ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Kisplyx 4 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kisplyx 4 mg hard capsules
Each hard capsule contains 4 mg of lenvatinib (as mesilate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Kisplyx 4 mg hard capsules
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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Kisplyx treatment should be initiated and supervised by a health care professional experienced in the use of anticancer therapies.

Posology
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.

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 there is clinical benefit or until unacceptable toxicity occurs.

Optimal medical management (i.e. treatment or therapy) for nausea, vomiting, and diarrhoea should be initiated prior to any lenvatinib therapy interruption or dose reduction; however, gastrointestinal toxicity should be actively treated in order to reduce the risk of development of renal impairment or renal failure (see section 4.4 Renal failure and impairment).

Dose adjustment
Management of adverse reactions may require dose interruption, adjustment, or discontinuation of the combination therapy (see section 4.4). Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally

do not warrant interruption of the combination, unless intolerable to the patient despite optimal management. Severe (e.g., Grade 3) or intolerable adverse reactions require interruption of the combination of medicines until improvement of the reaction to Grade 0-1 or baseline.

For toxicities thought to be related to lenvatinib (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.

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

For toxicities thought to be related to both lenvatinib and everolimus, lenvatinib should be reduced (see Table 2) prior to reducing everolimus.

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

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

Table 1 Adverse reactions requiring dose modification of lenvatinib

Adverse reaction	**Severity**	**Action**	**Dose reduce and resume lenvatinib**
Hypertension	Grade 3 (despite optimal antihypertensive therapy)	Interrupt	Resolves to Grade 0, 1 or 2. See detailed guidance in Table 3 in section 4.4.
	Grade 4	Discontinue	Do not resume
Proteinuria	≥ 2 gm / 24 hours	Interrupt	Resolves to less than 2 gm / 24 hours.
Nephrotic syndrome	-------	Discontinue	Do not resume
Renal impairment or failure	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume
Cardiac dysfunction	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume
PRES/RPLS	Any grade	Interrupt	Consider resuming at reduced dose if resolves to Grade 0-1.
Hepatotoxicity	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume
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	Discontinue	Do not resume

Table 1 Adverse reactions requiring dose modification of lenvatinib

Adverse reaction	Severity	Action	Dose reduce and resume lenvatinib
	management)		

*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 [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

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 cancer (DTC; see Lenvima SmPC).

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

No data with the combination is available in patients with hepatic impairment. No adjustment of starting dose of the combination is required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. In patients with severe (Child-Pugh C) hepatic impairment, the recommended starting dose of lenvatinib is 10 mg taken once daily in combination with the dose of everolimus recommended for patients with severe hepatic impairment in the everolimus SmPC. Further dose adjustments may be necessary on the basis of individual tolerability. The combination should be used in patients with severe hepatic impairment only if the anticipated benefit exceeds the risk. Refer also to section 4.8, Other special populations.

Patients with renal impairment

No adjustment of starting dose is required on the basis of renal function in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended starting dose is 10 mg of lenvatinib with 5 mg of everolimus taken once daily. Further dose adjustments may be necessary based on individual tolerability. Patients with end-stage renal disease were not studied, therefore the use of lenvatinib in these patients is not recommended. Refer also to section 4.8, Other special populations.

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).

Body weight below 60 kg
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 RCC (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 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 can 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. 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 antihypertensive 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 3.

Table 3 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

Blood pressure (BP) level	Recommended action
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.

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.

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). Lenvatinib should be discontinued in the event of nephrotic syndrome.

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. 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).

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).

Hepatotoxicity
Liver-related adverse reactions most commonly reported in patients treated with lenvatinib included increases in alanine aminotransferase, increases in aspartate aminotransferase, and increases in 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 liver metastases. Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary (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).

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.

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.

In the case of bleeding, dose interruptions, adjustments, or discontinuation may be required (see Section 4.2, Table 2).

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 other areas of the body than stomach or intestines were observed in clinical trials and in post-marketing experience (e.g. tracheal, tracheo-oesophageal, oesophageal, cutaneous, female genital tract fistulae). Prior surgery and radiotherapy may be contributing risk factors. Lenvatinib should not be started in patients with fistulae 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 do 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 in all patients with a special attention for 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. Periodic monitoring of ECG and electrolytes (magnesium, potassium and calcium) should be considered during treatment. Blood calcium levels should be monitored at least monthly and calcium should be replaced as necessary during lenvatinib treatment. Lenvatinib dose should be interrupted or dose adjusted as necessary depending on severity, presence of ECG changes, and persistence of hypocalcaemia.

Impairment of thyroid stimulating hormone suppression / Thyroid dysfunction
Hypothyroidism has been reported in patients treated with lenvatinib (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.

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.

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.

Effect of lenvatinib on other medicinal products

CYP3A4 substrates
No data are available that can be used to exclude the risk that lenvatinib could be an inducer of CYP3A4 or P-gp in the gastrointestinal tract. This could potentially lead to decreased exposure to oral CYP3A4/P-gp substrates. This should be considered if co-administering oral CYP3A4/P-gp substrates for which retained efficacy is very important. CYP3A4 substrates known to have a narrow therapeutic index (e.g. astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine)) should therefore be administered with caution in patients receiving lenvatinib.

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, allowing characterisation only of common adverse drug reactions in RCC patients. The adverse reactions presented in this section are based on the combined safety data of 62 RCC patients (see section 5.1) and 458 DTC patients (see Lenvima SmPC).

The most frequently reported adverse reactions in the 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 haemorrhage (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 the 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%).

Tabulated list of adverse reactions for RCC and DTC studies

Similar adverse reactions were observed in clinical trials in RCC and DTC. 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.

Table 4 shows the frequency categories of adverse reactions observed in clinical trials for RCC and DTC.

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 4 Adverse reactions reported in patients in clinical trials

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]	Lymphopenia[a]	Splenic infarction	
Endocrine disorders	Hypothyroidism[**] Blood thyroid stimulating hormone increased‡[**]			
Metabolism and nutrition disorders	Hypocalcaemia‡ Hypercholesterolaemia[b**] Hypokalaemia Decreased appetite Weight decreased	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 Electrocardiogram QT prolonged Ejection fraction decreased		
Vascular disorders	Haemorrhage[d, †,‡] Hypertension[e,‡] Hypotension			
Respiratory, thoracic and mediastinal disorders	Dysphonia	Pulmonary embolism[†,]		

System Organ Class (MedDRA terminology[*])	**Very Common**	**Common**	**Uncommon**	**Not known**
Gastrointestinal disorders	Diarrhoea[‡**] Gastrointestinal and abdominal pains[f] Vomiting Nausea Oral inflammation[g] Oral pain[h] Constipation Dyspepsia Dry mouth	Anal fistula Flatulence		
Hepatobiliary disorders		Aspartate aminotransferase increased[‡] Hypoalbuminaemia[‡] Alanine aminotransferase increased[‡] Blood alkaline phosphatase increased Hepatic function abnormal Gamma-glutamyltransferase increased[k] Blood bilirubin increased[‡]	Hepatocellular damage/hepatitis[i]	
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			
Renal and urinary disorders	Proteinuria[‡]	Renal failure [j, †, ‡] Renal impairment[‡] Blood creatinine increased Blood urea increased		
General disorders and administration site conditions	Fatigue Asthenia Oedema peripheral	Malaise		Non-gastrointestinal fistula[k]

*: 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.

