap and 19 on the body with black ink containing off white to pale yellow granular powder.

3. INDICATION:

Lenvatinib 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).

Lenvatinib in combination with pembrolizumab is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

Lenvatinib is indicated in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

Lenvatinib is indicated as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy (see section 11.1).

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 platinum-containing therapy in any setting and are not candidates for curative surgery or radiation.

4. DOSAGE AND ADMINISTRATION

Lenvatinib 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; however, gastrointestinal toxicity should be actively treated in order to reduce the risk of development of renal impairment or failure (see section 6, Renal failure and impairment).

Posology

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.

Renal Cell Carcinoma (RCC)

Lenvatinib in combination with pembrolizumab

Initial dosing regimen

The recommended starting daily dose of lenvatinib is 20mg (two 10 mg capsules) once daily in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks. Refer to the pembrolizumab prescribing information for other pembrolizumab dosing information.

Lenvatinib in combination with everolimus

Initial dosing regimen

The recommended daily dose of lenvatinib is 18 mg (one 10 mg capsule and two 4 mg capsules) once daily in combination with 5 mg of everolimus once daily. The daily doses of lenvatinib and, if necessary, everolimus are to be modified as needed according to the dose/toxicity management plan.

Hepatocellular Carcinoma (HCC)

The recommended daily dose of lenvatinib is 8 mg (two 4 mg capsules) once daily for patients with a body weight of < 60 kg and 12 mg (three 4 mg capsules) once daily for patients with a body weight of ≥ 60 kg. 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.

Endometrial Carcinoma (EC)

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

Refer to the pembrolizumab prescribing information for additional dosing information.

Monitoring, dose modification and discontinuation

Management of adverse reactions may require dose interruption, adjustment, or discontinuation of lenvatinib therapy or the combination therapy (see section 6). Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of lenvatinib or of the combination, unless intolerable to the patient despite optimal management. Severe (e.g., Grade 3) or intolerable adverse reactions require interruption of lenvatinib or of the combination of medicines until improvement of the reaction to Grade 0-1 or baseline.

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 reactions (e.g., Grade 3).

Dose adjustment and discontinuations for DTC

For lenvatinib related toxicities (see Table 1), 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 Table 2.

Dose adjustment and discontinuations for RCC

In combination with pembrolizumab

For lenvatinib-related toxicities, upon resolution/improvement of an adverse reaction, treatment should be resumed at a reduced dose as suggested in Table 3. When used in combination with pembrolizumab, one or both medicines should be interrupted as appropriate. Lenvatinib should be withheld, dose reduced, or discontinued as appropriate. Withhold or discontinue pembrolizumab in accordance with the instructions in the prescribing information for pembrolizumab. No dose reductions are recommended for pembrolizumab.

In combination with everolimus

For toxicities thought to be related to everolimus, treatment should be interrupted, reduced to alternate day dosing, or discontinued (see the everolimus prescribing information for advice on specific adverse reactions).

For toxicities thought to be related to both lenvatinib and everolimus, lenvatinib should be reduced (see Table 3) prior to reducing everolimus.

Dose adjustment and Discontinuation for HCC

Management of some 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. Details for monitoring, dose adjustment and discontinuation are provided in Table 4.

Dose adjustment and Discontinuation for EC

For lenvatinib-related toxicities see Table 1. When administering lenvatinib in combination with pembrolizumab, interrupt, dose reduce, or discontinue lenvatinib as appropriate
(see table 5). Withhold or discontinue pembrolizumab in accordance with the instructions in the prescribing information for pembrolizumab. No dose reductions are recommended for pembrolizumab.

