1. NAME OF THE MEDICINAL PRODUCT

LENVIMA® 4 mg
LENVIMA® 10 mg

hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LENVIMA® 4 mg:
Each hard capsule contains 4 mg of lenvatinib (as mesylate).

LENVIMA® 10 mg:
Each hard capsule contains 10 mg of lenvatinib (as mesylate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

LENVIMA® 4 mg:
A yellowish-red body and yellowish-red cap, approximately 14.3 mm in length, marked in black ink with "Є" on the cap, and "LENV 4 mg" on the body. Diameter 5.3mm, length 14.3

LENVIMA® 10 mg:
A yellow body and yellowish-red cap, marked in black ink with "Є" on the cap, and "LENV 10 mg" on the body. Diameter 5.3mm, length 14.3,

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LENVIMA 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).

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

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

4.2 Posology and method of administration

LENVIMA 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 (see section 4.4, Renal failure and impairment).

Posology

Differentiated Thyroid carcinoma (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.

Clear cell renal cell carcinoma (RCC):
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.

Dose adjustment and discontinuations for DTC and Clear cell RCC
Management of adverse reactions may require dose interruption, adjustment, or discontinuation of lenvatinib or the combination therapy (see section 4.4). Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of lenvatinib or the combination therapy, unless intolerable to the patient despite optimal management. Severe (e.g., Grade 3) or intolerable adverse reactions require interruption of lenvatinib or the combination of medicines until improvement of the reaction to Grade 0-1 or baseline.

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 and Table 3.

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.

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).

Grades are based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).

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.

Dose adjustments 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.

Table 1 Adverse reactions requiring dose modification of lenvatinib in DTC, Clear cell RCC and HCC

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 5 in section 4.4.
	Grade 4	Discontinue	Do not resume
Proteinuria	≥ 2 g / 24 hours	Interrupt	Resolves to less than 2 g / 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
Arterial thromboembolisms	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

Table 1 Adverse reactions requiring dose modification of lenvatinib in DTC, Clear cell RCC and HCC

Adverse reaction	Severity	Action	Dose reduce and resume lenvatinib

*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 patients[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 Clear cell RCC patients[a]

Dose level	Daily dose	Number of capsules
Recommended daily dose	18 mg orally once daily	One 10 mg capsule plus two 4 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 patients

Starting Dose		**≥60 kg BW 12 mg (three 4 mg capsules orally once daily)**	**<60 kg BW 8 mg (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.

Grades are based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).

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 (see section 4.8, Other special populations).

Clear cell RCC

No adjustment of starting dose is required on the basis of body weight. Limited data are available on patients with a body weight below 60 kg with clear cell RCC (see also section 4.8, Other special populations).

No data with the combination 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 carcinoma (DTC).

DTC and Clear cell RCC
All patients other than those with severe hepatic or renal impairment (see below) should initiate treatment at the recommended dose (see Table 2 and Table 3 above), 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 4.4). Refer also to section 4.8, Other special populations.

Patients with hepatic impairment
Clear cell RCC
No data with the combination is available in patients with hepatic impairment.

DTC and Clear cell RCC
No adjustment of starting dose (of lenvatinib or 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 is:
for DTC patients - 14 mg taken once daily,
for clear cell RCC patients - lenvatinib 10 mg taken once daily in combination with the dose of everolimus recommended for patients with severe hepatic impairment in the everolimus prescribing information.
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. Refer also to section 4.8, Other special populations.

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 (see sections 4.4 and 5.2). Lenvatinib has not been studied in patients with severe hepatic imparement (Child-Pugh C) and is not recommended for use in these patients.

Patients with renal impairment

DTC and Clear cell 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:
for DTC patients - 14 mg taken once daily,
for clear cell RCC patients - 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. Refer also to section 4.8, Other special populations.

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.

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 (see also section 4.8, Other special populations).

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 5.3). The safety and efficacy of lenvatinib in children aged 2 to <18 years have not yet been established (see section 5.1). No data are available.

Race
No adjustment of starting dose is required on the basis of race (see section 5.2). Limited data are available on use in patients from ethnic origins other than Caucasian or Asian (see also section 4.8, Other special populations).

Patients with high ECOG performance status
Patients with an ECOG (Eastern Cooperative Oncology Group) performance status of 2 or higher were excluded from the clear cell RCC study (see section 5.1). 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 (see section 5.2). 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 6.1.
Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Hypertension
Hypertension has been reported in patients treated with lenvatinib, usually occurring early in the course of treatment (see section 4.8, Description of selected adverse reactions). 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 5.

Table 5 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 4.2)
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 has been reported in patients treated with lenvatinib, usually occurring early in the course of treatment (see section 4.8, Description of selected adverse reactions). Urine protein should be monitored regularly. If urine dipstick proteinuria ≥2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2). Cases of nephrotic syndrome have been reported in patients using lenvatinib. Lenvatinib should be discontinued in the event of nephrotic syndrome.

Hepatotoxicity

DTC and Clear cell RCC

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%; see section 4.8, Description of selected adverse reactions) have been reported in patients 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 4.8) 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.

Close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment (see also sections 4.2 and 5.2). 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 4.2).

If patients have severe hepatic impairment, the initial dose of lenvatinib should be adjusted (see sections 4.2 and 5.2).

Renal failure and impairment

Renal impairment and renal failure have been reported in patients treated with lenvatinib (see section 4.8, Description of selected adverse reactions). 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. 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 (for clear cell RCC patients). Dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

If patients have severe renal impairment, the initial dose of lenvatinib should be adjusted (see sections 4.2 and 5.2).

Diarrhoea

Diarrhoea has been reported frequently in patients treated with lenvatinib, usually occurring early in the course of treatment (see section 4.8, Description of selected adverse reactions). 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

Cardiac failure (<1%) and decreased left ventricular ejection fraction have been reported in patients treated with lenvatinib (see section 4.8, Description of selected adverse reactions).

Patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

Posterior reversible encephalopathy syndrome (PRES) / Reversible posterior leucoencephalopathy syndrome (RPLS)
PRES, also known as RPLS, has been reported in patients treated with lenvatinib (<1%; see section 4.8, Description of selected adverse reactions). 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 4.4, Hypertension).
In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

Arterial thromboembolisms
Arterial thromboembolisms (cerebrovascular accident, transient ischaemic attack, and myocardial infarction) have been reported in patients treated with lenvatinib (see section 4.8, Description of selected adverse reactions). 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 (see section 4.6). It is currently unknown if lenvatinib increases the risk of thromboembolic events when combined with oral contraceptives.

Haemorrhage
Serious tumour related bleeds, including fatal haemorrhagic events have occurred in clinical trials and have been reported in post-marketing experience (see section 4.8, Description of selected adverse reactions). 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. tracheo-oesophageal fistulae. 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 the case of bleeding, dose interruptions, adjustments, or discontinuation may be required (see Section 4.2, Table 2, Table 3 and Table 4).

Gastrointestinal perforation and fistula formation
Gastrointestinal perforation or fistulae have been reported in patients treated with lenvatinib (see section 4.8). 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 (see section 4.2).

Non-Gastrointestinal fistula
Patients may be at increased risk for the development of fistulae when treated with lenvatinib. Cases of fistula formation or enlargement that involve areas of the body other 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 4.2); 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
QT/QTc interval prolongation has been reported at a higher incidence in patients treated with lenvatinib than in patients treated with placebo (see section 4.8, Description of selected adverse reactions). 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, bradyarrhythmics, 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. ECG and 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
Hypothyroidism has been reported in patients treated with lenvatinib (see section 4.8, Description of selected adverse reactions). 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 (see section 4.8, Description of selected adverse reactions). 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.

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 4.8).

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 (see section 4.8, Other special populations).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on lenvatinib

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

CYP3A4 substrates
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 4.6).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in females
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 (see section 5.3).

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 (see section 5.3).

A risk to newborns or infants cannot be excluded and, therefore, lenvatinib is contraindicated during breast-feeding (see section 4.3).

Fertility
Effects in humans are unknown. However, testicular and ovarian toxicity has been observed in rats, dogs, and monkeys (see section 5.3).

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

Summary of the safety profile

The safety profile of lenvatinib in combination with everolimus is based on data from 62 subjects; The safety profile of lenvatinib is based on data from 452 DTC patients and 496 HCC patients, allowing characterisation only of common adverse drug reactions in clear cell RCC patients, DTC and HCC patients. The adverse reactions presented in this section are based on the combined safety data of 62 clear cell RCC patients, 452 DTC patients and 496 HCC patients (see section 5.1).

DTC and Clear cell RCC
The most frequently reported adverse reactions in the clear cell RCC and DTC patient populations (occurring in ≥30% of patients) were diarrhoea (80.6%), hypertension (70.1%)*, fatigue (59.7%), decreased appetite (53.7%), weight decreased (52.6%)*, vomiting (48.4%), nausea (45.2%), proteinuria (38.9%)*, stomatitis (36.9%)*, headache (35.8%)*, dysphonia (35.6%), palmar-plantar erythrodysaesthesia syndrome (PPE) (34.1%)*, peripheral oedema (33.9%), and hypercholesterolemia (30.6%). Hypertension and proteinuria tend to occur early during lenvatinib treatment (see sections 4.4 and 4.8, Description of selected adverse reactions; the asterisked frequencies are from the DTC patient population).