†: 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. 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: Haemorrhage includes: epistaxis, haemoptysis, haematuria, contusion, haematochezia, gingival bleeding, petechiae, pulmonary haemorrhage, rectal haemorrhage, blood urine present, haematoma, vaginal haemorrhage, conjunctival haemorrhage, haemorrhoidal haemorrhage, intracranial tumour haemorrhage, laryngeal haemorrhage, ecchymosis, increased tendency to bruise, post procedural haemorrhage, purpura, skin haemorrhage, aneurysm ruptured, arterial haemorrhage, eye haemorrhage, gastric haemorrhage, gastroduodenitis haemorrhagic, gastrointestinal haemorrhage, haematemesis, haemorrhage, haemorrhagic stroke,

melaena, metrorrhagia, nail bed bleeding, haemothorax, postmenopausal haemorrhage, proctitis haemorrhagic, renal haematoma, splenic haemorrhage, splinter haemorrhages, subarachnoid haemorrhage, tracheal haemorrhage, tumour haemorrhage.

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

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

g: Oral inflammation includes: aphthous ulcer, stomatitis, glossitis, mouth ulceration, and mucosal inflammation.

h: Oral pain includes: oral pain, glossodynia, and oropharyngeal pain.

i: Hepatocellular damage and hepatitis includes: drug-induced liver injury, hepatic steatosis, and cholestatic liver injury.

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

k: 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)

In the 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.

In the DTC study (see Lenvima SmPC), hypertension (including hypertension, hypertensive crisis, blood pressure diastolic increased, and blood pressure increased) 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.

Proteinuria (see section 4.4)

In the 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.

In the DTC study (see Lenvima SmPC), 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.

Renal failure and impairment (see section 4.4)

In the 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).

In the DTC study (see Lenvima SmPC), 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).

Cardiac dysfunction (see section 4.4)

In the 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.

In the DTC study (see Lenvima SmPC), 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).

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

In the DTC study (see Lenvima SmPC), there was 1 event of PRES (Grade 2) in the lenvatinib-treated group and no reports in the placebo group.

Amongst 1,166 patients treated with lenvatinib, there were 4 cases (0.3%) of PRES (0.3% were Grade 3 or 4), all of which resolved after treatment and/or dose interruption, or permanent discontinuation.

Hepatotoxicity (see section 4.4)
In the 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.

In the DTC study (see Lenvima SmPC), 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.

Arterial thromboembolisms (see section 4.4)
In the 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). In the DTC study (see Lenvima SmPC), arterial thromboembolic events were reported in 5.4% of lenvatinib-treated patients and 2.3% of patients in the placebo group.

Amongst 1,166 patients treated with lenvatinib, there were 5 cases (0.4%) of arterial thromboembolisms (3 cases of myocardial infarction and 2 cases of cerebrovascular accident) with a fatal outcome.

Haemorrhage (see section 4.4)
In the 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.

In the DTC study (see Lenvima SmPC), 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).

Amongst 1,166 patients treated with lenvatinib, Grade 3 or greater haemorrhage was reported in 2% of patients, 3 patients (0.3%) had a Grade 4 haemorrhage and 5 patients (0.4%) had a Grade 5 reaction including arterial haemorrhage, haemorrhagic stroke, intracranial tumour haemorrhage, haemoptysis and tumour haemorrhage.

Hypocalcaemia (see section 4.4, QT interval prolongation)
In the 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.

In the DTC study (see Lenvima SmPC), 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.

Gastrointestinal perforation and fistula formation (see section 4.4)
In the 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.

In the DTC study, events of gastrointestinal perforation or fistula were reported in 1.9% of lenvatinib-treated patients and 0.8% of patients in the placebo group.

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 a median latency of about 3 months.

QT interval prolongation (see section 4.4)
In the 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.
In the DTC study (see Lenvima SmPC), 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.

Blood thyroid stimulating hormone increased (see section 4.4 Impairment of thyroid stimulating hormone suppression / Thyroid dysfunction) (see section 4.4)
In the 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.

In the DTC study (see Lenvima SmPC), 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.

Diarrhoea (see section 4.4)
In the 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.

In the DTC study (see Lenvima SmPC), 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).

Paediatric population
See section 4.2 for information on paediatric use.

Other special populations

Elderly
There are limited data on patients of age ≥75 years with RCC. However in DTC, patients of age ≥75 years were more likely to experience Grade 3 or 4 hypertension, proteinuria, decreased appetite, and dehydration.

Gender
In patients with 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.

Ethnic origin
There are limited data on Asian patients with RCC. However in DTC Asian patients had a higher incidence than Caucasian patients of peripheral oedema, hypertension, fatigue, PPE, proteinuria, thrombocytopenia, and blood thyroid stimulating hormone increased.

Baseline hypertension
In 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). In RCC, patients with baseline hypertension had a higher incidence of Grade 3 or 4 dehydration, fatigue, and hypertension.

Baseline diabetes
In RCC, patients with baseline diabetes had a higher incidence of Grade 3 or 4 hypertension, hypertriglyceridemia and acute renal failure.

Hepatic impairment
There are limited data on patients with hepatic impairment in RCC. However in 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.

Renal impairment
In DTC, patients with baseline renal impairment had a higher incidence of Grade 3 or 4 hypertension, proteinuria, fatigue, stomatitis, oedema peripheral, thrombocytopenia, dehydration, prolonged electrocardiogram QT, hypothyroidism, hyponatraemia, blood thyroid stimulating hormone increased, 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. In RCC, patients with baseline renal impairment had a higher incidence of Grade 3 fatigue.

Patients with body weight <60 kg
There are limited data on patients with body weight <60 kg in RCC. However in 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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, diarrhea, 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.

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

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.

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 diarrhea 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

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 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 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 5 and Figure 1). 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 5 and Figure 2). 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 favor of the lenvatinib plus everolimus arm.