Table 1 Adverse reactions requiring dose modification of lenvatinib

Adverse reaction	Severity	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 6 in section 6.
	Grade 4	Discontinue	Do not resume
Proteinuria	≥ 2 gm / 24 hours	Interrupt	Resolves to less than 2 gm / 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
PRES/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

Table 1 Adverse reactions requiring dose modification of lenvatinib

Adverse reaction	Severity	Action	Dose reduce and resume lenvatinib
Arterial thromboembolis ms	Any grade	Discontinue	Do not resume
Haemorrhage	Grade 3	Interrupt	Resolves to Grade 0-1
	Grade 4	Discontinue	Do not resume
GI perforation or fistula	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume
Non-GI 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 2 Dose modifications from recommended lenvatinib daily dose in DTC[a]

Dose level	Daily dose	Number of capsules
Recommended daily dose	24 mg orally once daily	Two 10 mg capsules 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 capsule 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.		

Table 3 Dose modifications from recommended lenvatinib daily dose in RCC[a]

Dose level	Daily dose	Number of capsules
Recommended daily dose	18 mg orally once daily (in combination with everolimus) or 20 mg orally once daily (in combination with pembrolizumab)	One 10 mg capsule plus two 4 mg capsules Two 10 mg capsules
First dose reduction	14 mg orally once daily	One 10 mg capsule plus one 4 mg capsule
Second dose reduction	10 mg orally once daily	One 10 mg capsule
Third dose reduction	8 mg orally once daily	Two 4 mg capsules
[a] Limited data are available for doses below 8 mg		

Table 4 Dose modifications from recommended lenvatinib daily dose in HCC

Starting Dose		**≥60 kg BW 12 mg (three 4 mg capsules orally once daily)**	**<60 kg BW 8mg (two 4 mg 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] (<60 kg BW)**
First occurrence [c]	Interrupt until resolved to Grade 0-1 or baseline [d]	8 mg (two 4 mg capsules) orally once daily	4 mg (one 4 mg capsule) orally once daily
Second occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline [d]	4 mg (one 4 mg capsule) orally once daily	4 mg (one 4 mg capsule) orally every other day
Third occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline [d]	4 mg (one 4 mg 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 (12 mg, 8 mg, 4 mg or 4 mg 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.

Table 5 Dose modifications from recommended lenvatinib daily dose in EC

Starting Dose in combination with pembrolizumab		20 mg orally once daily (two 10 mg capsules)
Persistent and Intolerable Grade 2 or Grade 3 Toxicities		
Adverse Reaction	**Modification**	**Adjusted Dose**
First occurrence	Interrupt until resolved to Grade 0- 1 or baseline	14 mg orally once daily (one 10 mg capsule + one 4 mg capsule)
Second occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0- 1 or baseline	10 mg orally once daily (one 10 mg capsule)
Third occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0- 1 or baseline	8 mg orally once daily (two 4 mg capsules)
Life-threatening toxicities (Grade 4): Discontinue[b]		

a. Limited data are available for doses below 8 mg.
b. 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).

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 60 kg appear to have reduced tolerability to lenvatinib. 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.

RCC:

No data for the combination of lenvatinib and everolimus are available for most of the special populations. The following information is derived from the clinical experience on single agent lenvatinib in patients with differentiated thyroid cancer (DTC).

All patients other than those with severe hepatic or renal impairment (see below) should initiate treatment at the recommended dose of 20 mg of lenvatinib daily with pembrolizumab or 18 mg of lenvatinib with 5 mg of everolimus taken once daily as indicated, 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 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.

Patients with hypertension

Blood pressure should be well controlled prior to treatment with lenvatinib, and should be regularly monitored during treatment (see section 6).

Patients with hepatic impairment

DTC, RCC and EC

No dose adjustments are required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

The recommended dosage of lenvatinib for patients with severe hepatic impairment (Child Pugh C) is:

- DTC: 14 mg taken orally once daily
- RCC: 10 mg taken orally once daily
- EC: 10 mg taken orally once daily

Further dose adjustments may be necessary on the basis of individual tolerability.

Limited data are available for the combination of lenvatinib with pembrolizumab or everolimus in patients with hepatic impairment. Please refer to the respective prescribing information for pembrolizumab or everolimus for dosing in patients with hepatic impairment.