The most important serious adverse reactions were renal failure and impairment (11.3%), arterial thromboembolisms (3.9%)*, cardiac failure (1.6%), cerebral haemorrage (1.6%), intracranial tumour haemorrhage (0.7%)*, PRES / RPLS (0.2%)*, and hepatic failure (0.2%)* (the asterisked frequencies are from the DTC patient population).

In 452 patients with RAI-refractory DTC, dose reduction and discontinuation were the actions taken for an adverse reaction in 63.1% and 19.5% of patients, respectively. Adverse reactions that most commonly led to dose reductions (in ≥5% of patients) 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.

In the clear cell RCC study (see section 5.1), adverse reactions led to dose reductions in 67.7% of patients and 18 (29.0%) patients discontinued the treatment. The most common adverse reactions (≥5%) resulting in dose reductions in the lenvatinib plus everolimus treated group were diarrhoea (21.0%), thrombocytopenia (6.5%), and vomiting (6.5%).

HCC

The most frequently reported adverse reactions (occurring in ⩾30% of patients) are hypertension (44.0%), diarrhoea (38.1%), decreased appetite (34.9%), fatigue (30.6%), and decreased weight (30.4%).

The most important serious adverse reactions were hepatic failure (2.8%), hepatic encephalopathy (4.6%), oesophageal varices haemorrhage (1.4%), cerebral haemorrhage (0.6%), arterial thromboembolic events (2.0%) including myocardial infarction (0.8%), cerebral infarction (0.4%) and cerebrovascular accident (0.4%) and renal failure/impairment events (1.4%). There was a higher incidence of decreased neutrophil count in patients with HCC (8.7% on lenvatinib than in other non- HCC tumour types (1.4%)), which was not associated with infection, sepsis or bacterial peritonitis.

In 496 patients with HCC, dose modification (interruption or reduction) and discontinuation were the actions taken for an adverse reaction in 62.3% and 20.2% of patients, respectively. Adverse reactions that most commonly led to dose modifications (in ⩾5% of patients) were decreased appetite, diarrhoea, proteinuria, hypertension, fatigue, PPE and decreased platelet count. Adverse reactions that most commonly led to discontinuation of lenvatinib were hepatic encephalopathy, fatigue, increased blood bilirubin, proteinuria and hepatic failure.

Tabulated list of adverse reactions for clear cell RCC, DTC and HCC studies
Similar adverse reactions were observed in clinical trials in clear cell RCC, DTC and HCC. Adverse reactions that occur more frequently with combination therapy compared to lenvatinib monotherapy are hypothyroidism, (including increased blood thyroid stimulating hormone), hypercholesterolaemia, and severe diarrhoea.

Adverse reactions observed in clinical trials and reported from post-marketing use of lenvatinib are listed in Table 6.

Frequencies are defined as:
- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Not known (cannot be estimated from the available data)

Within each frequency category, undesirable effects are presented in order of decreasing seriousness.

Table 6 Adverse reactions reported in patients treated with lenvatinib

System Organ Class (MedDRA terminology*)	**Very Common**	**Common**	**Uncommon**	**Not known**
Infections and infestation	Urinary tract infection		Perineal abscess	
Blood and lymphatic disorders	Thrombocytopenia[a] Leukopenia[a] Neutropenia[a]	Lymphopenia[a]	Splenic infarction	
Endocrine disorders	Hypothyroidism[**] Increased blood thyroid stimulating hormone ‡[**]			
Metabolism and nutrition disorders	Hypocalcaemia‡ Hypercholesterolaemia[b**] Hypokalaemia Decreased appetite Decreased weight	Dehydration Hypomagnesaemia[b]		
Psychiatric disorders	Insomnia			
Nervous system disorders	Dizziness Headache Dysgeusia	Cerebrovascular accident †	Posterior reversible encephalopathy syndrome Monoparesis Transient ischaemic attack	
Cardiac disorders		Myocardial infarction[c,†] Cardiac failure Prolonged electrocardiogram QT Decreased ejection fraction		

System Organ Class (MedDRA terminology[*])	**Very Common**	**Common**	**Uncommon**	**Not known**
Vascular disorders	Haemorrhage[d, †,‡] Hypertension[e,‡] Hypotension			Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders	Dysphonia	Pulmonary embolism[†,]	Pneumothorax	
Gastrointestinal disorders	Diarrhoea[‡**] Gastrointestinal and abdominal pains[f] Vomiting Nausea Oral inflammation[g] Oral pain[h] Constipation Dyspepsia Dry mouth	Anal fistula Flatulence Increased lipase Increased amylase	Pancreatitis [i,†]	
Hepatobiliary disorders	Increased blood bilirubin [j, ‡] Hypoalbuminaemia[j, ‡] Increased alanine aminotransferase [‡] Increased aspartate aminotransferase [‡]	Hepatic failure[k,‡,†] Hepatic encephalopathy[l,‡,†] Increased blood alkaline phosphatase Hepatic function abnormal Increased gamma-glutamyltransferase Cholecystitis	Hepatocellular damage/hepatitis[m]	
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome Palmar erythema Rash Alopecia	Hyperkeratosis		
Musculoskeletal and connective tissue disorders	Back pain Arthralgia Myalgia Pain in extremity Musculoskeletal pain		Osteonecrosis of the jaw	
Renal and urinary disorders	Proteinuria[‡]	Renal failure cases[n, †,] Renal impairment[‡] Increased blood creatinine Increased blood urea	Nephrotic syndrome	
General disorders and administration site conditions	Fatigue Asthenia Peripheral Oedema	Malaise	Impaired healing[***]	Non-gastrointestinal fistula[o]

*: Medical Dictionary for Regulatory Activities (MedDRA) version 17.1. Preferred terms have been reassigned to the SOC most relevant to the target organ.
**: These adverse reactions occur more frequently with combination therapy compared to lenvatinib monotherapy.
***: Identified from post-marketing use of lenvatinib
†: Includes cases with a fatal outcome.
‡: See section 4.8 Description of selected adverse reactions for further characterisation.
The following terms have been combined:
a: Thrombocytopenia includes thrombocytopenia and decreased platelet count. Neutropenia includes neutropenia and decreased neutrophil count decreased. 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 subjects with HCC were: epistaxis, haematuria, gingival bleeding, haemoptysis, oesophageal varices haemorrhage, haemorrhoidal haemorrhage, mouth haemorrhage, rectal haemorrhage and upper gastrointestinal haemorrhage.
e: Hypertension includes: hypertension, hypertensive crisis, increased diastolic blood pressure, orthostatic hypertension, and increased blood pressure.
f: Gastrointestinal and abdominal pain includes: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, 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: Hyperbilirubinaeamia 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 includes: drug-induced liver injury, hepatic steatosis, and cholestatic liver injury.
n: Renal failure cases 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, female genital tract fistula, and cutaneous fistula.

Description of selected adverse reactions

Hypertension (see section 4.4)

Clear cell RCC
In the clear cell RCC study (see section 5.1), hypertension was reported in 41.9% of patients in the lenvatinib plus everolimus-treated group (the incidence of Grade 3 or Grade 4 hypertension was 12.9%) and 10.0% of patients in the everolimus-treated group (the incidence of Grade 3 or Grade 4 hypertension was 2.0%). The median time to onset was 4.9 weeks (any grade) and 6.9 weeks (Grade ≥ 3) in the lenvatinib plus everolimus-treated group.

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), hypertension (including hypertension, hypertensive crisis, increased diastolic blood pressure, and increased blood pressure) was reported in 72.8% of lenvatinib-treated patients and 16.0% of patients in the placebo-treated group. The median time to onset in lenvatinib-treated patients was 16 days. Reactions of Grade 3 or higher (including 1 reaction of Grade 4) occurred in 44.4% of lenvatinib-treated patients compared with 3.8% of placebo-treated patients. The majority of cases recovered or resolved following dose interruption or reduction, which occurred in 13.0% and 13.4% of patients, respectively. In 1.1% of patients, hypertension led to permanent treatment discontinuation.

HCC
In the Phase 3 -REFLECT trial (see section 5.1), hypertension (including hypertension, increased blood pressure, increased diastolic blood pressure and orthostatic hypertension) was reported in 44.5% of lenvatinib-treated patients and Grade 3 hypertension occurred in 23.5%. The median time to onset was 26 days. The majority of cases recovered following dose interruption or reduction, which occurred in 3.6% and 3.4% of patients respectively. One subject (0.2%) discontinued lenvatinib due to hypertension.