Table 5 Efficacy results in 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 cutoff 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 cutoff date = 31 Jul 2015

Figure 1: Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment)

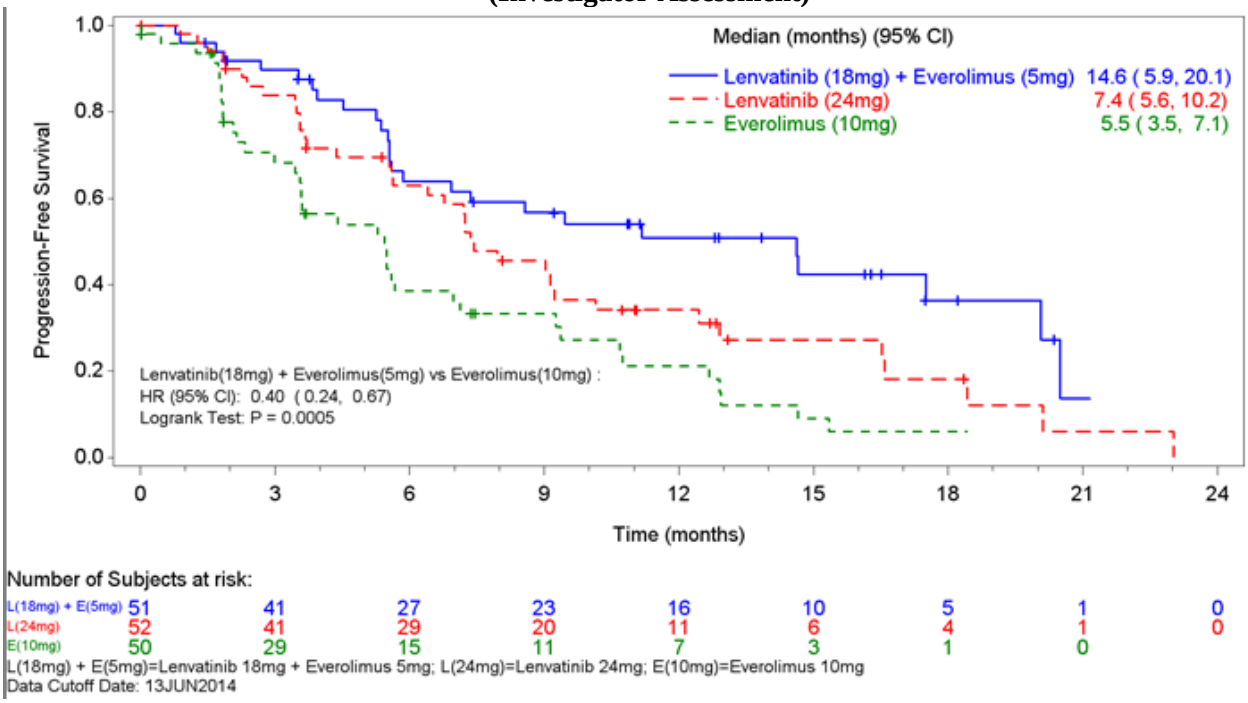
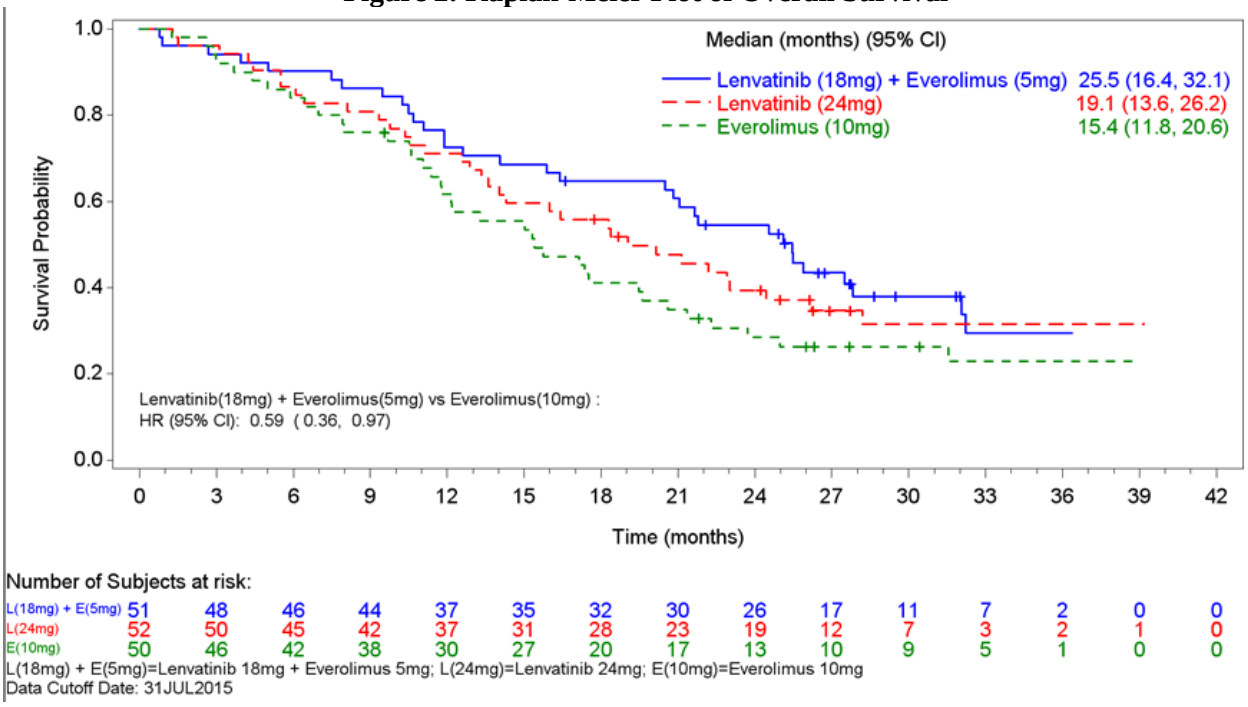


Figure 2: Kaplan-Meier Plot of Overall Survival



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with lenvatinib in all subsets of the paediatric population in Renal Cell Carcinoma (RCC).

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 suggests that it is in the order of 85%.

Distribution
In vitro binding of lenvatinib to human plasma proteins is high and ranged from 98% to 99% (0.3 - 30 μg/mL, mesilate). This binding was mainly to albumin with minor binding to α1-acid glycoprotein and γ-globulin.

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

In vitro studies indicate that lenvatinib is a substrate for P-gp and BCRP. Lenvatinib shows minimal or no inhibitory activities toward P-gp mediated and BCRP mediated transport activities. Similarly, no induction of P-gp mRNA expression was observed. Lenvatinib is not a substrate for OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, or the BSEP. In human liver cytosol, lenvatinib did not inhibit aldehyde oxidase activity.