HCC

No dose adjustments are required on the basis of hepatic function in patients with HCC and mild hepatic impairment (Child-Pugh A). There are limited data in patients with HCC and moderate hepatic impairment (Child-Pugh B). On the basis of that data, the recommended starting dose in patients with moderate hepatic impairment (Child-Pugh B) is 8 mg, regardless of body weight. Patients with moderate hepatic impairment may require additional monitoring for adverse reactions requiring dose adjustments. The available data do not allow for a dosing recommendation for patients with HCC and severe hepatic impairment (Child-Pugh C).

Patients with renal impairment

DTC, RCC and EC

No dose adjustments are required on the basis of renal function in patients with mild or moderate renal impairment.

The recommended dosage of lenvatinib for patients with severe renal impairment (creatinine clearance less than 30 mL/min calculated by Cockcroft-Gault equation using actual body weight) is:

- DTC: 14 mg taken orally once daily
- RCC: 10 mg taken orally once daily
- EC: 10 mg taken orally once daily

Further dose adjustments may be necessary on the basis of individual tolerability. Patients with end-stage renal disease have not been studied, therefore the use of lenvatinib in these patients is not recommended.

Limited data are available for the combination of lenvatinib with pembrolizumab or everolimus in patients with renal impairment. Please refer to the respective prescribing information for pembrolizumab or everolimus for dosing in patients with renal impairment.

HCC

No dose adjustments are required on the basis of renal function in HCC 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.

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.

Paediatric population

Lenvatinib should not be used in children younger than 2 years of age because of safety concerns identified in animal studies (see section 11.3). The safety and efficacy of lenvatinib in children aged 2 to < 18 years have not yet been established (see section 11.1). No data are available.

Race

No adjustment of starting dose is required on the basis of race (see section 11.2). Limited data are available on use in patients from ethnic origins other than Caucasian or Asian.

Body weight below 60 kg in RCC

No adjustment of starting dose is required on the basis of body weight. Limited data are available on treatment with lenvatinib in combination with everolimus in patients with a body weight below 60 kg with RCC.

Patients with high ECOG performance status in RCC

Patients with an ECOG (Eastern Cooperative Oncology Group) performance status of 2 or higher were excluded from the RCC Study 205 (see section 11.1). Patients with a KPS (Karnofsky Performance Status) <70 were excluded from Study 307 (CLEAR). Benefit-risk in these patients has not been evaluated.

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.

5 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 2.

Breast-feeding (see section 8).

6 WARNINGS AND PRECAUTIONS

Hypertension

Hypertension has been reported in patients treated with lenvatinib, usually occurring early in the course of treatment. Blood pressure (BP) 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. Serious complications of poorly controlled hypertension, including aortic dissection, have been reported. The early detection and effective management of hypertension are important to minimise the need for lenvatinib dose interruptions and reductions. Antihypertensive agents should be started as soon as elevated BP is confirmed. BP should be monitored after 1 week of treatment with lenvatinib, then every 2 weeks for the first 2 months, and monthly thereafter. The choice of antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice. For previously normotensive subjects, monotherapy with one of the classes of antihypertensives should be started when elevated BP is observed. For those patients already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added. When necessary, manage hypertension as recommended in Table 6.

Table 6 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 (see section 4)
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.

Women of childbearing potential

Women of childbearing potential must use highly effective contraception while taking lenvatinib and for one month after stopping treatment (see section 8). It is currently unknown if lenvatinib increases the risk of thromboembolic events when combined with oral contraceptives.

Proteinuria

Proteinuria has been reported 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 (see section 4). Cases of nephrotic syndrome have been reported in patients using lenvatinib. Lenvatinib should be discontinued in the event of nephrotic syndrome.

Renal failure and impairment/Gastrointestinal Toxicity

Renal impairment and renal failure have been reported 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. In RCC, caution should be taken in patients receiving agents acting on the
renin-angiotensin aldosterone system given a potentially higher risk for acute renal failure with the combination treatment. Dose interruptions, adjustments, or discontinuation may be necessary (see section 4).

If patients have severe renal impairment, the initial dose of lenvatinib should be adjusted (see sections 4 and 11.2).