Proteinuria (see section 4.4)

Clear cell RCC
In the clear cell RCC study (see section 5.1), proteinuria was reported in 30.6% of patients in the lenvatinib plus everolimus-treated group (8.1% were Grade ≥ 3) and 14.0% of patients in the everolimus-treated group (2.0% were Grade ≥3). The median time to onset of proteinuria was 6.1 weeks (any grade) and 20.1 weeks (Grade ≥ 3) in the lenvatinib plus everolimus-treated group. Proteinuria led to permanent treatment discontinuation in 4.8% of patients.

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), proteinuria was reported in 33.7% of lenvatinib-treated patients and 3.1% of patients in the placebo-treated group. The median time to onset was 6.7 weeks. Grade 3 reactions occurred in 10.7% of lenvatinib-treated patients and none in placebo-treated patients. The majority of cases had an outcome of recovered or resolved following dose interruption or reduction, which occurred in 16.9% and 10.7% of patients, respectively. Proteinuria led to permanent treatment discontinuation in 0.8% of patients.

HCC
In the Phase 3 REFLECT trial (see section 5.1), proteinuria was reported in 26.3% of lenvatinib-treated patients and Grade 3 reactions occurred in 5.9%. The median time to onset was 6.1 weeks. The majority of cases recovered following dose interruption or reduction,

which occurred in 6.9% and 2.5% of patients respectively. Proteinuria led to permanent treatment discontinuation in 0.6% of patients.

Renal failure and impairment (see section 4.4)

Clear cell RCC
In the clear cell RCC study (see section 5.1), 8.1% of patients in the lenvatinib plus everolimus treated group developed renal failure and 3.2% developed renal impairment, (9.7% of patients had a Grade 3 event of renal failure or impairment). In the everolimus monotherapy group 2.0% of patients developed renal failure (2.0% were Grade 3).

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), 5.0% of patients developed renal failure and 1.9% developed renal impairment, (3.1% of patients had a Grade ≥ 3 event of renal failure or impairment). In the placebo group 0.8% of patients developed renal failure or impairment (0.8% were Grade ≥ 3).

HCC
In the Phase 3 REFLECT trial (see section 5.1), 7.1% of lenvatinib-treated patients developed a renal failure/impairment event. Grade 3 or greater reactions occurred in 1.9% of lenvatinib-treated patients.

Cardiac dysfunction (see section 4.4)

Clear cell RCC
In the clear cell RCC study (see section 5.1), decreased ejection fraction/cardiac failure was reported in 4.8% of patients (3.2% were Grade ≥ 3) in the lenvatinib plus everolimus treated group, and 4.0% in the everolimus group (2.0% were Grade ≥ 3). The median time to onset of decreased ejection fraction and cardiac failure was 15.7 weeks (any grade) and 32.8 weeks (Grade ≥ 3) in the lenvatinib plus everolimus-treated group.

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), decreased ejection fraction/cardiac failure was reported in 6.5% of patients (1.5% were Grade ≥ 3) in the lenvatinib treated group, and 2.3% in the placebo group (none were Grade ≥ 3).

HCC
In the Phase 3 REFLECT trial (see section 5.1), cardiac dysfunction (including congestive cardiac failure, cardiogenic shock, and cardiopulmonary failure) was reported in 0.6% of patients (0.4% were Grade ≥ 3) in the lenvatinib-treated group.

Posterior reversible encephalopathy syndrome (PRES) / Reversible posterior leucoencephalopathy syndrome (RPLS) (see section 4.4)

Clear cell RCC
In the clear cell RCC study (see section 5.1), there was 1 event of PRES (Grade 3) in the lenvatinib-treated group, occurring after 18.4 weeks of treatment. There were no reports in the lenvatinib plus everolimus or everolimus monotherapy groups.

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), there was 1 event of PRES (Grade 2) in the lenvatinib-treated group and no reports in the placebo group.

HCC
In the Phase 3 REFLECT trial (see section 5.1), there was 1 event of PRES (Grade 2) in the lenvatinib-treated group.

Amongst 1,823 patients treated with lenvatinib monotherapy in clinical trials, there were 5 cases (0.3%) of PRES (0.2% were Grade 3 or 4), all of which resolved after treatment and/or dose interruption, or permanent discontinuation.

Hepatotoxicity (see section 4.4)

Clear cell RCC
In the clear cell RCC study (see section 5.1), the most commonly reported liver-related adverse reactions in the lenvatinib plus everolimus-treated group were elevations of liver enzyme levels, including increases in alanine aminotransferase (9.7%), aspartate aminotransferase (4.8%), alkaline phosphatase (4.8%), and blood bilirubin (3.2%). The median time to onset of liver events was 6.7 weeks (any grade) and 14.2 weeks (Grade ≥ 3) in the lenvatinib plus everolimus-treated group. Grade 3 liver-related reactions occurred in 3.2% of lenvatinib plus everolimus-treated patients. Liver-related reactions led to dose interruptions and reductions in 1.6% and 1.6% of patients, respectively, and to permanent discontinuation in 3.2% of patients.

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), the most commonly reported liver-related adverse reactions were hypoalbuminaemia (9.6% lenvatinib vs. 1.5% placebo) and elevations of liver enzyme levels, including increases in alanine aminotransferase (7.7% lenvatinib vs. 0 placebo), aspartate aminotransferase (6.9% lenvatinib vs. 1.5% placebo), and blood bilirubin (1.9% lenvatinib vs. 0 placebo). The median time to onset of liver reactions in lenvatinib-treated patients was 12.1 weeks. Liver-related reactions of Grade 3 or higher (including 1 Grade 5 case of hepatic failure) occurred in 5.4% of lenvatinib-treated patients compared with 0.8% in placebo-treated patients. Liver-related reactions led to dose interruptions and reductions in 4.6% and 2.7% of patients, respectively, and to permanent discontinuation in 0.4%.

Amongst 1,166 patients treated with lenvatinib, there were 3 cases (0.3%) of hepatic failure, all with a fatal outcome. One occurred in a patient with no liver metastases. There was also a case of acute hepatitis in a patient without liver metastases.

HCC
In the Phase 3 REFLECT trial (see section 5.1), the most commonly reported hepatotoxicity adverse reactions were increased blood bilirubin (14.9%), increased aspartate aminotransferase (13.7%), increased alanine aminotransferase (11.1%), hypoalbuminaemia (9.2%), hepatic encephalopathy (8.0%), increased gamma-glutamyltransferase (7.8%) and increased blood alkaline phosphatase (6.7%). The median time to onset of hepatotoxocity adverse reactions was 6.4 weeks. Hepatotoxicity reactions of ≥ Grade 3 occurred in 26.1% of lenvatinib-treated patients. Hepatic failure (including fatal events in 12 patients) occurred in 3.6% of patients (all were ≥ Grade 3). Hepatic encephalopathy (including fatal events in 4 patients) occurred in 8.4% of patients (5.5% were ≥ Grade 3). There were 17 (3.6%) deaths due to hepatotoxicity events in the lenvatinib arm and 4 (0.8%) deaths in the sorafenib arm. Hepatotoxicity adverse reactions led to dose interruptions and reductions in 12.2% and 7.4% of lenvatinib-treated patients respectively, and to permanent discontinuation in 5.5%.

Across clinical studies in which 1327 patients received lenvatinib monotherapy in indications other than HCC, hepatic failure (including fatal events) was reported in 4 patients (0.3%), liver injury in 2 patients (0.2%), acute hepatitis in 2 patients (0.2%), and hepatocellular injury in 1 patient (0.1%).

Arterial thromboembolisms (see section 4.4)

Clear cell RCC
In the clear cell RCC study (see section 5.1), 1.6% of patients in the lenvatinib plus everolimus-treated group reported arterial thromboembolic events. The time to onset was 69.6 weeks. In the everolimus group, 6.0% of patients reported an arterial thromboembolism (4.0% were Grade ≥ 3).

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), arterial thromboembolic events were reported in 5.4% of lenvatinib-treated patients and 2.3% of patients in the placebo group.

HCC
In the Phase 3 REFLECT trial (see section 5.1), arterial thromboembolic events were reported in 2.3% of patients treated with lenvatinib.

Amongst 1,823 patients treated with lenvatinib monotherapy in clinical studies, there were 10 cases (0.5%) of arterial thromboembolisms (5 cases of myocardial infarction and 5 cases of cerebrovascular accident) with a fatal outcome.

Haemorrhage (see section 4.4)

Clear cell RCC
In the clear cell RCC study (see section 5.1), haemorrhage was reported in 38.7% (8.1% were Grade ≥ 3) of patients in the lenvatinib plus everolimus-treated group. Reactions that occurred at an incidence of ≥2.0% were: epistaxis (22.6%), haematuria (4.8%), haematoma (3.2%), and gastric haemorrhage (3.2%). The median time to first onset of was 10.2 weeks (any grade) and 7.6 weeks (Grade ≥ 3) in the lenvatinib plus everolimus-treated group. The incidence of serious haemorrhage was 4.8% (cerebral haemorrhage, gastric haemorrhage and haemarthrosis). Discontinuation due to haemorrhagic events occurred in 3.2% of patients in the lenvatinib plus everolimus-treated group. There was one case of fatal cerebral haemorrhage in the lenvatinib plus everolimus-treated group and one case of fatal intracranial haemorrhage in the lenvatinib-treated group.