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 (chlorbenzyl 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
Please see distribution section.

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-fourth 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).

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. 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).

Lenvatinib exposure, based on dose-adjusted AUC0-t and AUC0-inf data, was 119%, 107%, and 180% of normal for subjects with mild, moderate, and severe hepatic impairment, respectively. It is unknown whether there is a change in the plasma protein binding in hepatically impaired subjects. See section 4.2 for dosing recommendation.

Renal impairment

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

Lenvatinib exposure, based on AUC0-inf data, was 101%, 90%, and 122% of normal for subjects with mild, moderate, and severe renal impairment, respectively. It 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 asociated with signs of hepatotoxicity, were also observed in rats, dogs and monkeys. Reversibility of the toxicologic changes was observed at the end of a 4-week recovery period in all animal species investigated.

Genotoxicity
Lenvatinib was not genotoxic.

Carcinogenicity studies have not been conducted with lenvatinib.

Reproductive and developmental toxicity
No specific studies with lenvatinib have been conducted in animals to evaluate the effect on fertility. However, testicular (hypocellularity of the seminiferous epithelium) and ovarian changes (follicular atresia) were observed in repeated-dose toxicity studies in animals at exposures 11 to 15 times (rat) or 0.6 to 7 times (monkey) the anticipated clinical exposure (based on AUC) at the maximum tolerated human dose. These findings were reversible at the end of a 4-week recovery period.

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

Lenvatinib and its metabolites are excreted in rat milk.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Calcium carbonate
Mannitol
Microcrystalline cellulose
Hydroxypropylcellulose
Low-substituted hydroxypropylcellulose
Talc

Capsule shell
Hypromellose
Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172)

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

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

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

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

7. MARKETING AUTHORISATION HOLDER

Eisai Europe Ltd.
European Knowledge Centre
Mosquito Way
Hatfield
Herts AL10 9SN
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1128/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 August 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Kisplyx 10 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kisplyx 10 mg hard capsules
Each hard capsule contains 10 mg of lenvatinib (as mesilate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Kisplyx 10 mg hard capsules
A yellow body and yellowish-red cap, approximately 14.3 mm in length, marked in black ink with "Є" on the cap, and "LENV 10 mg" on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Kisplyx treatment should be initiated and supervised by a health care professional experienced in the use of anticancer therapies.

Posology
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.

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 there is clinical benefit or until unacceptable toxicity occurs.

Optimal medical management (i.e. treatment or therapy) for nausea, vomiting, and diarrhoea should be initiated prior to any lenvatinib therapy interruption or dose reduction; however, gastrointestinal toxicity should be actively treated in order to reduce the risk of development of renal impairment or renal failure (see section 4.4 Renal failure and impairment).

Dose adjustment
Management of adverse reactions may require dose interruption, adjustment, or discontinuation of the combination therapy (see section 4.4). Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally

do not warrant interruption of the combination, unless intolerable to the patient despite optimal management. Severe (e.g., Grade 3) or intolerable adverse reactions require interruption of the combination of medicines until improvement of the reaction to Grade 0-1 or baseline.

For toxicities thought to be related to lenvatinib (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.

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

For toxicities thought to be related to both lenvatinib and everolimus, lenvatinib should be reduced (see Table 2) prior to reducing everolimus.

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

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

Table 1 Adverse reactions requiring dose modification of lenvatinib

Adverse reaction	**Severity**	**Action**	**Dose reduce and resume lenvatinib**
Hypertension	Grade 3 (despite optimal antihypertensive therapy)	Interrupt	Resolves to Grade 0, 1 or 2. See detailed guidance in Table 3 in section 4.4.
	Grade 4	Discontinue	Do not resume
Proteinuria	≥ 2 gm / 24 hours	Interrupt	Resolves to less than 2 gm / 24 hours.
Nephrotic syndrome	-------	Discontinue	Do not resume
Renal impairment or failure	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume
Cardiac dysfunction	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume
PRES/RPLS	Any grade	Interrupt	Consider resuming at reduced dose if resolves to Grade 0-1.
Hepatotoxicity	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume
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

Table 1 Adverse reactions requiring dose modification of lenvatinib

Adverse reaction	Severity	Action	Dose reduce and resume lenvatinib
Diarrhoea	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4 (despite medical management)	Discontinue	Do not resume

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

Table 2 Dose modifications from recommended lenvatinib daily dose [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

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 cancer (DTC; see Lenvima SmPC).

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

No data with the combination is available in patients with hepatic impairment. No adjustment of starting dose of the combination is required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. In patients with severe (Child-Pugh C) hepatic impairment, the recommended starting dose of lenvatinib is 10 mg taken once daily in combination with the dose of everolimus recommended for patients with severe hepatic impairment in the everolimus SmPC. Further dose adjustments may be necessary on the basis of individual tolerability. The combination should be used in patients with severe hepatic impairment only if the anticipated benefit exceeds the risk. Refer also to section 4.8, Other special populations.

Patients with renal impairment

No adjustment of starting dose is required on the basis of renal function in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended starting dose is 10 mg of lenvatinib with 5 mg of everolimus taken once daily. Further dose adjustments may be necessary based on individual tolerability. Patients with end-stage renal disease were not studied, therefore the use of lenvatinib in these patients is not recommended. Refer also to section 4.8, Other special populations.

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).

Body weight below 60 kg
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 RCC (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 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 can 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. 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 antihypertensive 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 3.

Table 3 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

Blood pressure (BP) level	Recommended action
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.

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.

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). Lenvatinib should be discontinued in the event of nephrotic syndrome.

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. 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).

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).

Hepatotoxicity
Liver-related adverse reactions most commonly reported in patients treated with lenvatinib included increases in alanine aminotransferase, increases in aspartate aminotransferase, and increases in 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 liver metastases. Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary (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).

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.

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.

In the case of bleeding, dose interruptions, adjustments, or discontinuation may be required (see Section 4.2, Table 2).

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 other areas of the body than stomach or intestines were observed in clinical trials and in post-marketing experience (e.g. tracheal, tracheo-oesophageal, oesophageal, cutaneous, female genital tract fistulae). Prior surgery and radiotherapy may be contributing risk factors. Lenvatinib should not be started in patients with fistulae 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 do 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 in all patients with a special attention for 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. Periodic monitoring of ECG and electrolytes (magnesium, potassium and calcium) should be considered during treatment. Blood calcium levels should be monitored at least monthly and calcium should be replaced as necessary during lenvatinib treatment. Lenvatinib dose should be interrupted or dose adjusted as necessary depending on severity, presence of ECG changes, and persistence of hypocalcaemia.