Cardiac dysfunction

Cardiac failure (< 1%) and decreased left ventricular ejection fraction have been reported in patients treated with lenvatinib. Patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or discontinuation may be necessary (see section 4).

Posterior reversible encephalopathy syndrome (PRES) / Reversible posterior leucoencephalopathy syndrome (RPLS)

PRES, also known as RPLS, has been reported in patients treated with lenvatinib < 1%. 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 (see section 6,Hypertension). In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary (see section 4).

Hepatotoxicity

In DTC and RCC patients, 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% have been reported in patients with DTC treated with lenvatinib. The hepatic failure cases were generally reported in patients with progressive metastatic liver metastases disease.

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 (see Section 9) compared to patients treated with sorafenib . Patients with worse hepatic impairment and/or greater liver tumour 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.

In EC, liver-related adverse reactions most commonly reported in patients treated with lenvatinib and pembrolizumab included increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Hepatic failure and hepatitis (<1%; see section 9) have been reported in patients with EC treated with lenvatinib and pembrolizumab.

Close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment (see also sections 4 and 11.2). 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 (see section 4).

Arterial thromboembolisms

Arterial thromboembolisms (cerebrovascular accident, transient ischaemic attack, and myocardial infarction) have been reported 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.

Haemorrhage

Serious tumour related bleeds, including fatal haemorrhagic events have occurred in clinical trials and have been reported in post-marketing experience. In post-marketing surveillance, serious and fatal carotid artery haemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than in DTC or other tumour types. The degree of tumour invasion/infiltration of major blood vessels (e.g. carotid artery) should be considered because of the potential risk of severe haemorrhage associated with tumour shrinkage/necrosis following lenvatinib therapy. Some cases of bleeding have occurred secondarily to tumour shrinkage and fistula formation, e.g. tracheooesophageal fistula. Cases of fatal intracranial haemorrhage have been reported in some patients with or without brain metastases. Bleeding in sites other than the brain (e.g. trachea, intra-abdominal, lung) has also been reported. One fatal case of hepatic tumour haemorrhage in a patient with HCC has been reported.

Screening for and subsequent treatment of oesophageal varices in patients with liver cirrhosis should be performed as per standard of care before starting treatment with lenvatinib.

In RCC, serious cases of haemorrhage have been reported in patients treated with lenvatinib. Cases of fatal intracranial haemorrhage have been reported in some patients with or without brain metastases.

In the case of bleeding, dose interruptions, adjustments, or discontinuation may be required (see Section 4, Table 1).

Gastrointestinal perforation and fistulae formation

Gastrointestinal perforation or fistula has been reported in patients treated with lenvatinib
(see section 9). In most cases, gastrointestinal perforation and fistula 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 (see section 4).

Non-Gastrointestinal fistula

Patients may be at increased risk for the development of fistula when treated with lenvatinib in DTC. Cases of fistula formation or enlargement that involve other areas of the body than stomach or intestines were observed in clinical trials and in post-marketing experience (e.g. tracheal, tracheo-oesophageal, oesophageal, cutaneous, female genital tract fistulae).

In addition, pneumothorax has been reported with and without clear evidence of a bronchopleural fistula. Some reports of fistula and pneumothorax occurred in association with tumour 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 (see section 4); 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 other agents of the same class.

QT interval prolongation

QT/QTc interval prolongation has been reported at a higher incidence in patients treated with lenvatinib than in patients treated with placebo. Electrocardiograms should be monitored at baseline and periodically during treatment in all patients with a special attention for 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.

Front Page

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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. Periodic monitoring of ECG and electrolytes (magnesium, potassium and calcium) should be considered 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

Hypothyroidism has been reported in patients treated with lenvatinib. 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.

Diarrhoea

Diarrhoea has been reported frequently in patients treated with lenvatinib, usually occurring early in the course of treatment. 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.