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), haemorrhage was reported in 34.9% (1.9% were Grade ≥ 3) of lenvatinib-treated patients versus 18.3% (3.1% were Grade ≥ 3) of placebo-treated patients. Reactions that occurred at an incidence of ≥0.75% above placebo were: epistaxis (11.9%), haematuria (6.5%), contusion (4.6%), gingival bleeding (2.3%), haematochezia (2.3%), rectal haemorrhage (1.5%), haematoma (1.1%), haemorrhoidal haemorrhage (1.1%), laryngeal haemorrhage (1.1%), petechiae (1.1%), and intracranial tumour haemorrhage (0.8%). In this trial, there was 1 case of fatal intracranial haemorrhage among 16 patients who received lenvatinib and had CNS metastases at baseline.

The median time to first onset in lenvatinib-treated patients was 10.1 weeks. No differences between lenvatinib- and placebo-treated patients were observed in the incidences of serious reactions (3.4% vs. 3.8%), reactions leading to premature discontinuation (1.1% vs. 1.5%), or reactions leading to dose interruption (3.4% vs. 3.8%) or reduction (0.4% vs. 0).

HCC
In the Phase 3 REFLECT trial (see section 5.1), haemorrhage was reported in 24.6% of patients and 5.0% were Grade ≥ 3. Grade 3 reactions occurred in 3.4%, Grade 4 reactions in 0.2% and 7 patients (1.5%) had a grade 5 reaction including cerebral haemorrhage, upper gastrointestinal haemorrhage, intestinal haemorrhage and tumour haemorrhage. The median time to first onset was 11.9 weeks. A haemorrhage event led to dose interruption or reduction in 3.2% and 0.8% patients respectively and to treatment discontinuation in 1.7% of patients.

Across clinical studies in which 1,327 patients received lenvatinib monotherapy in indications other than HCC, Grade ≥ 3 or greater haemorrhage was reported in 2% of patients, 3 patients (0.2%) had a Grade 4 haemorrhage and 8 patients (0.6%) had a Grade 5 reaction including arterial haemorrhage, haemorrhagic stroke, intracranial haemorrhage, intracranial tumour haemorrhage, haematemesis, melaena, haemoptysis and tumour haemorrhage.

Hypocalcaemia (see section 4.4, QT interval prolongation)

Clear cell RCC
In the clear cell RCC study (see section 5.1), hypocalcaemia was reported in 8.1% of patients in the lenvatinib plus everolimus-treated group (3.2% were Grade ≥ 3) and 4.0% of patients in the everolimus-treated group (none were Grade ≥ 3). The median time to onset of hypocalcaemia was 28.3 weeks (any grade) and 45.9 weeks (Grade ≥ 3) in the lenvatinib plus everolimus-treated group. There was one Grade 4 TEAE. No events of hypocalcaemia required dose reduction or interruption, and no patients discontinued treatment due to hypocalcaemia.

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), hypocalcaemia was reported in 12.6% of lenvatinib-treated patients vs. no cases in the placebo arm. The median time to first onset in lenvatinib-treated patients was 11.1 weeks. Reactions of Grade 3 or 4 severity occurred in 5.0% of lenvatinib-treated vs 0 placebo-treated patients. Most reactions resolved following supportive treatment, without dose interruption or reduction, which occurred in 1.5% and 1.1% of patients, respectively; 1 patient with Grade 4 hypocalcaemia discontinued treatment permanently.

HCC
In the Phase 3 REFLECT trial (see section 5.1), hypocalcaemia was reported in 1.1% of patients, with grade 3 reactions occurring in 0.4%. Lenvatinib dose interruption due to hypocalcaemia occurred in one subject (0.2%) and there were no dose reductions or discontinuations.

Gastrointestinal perforation and fistula formation (see section 4.4)

Clear cell RCC
In the clear cell RCC study (see section 5.1), 1.6% of cases of perforated appendicitis (of Grade 3) occurred in the lenvatinib plus everolimus-treated group; there were no reports in

the lenvatinib or everolimus groups.

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), events of gastrointestinal perforation or fistula were reported in 1.9% of lenvatinib-treated patients and 0.8% of patients in the placebo group.

HCC
In the Phase 3 REFLECT trial (see section 5.1), events of gastrointestinal perforation or fistula were reported in 1.9% of lenvatinib-treated patients.

Non-Gastrointestinal fistulae (see section 4.4)
Lenvatinib use has been associated with cases of fistulae including reactions resulting in death. Reports of fistulae that involve areas of the body other than stomach or intestines were observed across various indications. Reactions were reported at various time points during treatment ranging from two weeks to greater than 1 year from initiation of lenvatinib, with median latency of about 3 months.

QT interval prolongation (see section 4.4)

Clear cell RCC
In the clear cell RCC study (see section 5.1), QTc interval increases greater than 60 ms were reported in 11% of patients in the lenvatinib plus everolimus-treated group. The incidence of QTc interval greater than 500 ms was 6% in the lenvatinib plus everolimus-treated group. No reports of QTc interval prolongation greater than 500 ms or increases greater than 60 ms occurred in the everolimus-treated group.

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), QT/QTc interval prolongation was reported in 8.8% of lenvatinib-treated patients and 1.5% of patients in the placebo group. The incidence of QT interval prolongation of greater than 500 ms was 2% in the lenvatinib-treated patients compared to no reports in the placebo group.

HCC
In the Phase 3 REFLECT trial (see section 5.1), QT/QTc interval prolongation was reported in 6.9% of lenvatinib-treated patients. The incidence of QTcF interval prolongation of greater than 500ms was 2.4%.

Increased blood thyroid stimulating hormone (see section 4.4 Impairment of thyroid stimulating hormone suppression) / Thyroid dysfunction)

Clear cell RCC
In the clear cell RCC study (see section 5.1), hypothyroidism occurred in 24% of patients in the lenvatinib plus everolimus-treated group and 2% of patients in the everolimus-treated group. All events of hypothyroidism in the lenvatinib plus everolimus-treated group were of Grade 1 or 2. In patients with a normal TSH at baseline, an elevation of TSH level was observed post baseline in 60.5% of lenvatinib plus everolimus-treated patients as compared with none in patients receiving everolimus alone.

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), 88% of all patients had a baseline TSH level less than or equal to 0.5 mU/L. In those patients with a normal TSH at baseline, elevation of TSH level above 0.5 mU/L was observed post baseline in 57% of lenvatinib-treated patients as compared with 14% of placebo-treated patients.

HCC
In the Phase 3 REFLECT trial (see section 5.1), 89.6% of patients had a baseline TSH level of less than the upper limit of normal. Elevation of TSH above the upper limit of normal was observed post baseline in 69.6% of lenvatinib-treated patients.

Diarrhoea (see section 4.4)

Clear cell RCC
In the clear cell RCC study (see section 5.1), diarrhoea was reported in 80.6% of patients in the lenvatinib plus everolimus-treated group (21.0% were Grade ≥ 3) and in 34.0% of patients in the everolimus-treated group (2.0% were Grade ≥ 3). The median time to onset was 4.1 weeks (any grade) and 8.1 weeks (Grade ≥ 3) in the lenvatinib plus everolimus-treated group. Diarrhoea was the most frequent cause of dose interruption/reduction and recurred despite dose reduction. Diarrhoea resulted in discontinuation in one patient.

DTC
In the pivotal Phase 3 SELECT trial (see section 5.1), diarrhoea was reported in 67.4% of patients in the lenvatinib-treated group (9.2% were Grade ≥ 3) and in 16.8% of patients in the placebo group (none were Grade ≥ 3).

HCC
In the Phase 3 REFLECT trial (see section 5.1), diarrhoea was reported in 38.7% of patients treated with lenvatinib (4.2% were Grade ≥ 3).

Paediatric population
See section 4.2 for information on paediatric use.

Other special populations

Elderly

Clear cell RCC
There are limited data on patients of age ≥75 years with clear cell RCC.

DTC
Patients of age ≥75 years were more likely to experience Grade 3 or 4 hypertension, proteinuria, decreased appetite, and dehydration.

HCC
Patients of age ≥75 years were more likely to experience hypertension, proteinuria, decreased appetite, asthenia, dehydration, dizziness, malaise, peripheral oedema, pruritus and hepatic encephalopathy. Hepatic encephalopathy occurred at more than twice the incidence in patients aged ≥75 years (17.2%) than in those <75 years (7.1%). Hepatic encephalopathy tended to be associated with adverse disease characteristics at baseline or with the use of concomitant medications. Arterial thromboembolic events also occurred at an increased incidence in this age group.

Gender

DTC
Females had a higher incidence of hypertension (including Grade 3 or 4 hypertension), proteinuria, and PPE, while males had a higher incidence of decreased ejection fraction and gastrointestinal perforation and fistula formation.