Impairment of thyroid stimulating hormone suppression / Thyroid dysfunction
Hypothyroidism has been reported in patients treated with lenvatinib (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.

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.

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.

Effect of lenvatinib on other medicinal products

CYP3A4 substrates
No data are available that can be used to exclude the risk that lenvatinib could be an inducer of CYP3A4 or P-gp in the gastrointestinal tract. This could potentially lead to decreased exposure to oral CYP3A4/P-gp substrates. This should be considered if co-administering oral CYP3A4/P-gp substrates for which retained efficacy is very important. CYP3A4 substrates known to have a narrow therapeutic index (e.g. astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine)) should therefore be administered with caution in patients receiving lenvatinib.

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, allowing characterisation only of common adverse drug reactions in RCC patients. The adverse reactions presented in this section are based on the combined safety data of 62 RCC patients (see section 5.1) and 458 DTC patients (see Lenvima SmPC).

The most frequently reported adverse reactions in the 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 haemorrhage (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 the 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%).

Tabulated list of adverse reactions for RCC and DTC studies

Similar adverse reactions were observed in clinical trials in RCC and DTC. 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.

Table 4 shows the frequency categories of adverse reactions observed in clinical trials for RCC and DTC.

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 4 Adverse reactions reported in patients in clinical trials

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]	Lymphopenia[a]	Splenic infarction	
Endocrine disorders	Hypothyroidism[**] Blood thyroid stimulating hormone increased‡[**]			
Metabolism and nutrition disorders	Hypocalcaemia‡ Hypercholesterolaemia[b**] Hypokalaemia Decreased appetite Weight decreased	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 Electrocardiogram QT prolonged Ejection fraction decreased		
Vascular disorders	Haemorrhage[d, †,‡] Hypertension[e,‡] Hypotension			
Respiratory, thoracic and mediastinal disorders	Dysphonia	Pulmonary embolism[†,]		

System Organ Class (MedDRA terminology[*])	**Very Common**	**Common**	**Uncommon**	**Not known**
Gastrointestinal disorders	Diarrhoea[‡**] Gastrointestinal and abdominal pains[f] Vomiting Nausea Oral inflammation[g] Oral pain[h] Constipation Dyspepsia Dry mouth	Anal fistula Flatulence		
Hepatobiliary disorders		Aspartate aminotransferase increased[‡] Hypoalbuminaemia[‡] Alanine aminotransferase increased[‡] Blood alkaline phosphatase increased Hepatic function abnormal Gamma-glutamyltransferase increased[k] Blood bilirubin increased[‡]	Hepatocellular damage/hepatitis[i]	
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			
Renal and urinary disorders	Proteinuria[‡]	Renal failure [j, †, ‡] Renal impairment[‡] Blood creatinine increased Blood urea increased		
General disorders and administration site conditions	Fatigue Asthenia Oedema peripheral	Malaise		Non-gastrointestinal fistula[k]

*: 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.

†: 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. 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: Haemorrhage includes: epistaxis, haemoptysis, haematuria, contusion, haematochezia, gingival bleeding, petechiae, pulmonary haemorrhage, rectal haemorrhage, blood urine present, haematoma, vaginal haemorrhage, conjunctival haemorrhage, haemorrhoidal haemorrhage, intracranial tumour haemorrhage, laryngeal haemorrhage, ecchymosis, increased tendency to bruise, post procedural haemorrhage, purpura, skin haemorrhage, aneurysm ruptured, arterial haemorrhage, eye haemorrhage, gastric

haemorrhage, gastroduodenitis haemorrhagic, gastrointestinal haemorrhage, haematemesis, haemorrhage, haemorrhagic stroke, melaena, metrorrhagia, nail bed bleeding, haemothorax, postmenopausal haemorrhage, proctitis haemorrhagic, renal haematoma, splenic haemorrhage, splinter haemorrhages, subarachnoid haemorrhage, tracheal haemorrhage, tumour haemorrhage.

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

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

g: Oral inflammation includes: aphthous ulcer, stomatitis, glossitis, mouth ulceration, and mucosal inflammation.

h: Oral pain includes: oral pain, glossodynia, and oropharyngeal pain.

i: Hepatocellular damage and hepatitis includes: drug-induced liver injury, hepatic steatosis, and cholestatic liver injury.

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

k: 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)

In the 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.

In the DTC study (see Lenvima SmPC), hypertension (including hypertension, hypertensive crisis, blood pressure diastolic increased, and blood pressure increased) 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.

Proteinuria (see section 4.4)

In the 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.

In the DTC study (see Lenvima SmPC), 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.

Renal failure and impairment (see section 4.4)

In the 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).

In the DTC study (see Lenvima SmPC), 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).

Cardiac dysfunction (see section 4.4)

In the 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.

In the DTC study (see Lenvima SmPC), 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).

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

In the DTC study (see Lenvima SmPC), there was 1 event of PRES (Grade 2) in the lenvatinib-treated group and no reports in the placebo group.

Amongst 1,166 patients treated with lenvatinib, there were 4 cases (0.3%) of PRES (0.3% were Grade 3 or 4), all of which resolved after treatment and/or dose interruption, or permanent discontinuation.

Hepatotoxicity (see section 4.4)
In the 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.

In the DTC study (see Lenvima SmPC), 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.

Arterial thromboembolisms (see section 4.4)
In the 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). In the DTC study (see Lenvima SmPC), arterial thromboembolic events were reported in 5.4% of lenvatinib-treated patients and 2.3% of patients in the placebo group.

Amongst 1,166 patients treated with lenvatinib, there were 5 cases (0.4%) of arterial thromboembolisms (3 cases of myocardial infarction and 2 cases of cerebrovascular accident) with a fatal outcome.

Haemorrhage (see section 4.4)
In the 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.

In the DTC study (see Lenvima SmPC), 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).

Amongst 1,166 patients treated with lenvatinib, Grade 3 or greater haemorrhage was reported in 2% of patients, 3 patients (0.3%) had a Grade 4 haemorrhage and 5 patients (0.4%) had a Grade 5 reaction including arterial haemorrhage, haemorrhagic stroke, intracranial tumour haemorrhage, haemoptysis and tumour haemorrhage.

Hypocalcaemia (see section 4.4, QT interval prolongation)
In the 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.

In the DTC study (see Lenvima SmPC), 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.

Gastrointestinal perforation and fistula formation (see section 4.4)
In the 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.
In the DTC study, events of gastrointestinal perforation or fistula were reported in 1.9% of lenvatinib-treated patients and 0.8% of patients in the placebo group.

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)
In the 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.
In the DTC study (see Lenvima SmPC), 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.

Blood thyroid stimulating hormone increased (see section 4.4 Impairment of thyroid stimulating hormone suppression / Thyroid dysfunction) (see section 4.4)
In the 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.