Osteonecrosis of the jaw (ONJ)

Cases of ONJ have been reported in patients treated with lenvatinib. Some cases were reported in patients who had received prior or concomitant treatment with antiresorptive bone therapy, and/or other angiogenesis inhibitors, e.g. bevacizumab, TKI, mTOR inhibitors. Caution should therefore be exercised when lenvatinib is used either simultaneously or sequentially with antiresorptive therapy and/or other angiogenesis inhibitors.

Invasive dental procedures are an identified risk factor. Prior to treatment with lenvatinib, a dental examination and appropriate preventive dentistry should be considered. In patients who have previously received or are receiving intravenous bisphosphonates, invasive dental procedures should be avoided if possible (see section 9).

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 of 4 weeks.

Patients with ECOG PS ≥ 2 were excluded from clinical studies (except for thyroid carcinoma).

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.

7 INTERACTION WITH OTHER MEDICAMENTS

Effect of other medicinal products on lenvatinib

Interaction with other medicinal products and other forms of interaction below are relevant to the use of lenvatinib monotherapy. Population pharmacokinetic analysis demonstrated that lenvatinib does not significantly affect the pharmacokinetics of either everolimus or pembrolizumab. When using lenvatinib in combination with everolimus or pembrolizumab, also refer to the manufacturer's prescribing information for everolimus or pembrolizumab.

Chemotherapeutic agents

Concomitant administration of lenvatinib, carboplatin, and paclitaxel has no significant impact on the pharmacokinetics of any of these 3 substances. Additionally, in patients with RCC the pharmacokinetics of lenvatinib was not significantly affected by concomitant everolimus.

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. Additionally, in patients with RCC the pharmacokinetics of everolimus was not significantly affected by concomitant 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 (see section 8).

8 FERTILITY, PREGNANCY AND LACTATION

Information on fertility, pregnancy and lactation below is relevant to use of lenvatinib monotherapy. When using lenvatinib in combination with everolimus or pembrolizumab, please see below and also refer to the manufacturer's prescribing information for everolimus or pembrolizumab.

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.

Pregnancy

There are no data on the use of lenvatinib in pregnant women. Lenvatinib was embryotoxic and teratogenic when administered to rats and rabbits.

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.

Breast-feeding

It is not known whether lenvatinib is excreted in human milk. Lenvatinib and its metabolites are excreted in rat milk. A risk to newborns or infants cannot be excluded and, therefore, lenvatinib is contraindicated during breast-feeding (see section 5).

Fertility

Effects in humans are unknown. However, testicular and ovarian toxicity has been observed in rats, dogs, and monkeys.

9 ADVERSE REACTIONS

The adverse reaction frequency category represents the most conservative estimate of frequency from the individual populations. Adverse reactions known to occur with lenvatinib or combination therapy components given alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical studies with combination therapy. For additional safety information when lenvatinib is administered in combination, refer to the package insert for the respective combination therapy components.

Frequencies are defined as:

- Very common (≥ 1/10)
- Common (≥ 1/100 to < 1/10)
- Uncommon (≥ 1/1,000 to < 1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data)

Within each frequency category, adverse reactions are presented in order of decreasing seriousness.

Table 7 Adverse reactions reported in patients treated with lenvatinib[§]