HCC
Females had a higher incidence of hypertension, fatigue, ECG QT prolongation and alopecia. Men had a higher incidence (26.5%) of dysphonia than women (12.3%), decreased weight and decreased platelet count. Hepatic failure events were observed in male patients only.

Ethnic origin

Clear cell RCC
There are limited data on Asian patients with clear cell RCC.

DTC
Asian patients had a higher (≥ 10% difference) incidence than Caucasian patients of peripheral oedema, hypertension, fatigue, PPE, proteinuria, stomatitis, thrombocytopenia, and myalgia; while Caucasian patients had a higher incidence of diarrhoea, weight decreased, nausea, vomiting, constipation, asthenia, abdominal pain, pain in extremity, and dry mouth. A larger proportion of Asian patients had a lenvatinib dose reduction compared to Caucasian patients. The median time to first dose reduction and the average daily dose taken were lower in Asian than in Caucasian patients.

HCC
Asian patients had a higher incidence than Caucasian patients of proteinuria, decreased neutrophil count, decreased platelet count, decreased white blood count and PPE syndrome, while Caucasian patients had a higher incidence of fatigue, hepatic encephalopathy, acute kidney injury, anxiety, asthenia, nausea, thrombocytopenia and vomiting.

Baseline hypertension

Clear cell RCC
Patients with baseline hypertension had a higher incidence of Grade 3 or 4 dehydration, fatigue, and hypertension.

DTC
Patients with baseline hypertension had a higher incidence of Grade 3 or 4 hypertension, proteinuria, diarrhoea, and dehydration, and experienced more serious cases of dehydration, hypotension, pulmonary embolism, malignant pleural effusion, atrial fibrillation, and GI symptoms (abdominal pain, diarrhoea, vomiting).

Baseline diabetes

Clear cell RCC
Patients with baseline diabetes had a higher incidence of Grade 3 or 4 hypertension, hypertriglyceridemia and acute renal failure.

Hepatic impairment

Clear cell RCC
There are limited data on patients with hepatic impairment in clear cell RCC.

DTC
Patients with baseline hepatic impairment had a higher incidence of hypertension and PPE, and a higher incidence of Grade 3 or 4 hypertension, asthenia, fatigue, and hypocalcaemia compared with patients with normal hepatic function.

HCC
Patients with a baseline Child Pugh (CP) score of 6 (about 20% patients in the REFLECT study) had a higher incidence of decreased appetite, fatigue, proteinuria, hepatic encephalopathy and hepatic failure compared to patients with a baseline CP score of 5. Hepatotoxicity events and haemorrhage events also occurred at a higher incidence in CP score 6 patients compared to CP score 5 patients.

Renal impairment

Clear cell RCC
Patients with baseline renal impairment had a higher incidence of Grade 3 fatigue.

DTC
Patients with baseline renal impairment had a higher incidence of Grade 3 or 4 hypertension, proteinuria, fatigue, stomatitis, oedema peripheral, thrombocytopenia, dehydration, prolonged QT, hypothyroidism, hyponatraemia, increased blood thyroid stimulating hormone, pneumonia compared with subjects with normal renal function. These patients also had a higher incidence of renal reactions and a trend towards a higher incidence of liver reactions.

HCC
Patients with baseline renal impairment had a higher incidence of fatigue, hypothyroidism, dehydration, diarrhoea, decreased appetite, proteinuria and hepatic encephalopathy. These patients also had a higher incidence of renal reactions and arterial thromboembolic events.

Patients with body weight <60 kg

Clear cell RCC
There are limited data on patients with body weight <60 kg in clear cell RCC.

DTC
Patients with low body weight (<60 kg) had a higher incidence of PPE, proteinuria, of Grade 3-or 4 hypocalcaemia and hyponatraemia, and a trend towards a higher incidence of Grade 3 or 4 decreased appetite.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 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 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 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 hypercholesterolemia with the combination has not been studied directly and is not fully elucidated.

Although not studied directly, the MOA for the worsening of diarrhoea with the combination 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.

Clinical efficacy and safety - **DTC**

Radioiodine-refractory differentiated thyroid carcinoma

The SELECT study was a multicentre, randomised, double-blind, placebo-controlled trial that was conducted in 392 patients with radioiodine-refractory differentiated thyroid carcinoma with independent, centrally reviewed, radiographic evidence of disease progression within 12 months (+1 month window) prior to enrolment. Radioiodine-refractory was defined as one or more measurable lesions either with a lack of iodine uptake or with progression in spite of radioactive-iodine (RAI) therapy, or having a cumulative activity of RAI of >600 mCi or 22 GBq with the last dose at least 6 months prior to study entry. Randomisation was stratified by geographic region (Europe, North America, and Other), prior VEGF/VEGFR-targeted therapy (patients may have received 0 or 1 prior VEGF/VEGFR-targeted therapy), and age (≤65 years or >65 years). The main efficacy outcome measure was progression-free survival (PFS) as determined by blinded independent radiologic review using Response Evaluation Criteria in Solid Tumours (RECIST) 1.1. Secondary efficacy outcome measures included overall response rate and overall survival. Patients in the placebo arm could opt to receive lenvatinib treatment at the time of confirmed disease progression.

Eligible patients with measurable disease according to RECIST 1.1 were randomised 2:1 to receive lenvatinib 24 mg once daily (n=261) or placebo (n=131). Baseline demographics and disease characteristics were well balanced for both treatment groups. Of the 392 patients randomised, 76.3% were naïve to prior VEGF/VEGFR-targeted therapies, 49.0% were female, 49.7% were European, and the median age was 63 years. Histologically, 66.1% had a confirmed diagnosis of papillary thyroid cancer and 33.9% had follicular thyroid cancer which included Hürthle cell 14.8% and clear cell 3.8%. Metastases were present in 99% of the patients: lungs in 89.3%, lymph nodes in 51.5%, bone in 38.8%, liver in 18.1%, pleura in 16.3%, and brain in 4.1%. The majority of patients had an ECOG performance status of 0; 42.1% had a status of 1; 3.9% had a status above 1. The median cumulative RAI activity administered prior to study entry was 350 mCi (12.95 GBq).

A statistically significant prolongation in PFS was demonstrated in lenvatinib-treated patients compared with those receiving placebo ($p<0.0001$) (see figure 1). The positive effect on PFS was seen across the subgroups of age (above or below 65 years), sex, race, histological subtype, geographic region, and those who received 0 or 1 prior VEGF/VEGFR-targeted therapies. Following independent review confirmation of disease progression, 109 (83.2%) patients randomised to placebo had crossed over to open-label lenvatinib at the time of the primary efficacy analysis.

The objective response rate (complete response [CR] plus partial response [PR]) per independent radiological review was significantly ($p<0.0001$) higher in the lenvatinib-treated group (64.8%) than in the placebo-treated group (1.5%). Four (1.5%) subjects treated with lenvatinib attained a CR and 165 subjects (63.2%) had a PR, while no subjects treated with placebo had a CR and 2 (1.5%) subjects had a PR.

The median time to first dose reduction was 2.8 months. The median time to objective responsive was 2.0 (95% CI: 1.9, 3.5) months; however, of the patients who experienced a complete or partial response to lenvatinib, 70.4% were observed to develop the response on or within 30 days of being on the 24-mg dose.

An overall survival analysis was confounded by the fact that placebo-treated subjects with confirmed disease progression had the option to cross over to open-label lenvatinib. There was no statistically significant difference in overall survival between the treatment groups at the time of the primary efficacy analysis (HR=0.73; 95% CI: 0.50, 1.07, $p=0.1032$). The median OS had not been reached for either the lenvatinib group or the placebo crossover group.

Table 7 Efficacy results in DTC patients

	Lenvatinib N=261	Placebo N=131
Progression-Free Survival (PFS)[a]		
Number of progressions or deaths (%)	107 (41.0)	113 (86.3)
Median PFS in months (95% CI)	18.3 (15.1, NE)	3.6 (2.2, 3.7)
Hazard ratio (99% CI)[b,c]	0.21 (0.14, 0.31)	
P-value[b]	<0.0001	
Patients who had received 0 prior VEGF/VEGFR-targeted therapy (%)	195 (74.7)	104 (79.4)
Number of progressions or deaths	76	88
Median PFS in months (95% CI)	18.7 (16.4, NE)	3.6 (2.1, 5.3)
Hazard ratio (95% CI)[b,c]	0.20 (0.14, 0.27)	
Patients who had received 1 prior VEGF/VEGFR-targeted therapy (%)	66 (25.3)	27 (20.6)
Number of progressions or deaths	31	25
Median PFS in months (95% CI)	15.1 (8.8, NE)	3.6 (1.9, 3.7)
Hazard ratio (95% CI)[b,c]	0.22 (0.12, 0.41)	
Objective Response Rate[a]		
Number of objective responders (%)	169 (64.8)	2 (1.5)
(95% CI)	(59.0, 70.5)	(0.0, 3.6)
P-value[b]	<0.0001	
Number of complete responses	4	0
Number of partial responses	165	2
Median time to objective response,[d] months (95% CI)	2.0 (1.9, 3.5)	5.6 (1.8, 9.4)
Duration of response,[d] months, median (95% CI)	NE (16.8, NE)	NE (NE, NE)
Overall Survival		
Number of deaths (%)	71 (27.2)	47 (35.9)
Median OS in months (95% CI)	NE (22.0, NE)	NE (20.3, NE)
Hazard ratio (95% CI)[b, e]	0.73 (0.50, 1.07)	
P-value [b, e]	0.1032	

CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival; RPSFT, rank preserving structural failure time model; VEGF/VEGFR, vascular endothelial growth factor / vascular endothelial growth factor receptor.

a: Independent radiologic review.