In the DTC study (see Lenvima SmPC), 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.

Diarrhoea (see section 4.4)
In the 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.

In the DTC study (see Lenvima SmPC), 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).

Paediatric population
See section 4.2 for information on paediatric use.

Other special populations

Elderly
There are limited data on patients of age ≥75 years with RCC. However in DTC, patients of age ≥75 years were more likely to experience Grade 3 or 4 hypertension, proteinuria, decreased appetite, and dehydration.

Gender
In patients with 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.

Ethnic origin
There are limited data on Asian patients with RCC. However in DTC Asian patients had a higher incidence than Caucasian patients of peripheral oedema, hypertension, fatigue, PPE, proteinuria, thrombocytopenia, and blood thyroid stimulating hormone increased.

Baseline hypertension
In 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). In RCC, patients with baseline hypertension had a higher incidence of Grade 3 or 4 dehydration, fatigue, and hypertension.

Baseline diabetes
In RCC, patients with baseline diabetes had a higher incidence of Grade 3 or 4 hypertension, hypertriglyceridemia and acute renal failure.

Hepatic impairment
There are limited data on patients with hepatic impairment in RCC. However in 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.

Renal impairment
In DTC, patients with baseline renal impairment had a higher incidence of Grade 3 or 4 hypertension, proteinuria, fatigue, stomatitis, oedema peripheral, thrombocytopenia, dehydration, prolonged electrocardiogram QT, hypothyroidism, hyponatraemia, blood thyroid stimulating hormone increased, 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. In RCC, patients with baseline renal impairment had a higher incidence of Grade 3 fatigue.

Patients with body weight <60 kg
There are limited data on patients with body weight <60 kg in RCC. However in 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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, diarrhea, 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.

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

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.

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 diarrhea 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

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 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 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 5 and Figure 1). 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 5 and Figure 2). 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 favor of the lenvatinib plus everolimus arm.

Table 5 Efficacy results in 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 cutoff 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 cutoff date = 31 Jul 2015

Figure 1: Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment)

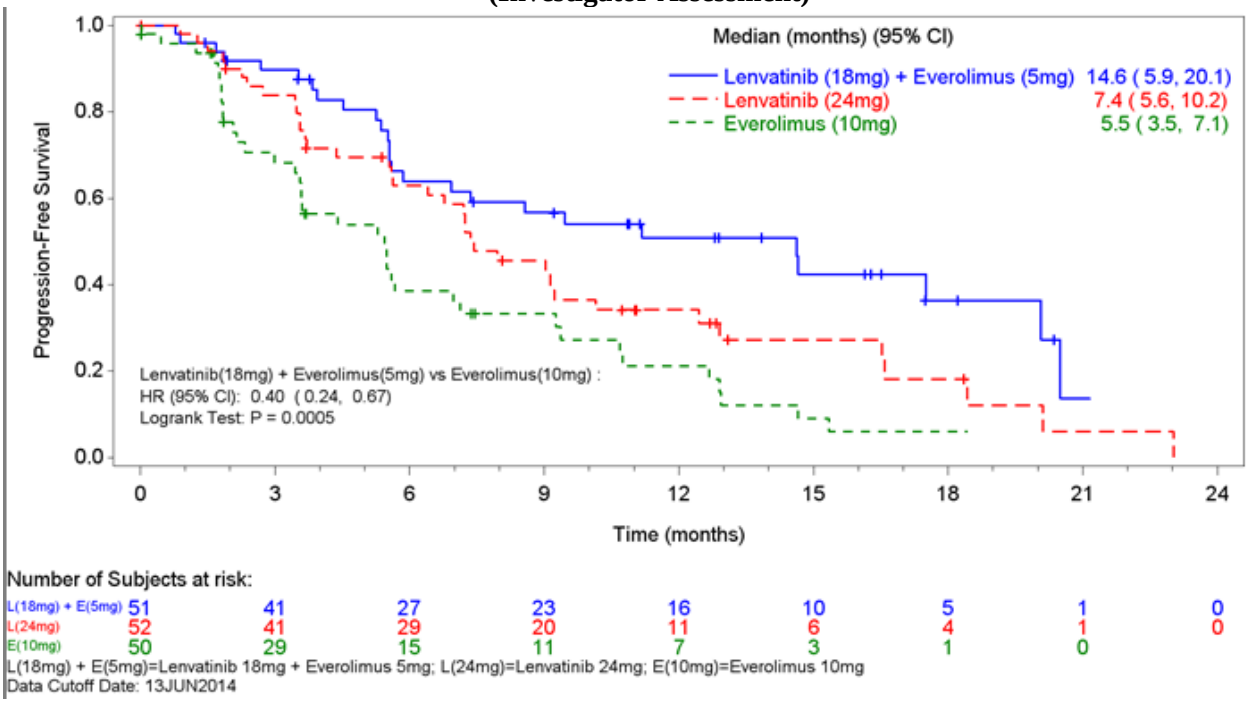
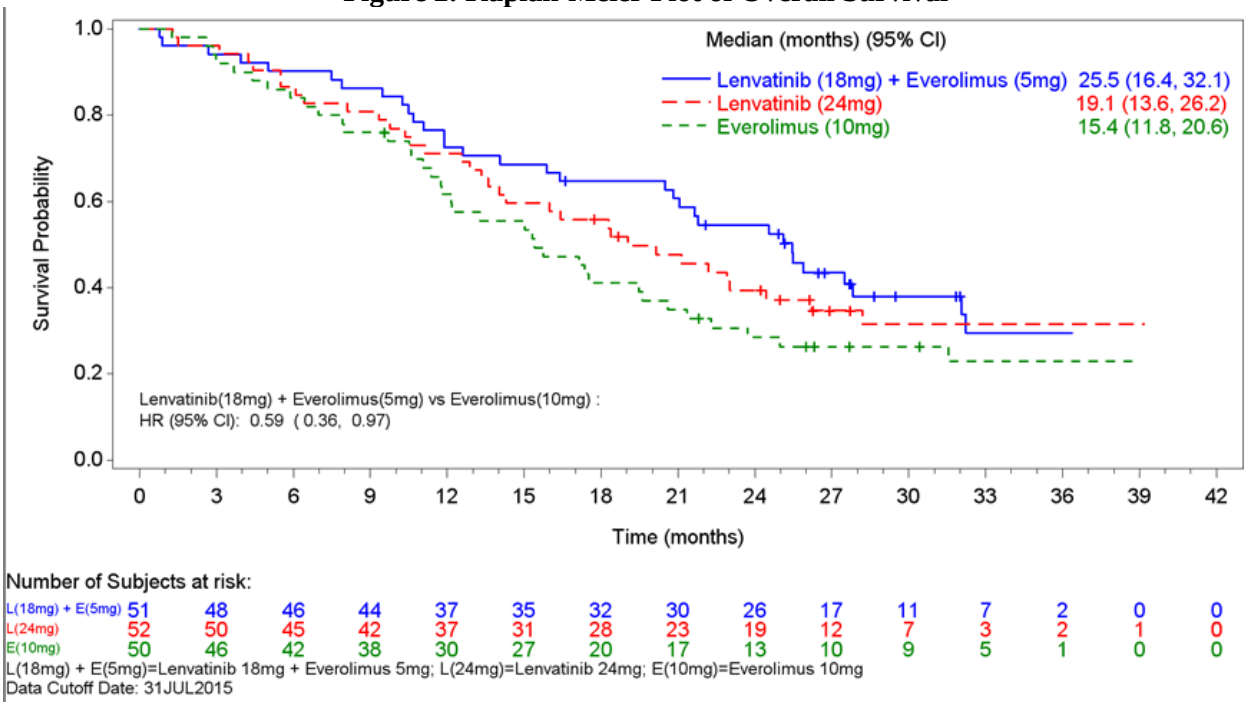