System organ class (MedDRA terminology)	Monotherapy/combination with everolimus	Combination with pembrolizumab
Infections and infestations		
Very common	Urinary tract infection	Urinary tract infection
Uncommon	Perineal abscess	Perineal abscess
Blood and lymphatic disorders		
Very common	Thrombocytopenia[a,‡] Lymphopenia[a,‡] Leukopenia[a,‡] Neutropenia[a,‡]	Thrombocytopenia[a,‡] Lymphopenia[a,‡] Leukopenia[a,‡] Neutropenia[a,‡] Anaemia
Uncommon	Splenic infarction	
Endocrine disorders		
Very common	Hypothyroidism Increased blood thyroid stimulating hormone[‡,*]	Hypothyroidism Increased blood thyroid stimulating hormone[‡,*] Hyperthyroidism
Metabolism and nutrition disorders		
Very common	Hypocalcaemia[*,‡] Hypercholesterolaemia[b,*] Hypokalaemia[‡] Hypomagnesaemia[b,‡] Decreased appetite Decreased weight	Hypocalcaemia[*,‡] Hypokalaemia[‡] Hypercholesterolaemia[b,‡] Hypomagnesaemia[b,‡] Decreased appetite Decreased weight
Common	Dehydration	Dehydration
Psychiatric disorders		
Very common	Insomnia	Insomnia
Nervous system disorders		
Very common	Dizziness Headache Dysgeusia	Dizziness Headache Dysgeusia
Common	Cerebrovascular accident[†]	
Uncommon	Posterior reversible encephalopathy syndrome Monoparesis Transient ischaemic attack	Cerebrovascular accident[†] Posterior reversible encephalopathy syndrome Monoparesis Transient ischaemic attack
Cardiac disorders		
Common	Myocardial infarction[c,†] Cardiac failure Prolonged electrocardiogram QT Decreased ejection fraction	Myocardial infarction[c,†] Prolonged electrocardiogram QT
Uncommon	Pericardial effusion Cardiac failure[†]	Pericardial effusion
Vascular disorders		
Very common	Haemorrhage[d,†,*] Hypertension[e,*] Hypotension	Haemorrhage[d,†,*] Hypertension[e,*]
Common		Hypotension
Not known	Aneurysms and artery dissections	Aneurysms and artery dissections[†]
Respiratory, thoracic and mediastinal disorders		
Very common	Dysphonia	Dysphonia
Common	Pulmonary embolism[†]	Pulmonary embolism[†]
Uncommon	Pneumothorax	Pneumothorax
Gastrointestinal disorders		
Very common	Diarrhoea Gastrointestinal and abdominal pains[f] Vomiting Nausea Oral inflammation[g] Oral pain[h] Constipation Dyspepsia Dry mouth Increased lipase[‡] Increased amylase[‡]	Diarrhoea Gastrointestinal and abdominal pains[f] Vomiting Nausea Oral inflammation[g] Oral pain[h] Constipation Dyspepsia Dry mouth Increased lipase Increased amylase[‡]
Common	Anal fistula Flatulence Gastrointestinal perforation	Pancreatitis[i] Flatulence Colitis Gastrointestinal perforation
Uncommon	Pancreatitis[i] Colitis	Anal fistula
Hepatobiliary disorders		
Very common	Increased blood bilirubin[j,*,‡]	Increased blood bilirubin[j,*,‡]
	Hypoalbuminaemia[j,*,‡] Increased aspartate aminotransferase[*,‡] Increased alanine aminotransferase[*,‡] Increased blood alkaline phosphatase[‡] Increased gamma-glutamyltransferase[‡]	Hypoalbuminaemia[j,*,‡] Increased aspartate aminotransferase[‡] Increased alanine aminotransferase Increased blood alkaline phosphatase[‡]
Common	Hepatic failure[k,*, †] Hepatic encephalopathy[l,*, †] Cholecystitis Abnormal hepatic function	Cholecystitis Abnormal hepatic function Increased gamma-glutamyltransferase
Uncommon	Hepatocellular damage/hepatitis[m]	Hepatic failure[k,*, †] Hepatic encephalopathy[l, †] Hepatocellular damage and hepatitis[m]
Skin and subcutaneous tissue disorders		
Very common	Palmar-plantar erythrodysaesthesia syndrome Palmar erythema Rash Alopecia	Palmar-plantar erythrodysaesthesia syndrome Rash
Common	Hyperkeratosis	Alopecia Hyperkeratosis
Uncommon		Palmar erythema
Musculoskeletal and connective tissue disorders		
Very common	Back pain Arthralgia Myalgia Pain in extremity Musculoskeletal pain	Back pain Arthralgia Myalgia Pain in extremity Musculoskeletal pain
Uncommon	Osteonecrosis of jaw	
Renal and urinary disorders		
Very common	Proteinuria[*] Increased blood creatinine[‡]	Proteinuria[*] Increased blood creatinine [‡]
Common	Renal failure [n,*,†] Renal impairment[*] Increased blood urea	Renal failure[n,*,†] Increased blood urea
Uncommon	Nephrotic syndrome	Renal impairment[*] Nephrotic syndrome
General disorders and administration site conditions		
Very common	Fatigue Asthenia Oedema peripheral	Fatigue Asthenia Oedema peripheral
Common	Malaise	Malaise
Uncommon	Impaired healing	Non-gastrointestinal fistula[o] Impaired healing
Not Known	Non-gastrointestinal fistula[o]	