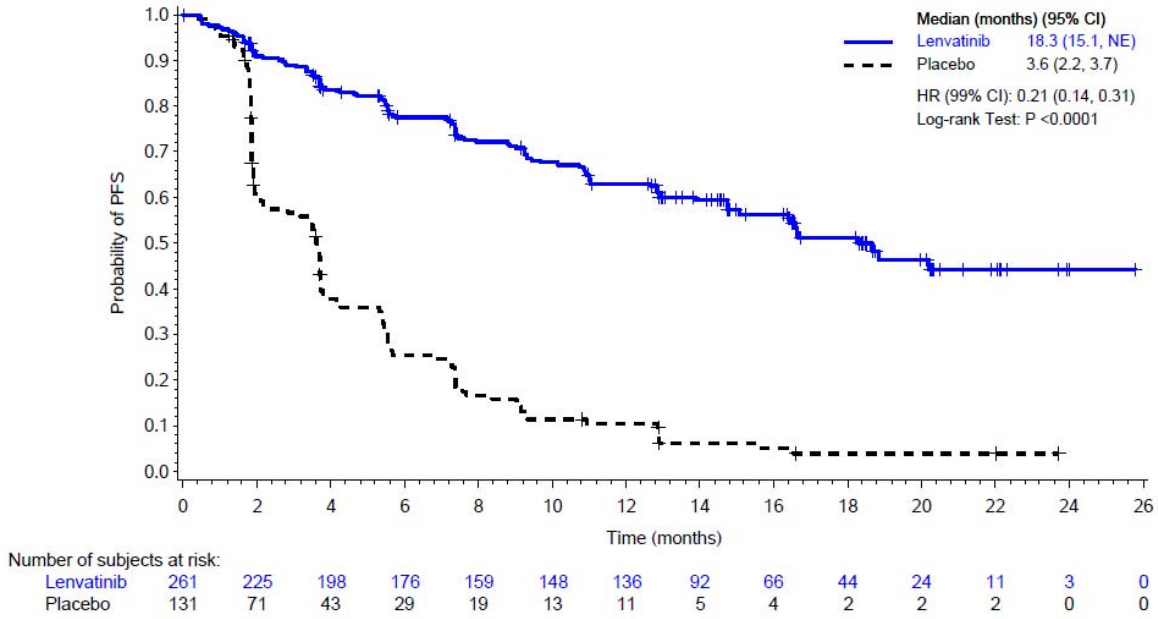
b: Stratified by region (Europe vs. North America vs. Other), age group (≤65 years vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs. 1).

c: Estimated with Cox proportional hazard model.

d: Estimated using the Kaplan-Meier method; the 95% CI was constructed with a generalised Brookmeyer and Crowley method in patients with a best overall response of complete response or partial response.

e: Not adjusted for crossover effect.

Figure 1 Kaplan-Meier Curve of Progression-Free Survival - DTC



CI, confidence interval; NE, not estimable.

Hepatocellular Carcinoma

The clinical efficacy and safety of lenvatinib have been evaluated in an international, multicenter, open-label, randomised phase 3 study (REFLECT) in patients with unresectable hepatocellular carcinoma (HCC).

In total, 954 patients were randomised 1:1 to receive either lenvatinib (12 mg [baseline body weight ≥60 kg] or 8 mg [baseline body weight <60 kg]) given orally once daily or sorafenib 400 mg given orally twice daily.

Patients were eligible to participate if they had a liver function status of Child-Pugh class A and Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1. Patients were excluded who had prior systemic anticancer therapy for advanced/unresectable HCC or any prior anti-VEGF therapy. Target lesions previously treated with radiotherapy or locoregional therapy had to show radiographic evidence of disease progression. Patients with ⩾50% liver occupation, clear invasion into the bile duct or a main branch of the portal vein (Vp4) on imaging were also excluded.

- Demographic and baseline disease characteristics were similar between the lenvatinib and the sorafenib groups and are shown below for all 954 randomised patients:
- Median age: 62 years
- Male: 84%
- White: 29%, Asian: 69%, Black or African American: 1.4%
- Body weight: <60 kg -31%, 60-80 kg – 50%, >80 kg - 19%
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0: 63%, ECOG PS of 1: 37%
- Child-Pugh A: 99%, Child-Pugh B: 1%
- Aetiology: Hepatitis B (50%), Hepatitis C (23%), alcohol (6%)
- Absence of macroscopic portal vein invasion (MPVI): 79%
- Absence of MPVI, extra-hepatic tumour spread (EHS) or both: 30%
- Underlying cirrhosis (by independent imaging review): 75%
- Barcelona Clinic Liver Cancer (BCLC) stage B: 20%; BCLC stage C: 80%
- Prior treatments: hepatectomy (28%), radiotherapy (11%), loco-regional therapies including transarterial (chemo) embolisation (52%), radiofrequency ablation (21%) and percutaneous ethanol injection (4%)

The primary efficacy endpoint was Overall Survival (OS). Lenvatinib was non-inferior for OS to sorafenib with HR = 0.92 [95% CI of (0.79, 1.06)] and a median OS of 13.6 months vs 12.3 months (see Table 8 and Figure 2). The results for surrogate endpoints (PFS and ORR) are presented in Table 8 below.

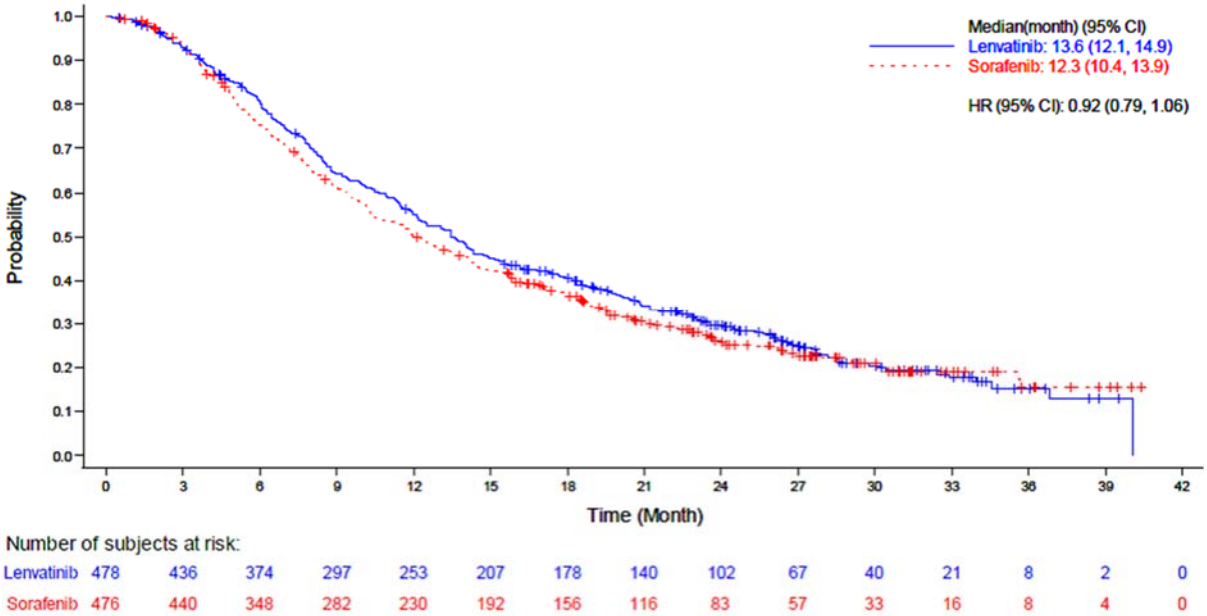
Table 8: Efficacy Results from the REFLECT study in HCC

Efficacy parameter	Hazard ratio[a, b] (95% CI)	P-value [d]	Median (95% CI) [e]	
			Lenvatinib (N= 478)	Sorafenib (N=476)
OS	0.92 (0.79,1.06)	NA	13.6 (12.1, 14.9)	12.3 (10.4, 13.9)
PFS[g] (mRECIST)	0.64 (0.55, 0.75)	<0.00001	7.3 (5.6, 7.5)	3.6 (3.6, 3.7)
			Percentages (95% CI)	
ORR[c, f, g] (mRECIST)	NA	<0.00001	41% (36%, 45%)	12% (9%, 15%)

Data cut-off date: 13 Nov 2016.

a. Hazard ratio is for lenvatinib vs. sorafenib, based on a Cox model including treatment group as a factor.
b. Stratified by region (Region 1: Asia-Pacific; Region 2: Western), macroscopic portal vein invasion or extrahepatic spread or both (yes, no), ECOG PS (0, 1) and body weight (<60 kg, ⩾ 60 kg).
c. Results are based on confirmed and unconfirmed responses.
d. P-value is for the superiority test of lenvatinib versus sorafenib.
e. Quartiles are estimated by the Kaplan-Meier method, and the 95% CIs are estimated with a generalized Brookmeyer and Crowley method
f. Response rate (complete or partial response)
g. Per independent radiology review retrospective analysis. The median duration of objective response was 7.3 (95% CI 5.6, 7.4) months in the lenvatinib arm and 6.2 (95% CI 3.7, 11.2) months in the sorafenib arm.