Figure 2: Kaplan-Meier Plot of Overall Survival



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with lenvatinib in all subsets of the paediatric population in Renal Cell Carcinoma (RCC).

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 suggests that it is in the order of 85%.

Distribution
In vitro binding of lenvatinib to human plasma proteins is high and ranged from 98% to 99% (0.3 - 30 μg/mL, mesilate). This binding was mainly to albumin with minor binding to α1-acid glycoprotein and γ-globulin.

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

In vitro studies indicate that lenvatinib is a substrate for P-gp and BCRP. Lenvatinib shows minimal or no inhibitory activities toward P-gp mediated and BCRP mediated transport activities. Similarly, no induction of P-gp mRNA expression was observed. Lenvatinib is not a substrate for OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, or the BSEP. In human liver cytosol, lenvatinib did not inhibit aldehyde oxidase activity.

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 (chlorbenzyl 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
Please see distribution section.

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-fourth 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).

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. 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).

Lenvatinib exposure, based on dose-adjusted AUC0-t and AUC0-inf data, was 119%, 107%, and 180% of normal for subjects with mild, moderate, and severe hepatic impairment, respectively. It is unknown whether there is a change in the plasma protein binding in hepatically impaired subjects. See section 4.2 for dosing recommendation.

Renal impairment

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

Lenvatinib exposure, based on AUC0-inf data, was 101%, 90%, and 122% of normal for subjects with mild, moderate, and severe renal impairment, respectively. It 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 asociated with signs of hepatotoxicity, were also observed in rats, dogs and monkeys. Reversibility of the toxicologic changes was observed at the end of a 4-week recovery period in all animal species investigated.

Genotoxicity
Lenvatinib was not genotoxic.

Carcinogenicity studies have not been conducted with lenvatinib.

Reproductive and developmental toxicity
No specific studies with lenvatinib have been conducted in animals to evaluate the effect on fertility. However, testicular (hypocellularity of the seminiferous epithelium) and ovarian changes (follicular atresia) were observed in repeated-dose toxicity studies in animals at exposures 11 to 15 times (rat) or 0.6 to 7 times (monkey) the anticipated clinical exposure (based on AUC) at the maximum tolerated human dose. These findings were reversible at the end of a 4-week recovery period.

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

Lenvatinib and its metabolites are excreted in rat milk.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Calcium carbonate
Mannitol
Microcrystalline cellulose
Hydroxypropylcellulose
Low-substituted hydroxypropylcellulose
Talc

Capsule shell
Hypromellose
Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172)

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

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

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

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

7. MARKETING AUTHORISATION HOLDER

Eisai Europe Ltd.
European Knowledge Centre
Mosquito Way
Hatfield
Herts AL10 9SN
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1128/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 August 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
Eisai Manufacturing Ltd.
Mosquito Way
Hatfield
AL10 9SN
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kisplyx 4 mg hard capsules
lenvatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 4 mg lenvatinib (as mesilate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai Europe Ltd.
Mosquito Way
Hatfield
Herts AL10 9SN
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1128/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kisplyx 4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Kisplyx 4 mg hard capsules
lenvatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Eisai Europe Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kisplyx 10 mg hard capsules
lenvatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 10 mg lenvatinib (as mesylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai Europe Ltd.
Mosquito Way
Hatfield
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United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1128/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kisplyx 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Kisplyx 10 mg hard capsules
lenvatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Eisai Europe Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Kisplyx 4 mg hard capsules
Kisplyx 10 mg hard capsules

lenvatinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Kisplyx is and what it is used for

What Kisplyx is
Kisplyx is a medicine that contains the active substance lenvatinib. It is used in combination with everolimus to treat patients with advanced kidney cancer (advanced renal cell carcinoma) where other treatments (so-called “VEGF-targeted therapy”) have not helped stop the disease.

How Kisplyx works
Kisplyx blocks the action of proteins called receptor tyrosine kinases (RTKs), which are involved in the development of new blood vessels that supply oxygen and nutrients to cells and help them to grow. These proteins can be present in high amounts in cancer cells, and by blocking their action Kisplyx may slow the rate at which the cancer cells multiply and the tumour grows and help to cut off the blood supply that the cancer needs.

2. What you need to know before you take Kisplyx

Do not take Kisplyx if:
- you are allergic to lenvatinib or any of the other ingredients of this medicine (listed in section 6).
- you are breast-feeding (see the section below on Contraception, pregnancy and breast-feeding).

Warnings and precautions
Talk to your doctor before taking Kisplyx if you:
- have high blood pressure
- are a woman able to become pregnant (see the section“Contraception, pregnancy and breast-feeding” below)

- have a history of heart problems or stroke
- have liver or kidney problems
- have had recent surgery or radiotherapy
- are over 75 years old
- belong to an ethnic group other than White or Asian
- weigh less than 60 kg
- have a history of abnormal passageways (known as a fistula) between different organs in the body or from an organ to the skin

Before taking Kisplyx, your doctor may carry out some blood tests, for example to check your blood pressure and your liver or kidney function and to see if you have low levels of salt and high levels of thyroid stimulating hormone in your blood. Your doctor will discuss the results of these tests with you and decide whether you can be given Kisplyx. You may need to have additional treatment with other medicines, to take a lower dose of Kisplyx, or to take extra care due to an increased risk of side effects.

If you are not sure talk to your doctor before taking Kisplyx.

Children and adolescents
Kisplyx is not recommended for use in children and adolescents. The effects of Kisplyx in people younger than 18 years old are not known.