[§]: Adverse reaction frequencies presented in Table 7 may not be fully attributable to lenvatinib alone but may contain contributions from the underlying disease or from other medicinal products used in a combination.

*: See section 9 reactions for further characterisation.

†: Includes cases with a fatal outcome.

‡: Frequency based on laboratory data

The following terms have been combined:

a: Thrombocytopenia includes thrombocytopenia and decreased platelet count. Neutropenia includes neutropenia and decreased neutrophil count. Leukopenia includes leukopenia and decreased white blood cell count. Lymphopenia includes lymphopenia and decreased lymphocyte count.

b: Hypomagnesaemia includes hypomagnesaemia and decreased blood magnesium. Hypercholesterolaemia includes hypercholesterolaemia and increased blood cholesterol.

c: Myocardial infarction includes myocardial infarction and acute myocardial infarction.

d: Includes all haemorrhage terms:
Haemorrhage terms that occurred in 5 or more subjects with DTC were: epistaxis, haemoptysis, haematuria, contusion, haematochezia, gingival bleeding, petechial, pulmonary haemorrhage, rectal haemorrhage, blood urine present, haematoma and vaginal haemorrhage.
Haemorrhage terms that occurred in 5 or more patients with RCC in lenvatinib plus pembrolizumab were: epistaxis, haematuria, contusion, gingival bleeding, rectal haemorrhage, haemoptysis, ecchymosis, and haematochezia. Haemorrhage terms that occurred in 5 or more subjects with HCC were: epistaxis, haematuria, gingival bleeding, haemoptysis, oesophageal varices haemorrhage, haemorrhoidal haemorrhage, mouth haemorrhage, rectal haemorrhage and upper gastrointestinal haemorrhage.
Haemorrhage term that occurred in 5 or more subjects with EC was: vaginal haemorrhage.

e: Hypertension includes: hypertension, hypertensive crisis, increased diastolic blood pressure, orthostatic hypertension and increased blood pressure.

f: Gastrointestinal and abdominal pains include: abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal pain.

g: Oral inflammation includes: aphthous stomatitis, aphthous ulcer, gingival erosion, gingival ulceration, oral mucosal blistering, stomatitis, glossitis, mouth ulceration, and mucosal inflammation.

h: Oral pain includes: oral pain, glossodynia, gingival pain, oropharyngeal discomfort, oropharyngeal pain and tongue discomfort.

i: Pancreatitis includes: pancreatitis and acute pancreatitis.

j: Increased blood bilirubin includes: hyperbilirubinaemia, increased blood bilirubin, jaundice and increased bilirubin conjugated. Hypoalbuminaemia includes hypoalbuminaemia and decreased blood albumin.

k: Hepatic failure includes: hepatic failure, acute hepatic failure and chronic hepatic failure.

l: Hepatic encephalopathy includes: hepatic encephalopathy, coma hepatic, metabolic encephalopathy and encephalopathy.

m:Hepatocellular damage and hepatitis include: drug-induced liver injury, hepatic steatosis, and cholestatic liver injury.

n: Renal failure includes: acute prerenal failure, renal failure, renal failure acute, acute kidney injury, and renal tubular necrosis.

o: Non-gastrointestinal fistula includes cases of fistula occurring outside of the stomach and intestines such as tracheal, tracheo-oesophageal, oesophageal, cutaneous fistula and female genital tract fistula.