Figure 2 Kaplan-Meier Curve of Overall Survival - HCC



1. Data cut-off date = 13 Nov 2016.
2. Noninferiority margin for hazard ratio (HR: lenvatinib vs sorafenib = 1.08).
3. Median was estimated with the Kaplan-Meier method and the 95% confidence interval was constructed with a generalised Brookmeyer and Crowley method.
4. HR was estimated from the Cox proportional hazard model with treatment as independent variable and stratified by IxRS stratification factors. The Efron method was used for ties.
5. + = censored observations.

In subgroup analyses by stratification factors (presence or absence of MPVI or EHS or both, ECOG PS 0 or 1, BW <60 kg or ⩾60 kg and region) the HR consistently favoured lenvatinib over sorafenib, with the exception of Western region [HR of 1.08 (95% CI 0.82, 1.42], patients without EHS [HR of 1.01 (95% CI 0.78, 1.30)] and patients without MPVI, EHS or both [HR of 1.05 (0.79, 1.40)]. The results of subgroup analyses should be interpreted with caution.
The median duration of treatment was 5.7 months (Q1: 2.9, Q3: 11.1) in the lenvatinib arm and 3.7 months (Q1: 1.8, Q3: 7.4) in the sorafenib arm.
In both treatment arms in the REFLECT study, median OS was approximately 9 months longer in subjects who received post-treatment anticancer therapy than in those who did not. In the lenvatinib arm, median OS was 19.5 months (95% CI: 15.7, 23.0) for subjects who received post-treatment anticancer therapy (43%) and 10.5 months (95% CI: 8.6, 12.2) for those who did not. In the sorafenib arm, median OS was 17.0 months (95% CI: 14.2, 18.8) for subjects who received posttreatment anticancer therapy (51%) and 7.9 months (95% CI: 6.6, 9.7) for those who did not. Median OS was longer by approximately 2.5 months in the lenvatinib compared with the sorafenib arm in both subsets of subjects (with or without post-treatment anticancer therapy).

QT interval prolongation

A single 32-mg dose of lenvatinib did not prolong the QT/QTc interval based on results from a thorough QT study in healthy volunteers; however, QT/QTc interval prolongation has been reported at a higher incidence in patients treated with lenvatinib than in patients treated with placebo (see sections 4.4 and 4.8).

Clinical efficacy and safety - **clear cell RCC**
A multicenter, randomised, open-label, trial was conducted to determine the safety and efficacy of lenvatinib administered alone or in combination with everolimus in subjects with unresectable advanced or metastatic clear cell RCC. The study consisted of a Phase 1b dose

finding and a Phase 2 portion. The Phase 1b portion included 11 patients who received the combination of 18 mg of lenvatinib plus 5 mg of everolimus. The Phase 2 portion enrolled a total of 153 patients with unresectable advanced or metastatic clear cell RCC following 1 prior VEGF-targeted treatment. A total of 62 patients received the combination of lenvatinib and everolimus at the recommended dose. Patients were required, among others, to have histological confirmation of predominant clear cell RCC, radiographic evidence of disease progression according to Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1), one prior VEGF-targeted therapy and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1.

Patients were randomly allocated to one of 3 arms: 18 mg of lenvatinib plus 5 mg of everolimus, 24 mg of lenvatinib or 10 mg of everolimus using a 1:1:1 ratio. Patients were stratified by hemoglobin level (≤13 g/dL vs. >13 g/dL for males and ≤11.5 g/dL vs >11.5 g/dL for females) and corrected serum calcium (≥10 mg/dL vs. <10 mg/dL). The median of average daily dose in the combination arm per subject was 13.5 mg of lenvatinib (75.0% of the intended dose of 18 mg) and 4.7 mg of everolimus (93.6% of the intended dose of 5 mg). The final dose level in the combination arm was 18 mg for 29% of patients, 14 mg for 31% of patients, 10 mg for 23% of patients, 8 mg for 16% of patients and 4 mg for 2% of patients.

Of the 153 patients randomly allocated, 73% were male, the median age was 61 years, 37% were 65 years or older, 7% were 75 years or older, and 97% were Caucasian. Metastases were present in 95% of the patients and unresectable advanced disease was present in 5%. All patients had a baseline ECOG PS of either 0 (55%) or 1 (45%) with similar distribution across the 3 treatment arms. Memorial Sloan Kettering Cancer Center (MSKCC) poor risk was observed in 39% of patients in the lenvatinib plus everolimus arm, 44% in the lenvatinib arm and 38% in the everolimus arm. International mRCC Database Consortium (IMDC) poor risk was observed in 20% of patients in the lenvatinib plus everolimus arm, 23% in the lenvatinib arm, and 24% in the everolimus arm. The median time from diagnosis to first dose was 32 months in the lenvatinib plus everolimus-treatment arm, 33 months in the lenvatinib arm and 26 months in the everolimus arm. All patients had been treated with 1 prior VEGF-inhibitor; 65% with sunitinib, 23% with pazopanib, 4% with tivozanib, 3% with bevacizumab, and 2% each with sorafenib or axitinib.

The primary efficacy outcome measure, based on investigator assessed tumour response, was progression-free survival (PFS) of the lenvatinib plus everolimus arm vs the everolimus arm and of the lenvatinib arm vs the everolimus arm. Other efficacy outcome measures included overall survival (OS) and investigator-assessed objective response rate (ORR). Tumour assessments were evaluated according to RECIST 1.1.

The lenvatinib plus everolimus arm showed a statistically significant and clinically meaningful improvement in PFS compared with the everolimus arm (see Table 9 and Figure 3). Based on the results of a post-hoc exploratory analysis in a limited number of patients per subgroup, the positive effect on PFS was seen regardless of which prior VEGF-targeted therapy was used: sunitinib (Hazard ratio [HR] = 0.356 [95% CI: 0.188, 0.674] or other therapies (HR = 0.350 [95% CI: 0.148, 0.828]). The lenvatinib arm also showed an improvement in PFS compared with the everolimus arm. Overall survival was longer in the lenvatinib plus everolimus arm (see Table 9 and Figure 4). The study was not powered for the OS analysis.

The treatment effect of the combination on PFS and ORR was also supported by a post-hoc retrospective independent blinded review of scans. The lenvatinib plus everolimus arm showed a statistically significant and clinically meaningful improvement in PFS compared with the everolimus arm. Results for ORR were consistent with that of the investigators' assessments, 35.3% in the lenvatinib plus everolimus arm, with one complete response and 17

partial responses; no subject had an objective response in the everolimus arm (P < 0.0001) in favour of the lenvatinib plus everolimus arm.

Table 9 Efficacy results in clear cell renal cell carcinoma

	lenvatinib 18 mg + everolimus 5 mg (N=51)	**lenvatinib 24 mg (N=52)**	**everolimus 10 mg (N=50)**
Progression-free survival (PFS)[a] by Investigator Assessment			
Median PFS in months (95% CI)	14.6 (5.9, 20.1)	7.4 (5.6, 10.2)	5.5 (3.5, 7.1)
Hazard Ratio (95% CI)[b] lenvatinib + everolimus vs everolimus	0.40 (0.24, 0.67)	-	-
P Value lenvatinib + everolimus vs everolimus	0.0005	-	-
Progression-free survival (PFS)[a] by Post-hoc Retrospective Independent Review			
Median PFS in months (95% CI)	12.8 (7.4, 17.5)	9.0 (5.6, 10.2)	5.6 (3.6, 9.3)
Hazard Ratio (95% CI)[b] lenvatinib + everolimus vs everolimus	0.45 (0.26, 0.79)	-	-
P Value lenvatinib + everolimus vs everolimus	0.003	-	-
Overall Survival[c]			
Number of deaths, n (%)	32 (63)	34 (65)	37 (74)
Median OS in months (95% CI)	25.5 (16.4, 32.1)	19.1 (13.6, 26.2)	15.4 (11.8, 20.6)
Hazard Ratio (95% CI) [b] lenvatinib + everolimus vs everolimus	0.59 (0.36, 0.97)	-	-
Objective Response Rate n (%) by Investigator Assessment			
Complete responses	1 (2)	0	0
Partial responses	21 (41)	14 (27)	3 (6)
Objective Response Rate	22 (43)	14 (27)	3 (6)
Stable disease	21 (41)	27 (52)	31 (62)
Duration of response, months, median (95% CI)	13.0 (3.7, NE)	7.5 (3.8, NE)	8.5 (7.5, 9.4)