Other medicines and Kisplyx
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes herbal preparations and medicines without a prescription.

Contraception, pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- Use highly effective contraception while taking this medicine, and for at least one month after you finish treatment.
- Do not take Kisplyx if you are planning to become pregnant during your treatment. This is because it may seriously harm your baby.
- If you become pregnant while being treated with Kisplyx, tell your doctor immediately. Your doctor will help you decide whether the treatment should be continued.
- Do not breast-feed if you are taking Kisplyx. This is because the medicine passes into breast milk and may seriously harm your breastfed baby.

Driving and using machines
Kisplyx may cause side effects that can affect your ability to drive or use machines. Avoid driving or using machines if you feel dizzy or tired.

3. How to take Kisplyx
Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
- The recommended daily dose of Kisplyx is 18 mg once a day (one 10 mg capsule and two 4 mg capsules) in combination with one 5-mg tablet of everolimus once a day.
- If you have severe liver or kidney problems the recommended dose of Kisplyx is 10 mg once a day (1 capsule of 10 mg) in combination with one 5-mg tablet of everolimus once a day.
- Your doctor may reduce your dose if you experience side effects.

Taking this medicine
- You can take the capsules with or without food.

- Swallow the capsules whole with water or dissolved. To dissolve them, pour a tablespoon of water or apple juice into a small glass and put the capsules into the liquid without breaking or crushing them. Leave for at least 10 minutes then stir for at least 3 minutes to dissolve the capsule shells. Drink the mixture. After drinking, add the same amount of water or apple juice, swirl and swallow.
- Take the capsules at about the same time each day.
- Caregivers should not open capsules to avoid exposure to the contents of the capsule.

How long to takeKisplyx
You will usually carry on taking this medicine as long as you are getting benefit.

If you take more Kisplyx than you should
If you take more Kisplyx than you should, talk to a doctor or pharmacist straight away. Take the medicine pack with you.

If you forget to take Kisplyx
Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

What to do if you forget to take your dose depends on how long it is until your next dose.
- If it is 12 hours or more until your next dose: take the missed dose as soon as you remember. Then take the next dose at the normal time.
- If it is less than 12 hours until your next dose: skip the missed dose. Then take the next dose at the normal time.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine.

Tell your doctor straight away if you notice any of the following side effects - you may need urgent medical treatment:
- feeling numb or weak on one side of your body, severe headache, seizure, confusion, difficulty talking, vision changes or feeling dizzy - these may be signs of a stroke, bleeding in your brain, or the effect on your brain of a severe increase in blood pressure.
- chest pain or pressure, pain in your arms, back, neck or jaw, being short of breath, rapid or irregular heart rate, coughing, bluish colour to lips or fingers, feeling very tired – these may be signs of a heart problem or a blood clot in your lung.
- severe pain in your belly (abdomen) - this may be due to a hole in the wall of your gut or a fistula (a hole in your gut which links through a tube-like passage to another part of your body or skin).
- black, tarry, or bloody stools, or coughing up of blood - these may be signs of bleeding inside your body.
- diarrhoea, feeling and being sick - these are very common side effects that can become serious if they cause you to become dehydrated, which can lead to kidney failure. Your doctor can give you medicine to reduce these side effects.

Tell your doctor straight away if you notice any of the side effects above.

Other side effects include:

Very common (may affect more than 1 in 10 people)
- high or low blood pressure
- loss of appetite or weight loss
- feeling and being sick, constipation, diarrhoea, abdominal pain, indigestion
- feeling very tired or weak
- hoarse voice
- swelling of the legs
- rash

- dry, sore, or inflamed mouth, odd taste sensation
- joint or muscle pain
- feeling dizzy
- hair loss
- bleeding (most commonly nose bleeds, but also other types of bleeding such as blood in the urine, bruising, bleeding from the gums or gut wall)
- trouble sleeping
- high levels of protein in the urine and urinary infections (increased frequency in urination and pain in passing urine)
- headache and back pain
- redness, soreness and swelling of the skin on the hands and feet (hand-foot syndrome)
- changes in blood test results for potassium levels (low), calcium levels (low), cholesterol (high) and thyroid stimulating hormone (high)
- underactive thyroid (tiredness, weight gain, constipation, feeling cold, dry skin)
- low levels of platelets in the blood which may lead to bruising and difficulty in wound healing

Common (may affect up to 1 in 10 people)
- loss of body fluids (dehydration)
- heart palpitations
- dry skin, thickening and itching of the skin
- feeling bloated or having gas in the bowel
- heart problems or blood clots in the lungs (difficulty breathing, chest pain) or other organs
- feeling unwell
- stroke
- anal fistula (a small channel that forms between the anus and the surrounding skin)
- changes in blood test results for liver enzymes, white blood cells (low), blood magnesium (low)
- changes in blood test results for kidney function and kidney failure

Uncommon (may affect up to 1 in 100 people)
- painful infection or irritation near the anus
- mini-stroke
- liver damage
- severe pain in the upper left part of the belly (abdomen) which may be associated with fever, chills, nausea and vomiting

Not Known (the following side effects have been reported since the marketing of lenvatinib but the frequency for them to occur is not known)
- other types of fistulae (an abnormal connection between different organs in the body or from the skin to an underlying structure such as throat and windpipe). Symptoms would depend on where the fistula is located. Talk to your doctor if you experience any new or unsual symptoms such as coughing when swallowing.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Kisplyx

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and blister after ‘EXP’. The expiry date refers to the last day of that month.
- Do not store above 25°C. Store in the original blister in order to protect from moisture.

- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Kisplyx contains

- The active substance is lenvatinib.
  - Kisplyx 4 mg hard capsules: - Each hard capsule contains 4 mg of lenvatinib (as mesilate).
  - Kisplyx 10 mg hard capsules: - Each hard capsule contains 10 mg of lenvatinib (as mesilate).

- The other ingredients are calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, low-substituted hydroxypropyl cellulose, talc. The capsule shell contains hypromellose, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172). The printing ink contains shellac, black iron oxide (E172), potassium hydroxide, propylene glycol.

What Kisplyx looks like and contents of the pack

- Kisplyx 4 mg hard capsule: 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.
- Kisplyx 10 mg hard capsule: yellow body and yellowish red cap, approximately 14.3 mm in length, marked in black ink with "Є" on the cap, and "LENV 10 mg" on the body.
- The capsules come in blisters of polyamide/aluminium/PVC with a push through aluminium foil lidding in cartons of 30 capsules.

Marketing Authorisation Holder
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E-mail: EUmedinfo@eisai.net

Manufacturer
Eisai Manufacturing Ltd, Mosquito Way, Hatfield, Herts AL10 9SN, United Kingdom.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.