10 OVERDOSE AND TREATMENT

The highest doses of lenvatinib studied clinically were 32 mg and 40 mg per day. Accidental medication errors resulting in single doses of 40 to 48 mg have also 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.

11. PHARMACOLOGICAL PROPERTIES

11.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EX08

Lenvatinib is a multikinase inhibitor which has shown mainly antiangiogenic properties in vitro and in vivo, and direct inhibition of tumour growth was also observed in in vitro models.

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. The combination of lenvatinib and everolimus showed increased antiangiogenic and antitumour activity as demonstrated by decreased human endothelial cell proliferation, tube formation, and VEGF signalling in vitro and tumour volume in mouse xenograft models of human renal cell cancer greater than each drug alone.

In syngeneic mouse tumor models, lenvatinib decreased tumor-associated macrophages, increased activated cytotoxic T cells, and demonstrated greater antitumor activity in combination with an anti-PD-1 monoclonal antibody compared to either treatment alone.

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.

Although not studied directly with lenvatinib, the mechanism of action (MOA) for hypertension is postulated to be mediated by the inhibition of VEGFR2 in vascular endothelial cells. Similarly, although not studied directly, the MOA for proteinuria is postulated to be mediated by downregulation of VEGFR1 and VEGFR2 in the podocytes of the glomerulus.

The mechanism of action for hypothyroidism is not fully elucidated.

The mechanism of action for the worsening of hypercholesterolaemia with the combination of lenvatinib and everolimus has not been studied directly and is not fully elucidated.

Although not studied directly, the MOA for the worsening of diarrhoea with the combination of lenvatinib and everolimus is postulated to be mediated by the impairment of intestinal function related to the MOAs for the individual agents – VEGF/VEGFR and c-KIT inhibition by lenvatinib coupled with mTOR/NHE3 inhibition by everolimus.

11.2 Pharmacokinetic properties

Pharmacokinetic parameters of lenvatinib have been studied in healthy adult subjects, adult subjects with hepatic impairment, renal impairment, and solid tumours.

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 to healthy subjects, peak plasma concentrations are delayed by 2 hours. Absolute bioavailability has not been determined in humans; however, data from a mass-balance study suggests 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, mesilate). This binding was mainly to albumin with minor binding to α1-acid glycoprotein and γ-globulin. A similar plasma protein binding (97% to 99%) with no dependencies on lenvatinib concentrations (0.2 to 1.2 µg/mL) was observed in plasma from hepatically impaired, renally impaired, and matching healthy subjects.

In vitro, the lenvatinib blood-to-plasma concentration ratio ranged from 0.589 to 0.608 (0.1-10 µg/mL, mesilate).

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 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 P450mediated 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 (see section 7).

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 $AUC_{(0\text{-inf})}$, lenvatinib accounted for 60% and 64% of the total radioactivity in plasma and blood, respectively.

Data from a human mass balance/excretion study indicate lenvatinib is extensively metabolised in humans. 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). These *in vivo* metabolic routes align with the data provided in the *in vitro* studies using human biomaterials.

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.

STORAGE CONDITION

Store below 30°C.

Protect from light and moisture.

SHELF LIFE

2 Years

Packaging Available

ENVA Lenvatinib Hard Capsules 4 mg

Each Blister Contains 10 Capsules.

Each carton contains 20, 30, or 100 hard capsules.

ENVA Lenvatinib Hard Capsules 10 mg

Each Blister Contains 10 Capsules.

Each carton contains 20, 30, or 100 hard capsules.

Name and Address of The Manufacturer

Shilpa Medicare Limited,

Plot No. S-20 to S-26, Pharma SEZ TSIIC,
Green Industrial Park, Polepally Village,
Jadcherla (Md), Mahabubnagar (Dt.),
Telangana State, India. Pin 509301.

Name & Address of Product Registration Holder (PRH):

Unimed Sdn Bhd

53, Jalan Tembaga SD 5/2B,
Bandar Sri Damansara 52200,
Kuala Lumpur, Malaysia.

Date of Revision of Package Insert

08/2025

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