Tumour assessment was based on RECIST 1.1 criteria. Data cut-off date = 13 Jun 2014
Percentages are based on the total number of subjects in the Full Analysis Set within relevant treatment group.
CI = confidence interval, NE = not estimable
[a]Point estimates are based on Kaplan-Meier method and 95% CIs are based on the Greenwood formula using log-log transformation.
[b]Stratified hazard ratio is based on a stratified Cox regression model including treatment as a covariate factor and hemoglobin and corrected serum calcium as strata. The Efron method was used for correction for tied events.
[c]Data cut-off date = 31 Jul 2015

Figure 3: Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment)

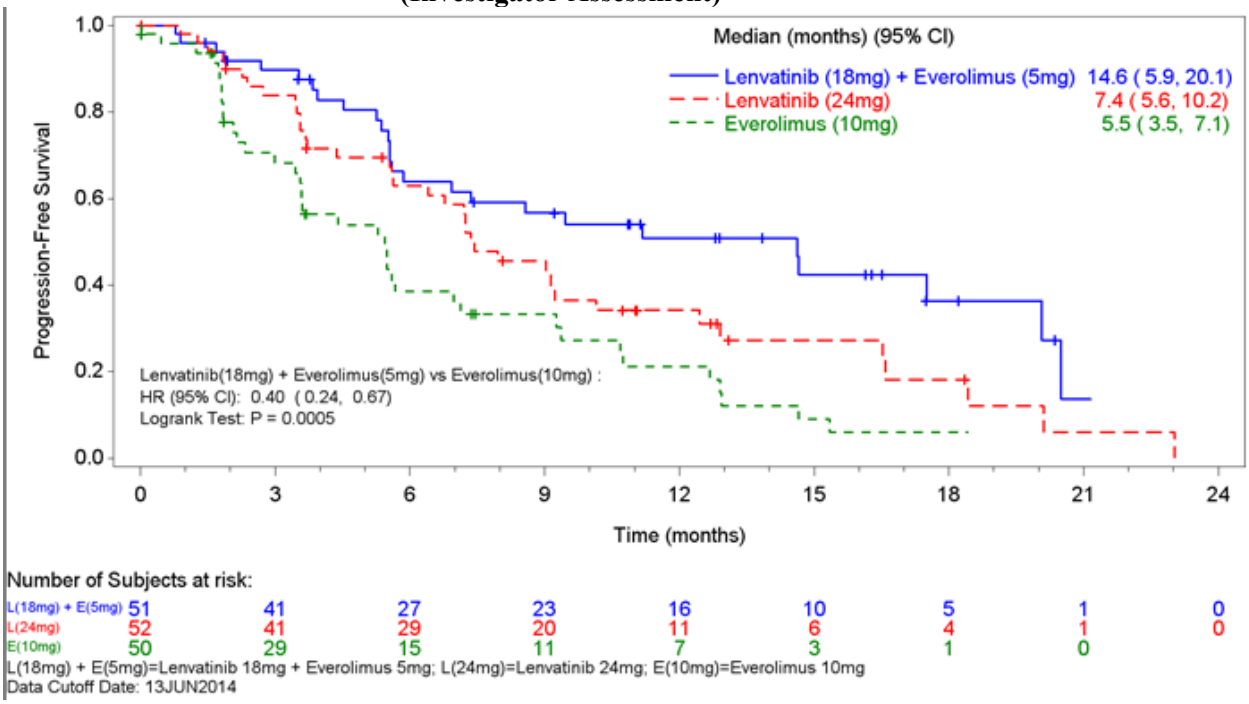
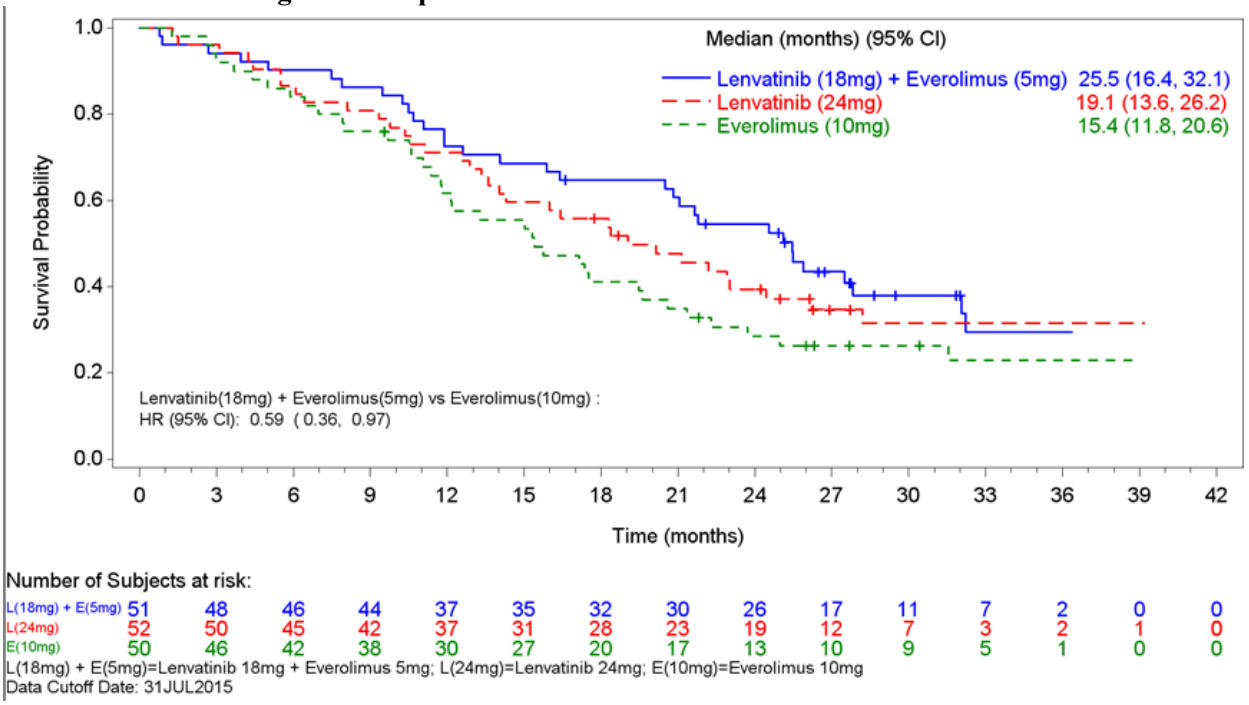


Figure 4: Kaplan-Meier Plot of Overall Survival



5.2 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 postdose. 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 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 (see section 4.5).

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 radiochromatograms 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.

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.

Following administration of radiolabelled lenvatinib to 6 patients with solid tumours, 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).

Linearity/non-linearity

Dose proportionality and accumulation

In patients with solid tumours administered single and multiple doses of lenvatinib once daily, exposure to lenvatinib (C_{max} and AUC) increased in direct proportion to the administered dose over the range of 3.2 to 32 mg once-daily.

Lenvatinib displays minimimal accumulation at steady state. Over this range, the median accumulation index (Rac) ranged from 0.96 (20 mg) to 1.54 (6.4 mg). The Rac in HCC subjects with mild and moderate liver impairment was similar to that reported for other solid tumours.

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-t} and AUC_{0-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. See section 4.2 for dosing recommendation.

There are not sufficient data for HCC patients with Child-Pugh B (moderate hepatic impairment, 3 patients treated with lenvima 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 $AUC_{0\text{-}inf}$ data, was 101%, 90%, and 122% of normal for subjects with mild, moderate, and severe renal impairment, respectively. It is unknown whether there is a change in the plasma protein binding in renally impaired subjects. See section 4.2 for dosing recommendation.

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 (see section 4.2).

Paediatric Population
Paediatric patients have not been studied.

5.3 Preclinical safety data

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 associated 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Calcium carbonate
Low-substituted hydroxypropylcellulose
Microcrystalline cellulose (PH-101, PH-102)
Mannitol
Hydroxypropylcellulose
Talc

Capsule shell
Hypromellose
Titanium dioxide
Yellow iron oxide (E172)
Red iron oxide (E172)

Printing ink
Black iron oxide (E172)
Shellac
Propylene glycol
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original blister in order to protect from moisture.

6.5 Nature and contents of container

Polyamide/Aluminium/PVC/Aluminium blisters containing 10 capsules. Each carton contains 30 capsules

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.

7. MANUFACTURER

Eisai Manufacturing Limited, Hatfield, UK.

8. REGISTRATION HOLDER

Neopharm Scientific Ltd.,
6 Hashiloach St. P.O.B. 7063, Petach Tikva 4917001.

9. REGISTRATION NUMBERS

LENVIMA® 4 mg: 155-36-34514
LENVIMA® 10 mg: 155-37-34530

Revised in July 2021 according to MOH's guidelines.