Hepatotoxicity:
Advise patients that they will need to undergo laboratory tests to monitor for liver function and to report any new symptoms indicating hepatic toxicity or failure *[see Warnings and Precautions (5.4)]*.

Diarrhea:
Advise patients when to start standard anti-diarrheal therapy and to maintain adequate hydration. Advise patients to contact their healthcare provider if they are unable to maintain adequate hydration *[see Warnings and Precautions (5.6)]*.

Proteinuria and Renal Failure/Impairment:
Advise patients that they will need to undergo regular laboratory tests to monitor for kidney function and protein in the urine *[see Warnings and Precautions (5.5, 5.7)]*.

Gastrointestinal perforation or fistula formation:
Advise patients that LENVIMA can increase the risk of gastrointestinal perforation or fistula and to seek immediate medical attention for severe abdominal pain *[see Warnings and Precautions (5.8)]*.

QTc Interval Prolongation
Advise patients who are at risk for QTc prolongation that they will need to undergo regular ECGs. Advise all patients that they will need to undergo laboratory tests to monitor electrolytes *[see Warnings and Precautions (5.9)]*.

Hemorrhagic Events:
Advise patients that LENVIMA can increase the risk for bleeding and to contact their healthcare provider for bleeding or symptoms of severe bleeding *[see Warnings and Precautions (5.12)]*.

Embryofetal Toxicity:
Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.14), Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 2 weeks following completion of therapy *[see Use in Specific Populations (8.3)]*.

Lactation:
Advise nursing women to discontinue breastfeeding during treatment with LENVIMA *[see Use in Specific Populations (8.2)]*.

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Woodcliff Lake, NJ 07677

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PATIENT INFORMATION
LENVIMA® (lehn-veema)
(lenvatinib)
capsules

What is LENVIMA?

LENVIMA is a prescription medicine that is used to treat certain kinds of cancer.

- LENVIMA is used by itself to treat differentiated thyroid cancer (DTC), a type of thyroid cancer that can no longer be treated with radioactive iodine and is progressing.
- LENVIMA is used along with another medicine everolimus to treat advanced renal cell carcinoma (RCC), a type of kidney cancer, after one course of treatment with another anti-cancer medicine.

It is not known if LENVIMA is safe and effective in children.

What should I tell my healthcare provider before taking LENVIMA?

Before you take LENVIMA, tell your healthcare provider if you:

- have high blood pressure
- have heart problems
- have a history of blood clots in your arteries (type of blood vessel), including stroke, heart attack, or change in vision
- have or have had kidney or liver problems
- have a history of a tear (perforation) in your stomach or intestine, or an abnormal connection between two parts of your gastrointestinal tract (fistula)
- have headaches, seizures, or vision problems
- have any bleeding problems
- are pregnant or plan to become pregnant. LENVIMA can harm your unborn baby.
  - Females who are able to become pregnant should use an effective method of birth control during treatment with LENVIMA and for at least 2 weeks after the last dose of LENVIMA. Talk with your healthcare provider about birth control methods you can use during this time.
  - Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with LENVIMA.
- are breastfeeding or plan to breastfeed. It is not known if LENVIMA passes into your breast milk. Do not breastfeed during treatment with LENVIMA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take LENVIMA?

- Take LENVIMA exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much LENVIMA to take and when to take it. Your healthcare provider may change your dose during treatment, stop treatment for some time, or completely stop treatment with LENVIMA if you have side effects.
- Take LENVIMA 1 time each day at the same time, with or without food.
- If you miss a dose of LENVIMA, take it as soon as you remember. If your next dose is due within 12 hours, skip the missed dose and take the next dose at your regular time.
- If you cannot swallow LENVIMA capsules whole:
  - Use a medicine cup to measure about one tablespoon of water or apple juice and place into a small glass.
  - Place the LENVIMA capsules into the small glass without breaking or crushing them.
  - Leave the capsules in the liquid for at least 10 minutes.
  - Stir the contents of the glass for at least 3 minutes.
  - Drink the mixture. After drinking, rinse the glass with a small amount of additional water or apple juice and swallow the liquid.
- If you take too much LENVIMA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of LENVIMA?
LENVIMA may cause serious side effects, including:

- **high blood pressure (hypertension).** High blood pressure is a common side effect of LENVIMA and can be serious. Your blood pressure should be well controlled before you start taking LENVIMA. Your healthcare provider should check your blood pressure regularly during treatment with LENVIMA. If you develop blood pressure problems, your healthcare provider may prescribe medicine to treat your high blood pressure, lower your dose of LENVIMA, or stop your treatment with LENVIMA.
- **heart problems.** Call your healthcare provider right away if you get symptoms of heart problems, such as shortness of breath or swelling of your ankles.
- **problem with blood clots in your blood vessels (arteries).** Get emergency medical help right away if you get any of the following symptoms:
  - severe chest pain or pressure
  - pain in your arms, back, neck or jaw
  - shortness of breath
  - numbness or weakness on one side of your body
  - trouble talking
  - sudden severe headache
  - sudden vision changes
- **liver problems.** LENVIMA may cause liver problems that may lead to liver failure and death. Your healthcare provider will check your liver function before and during treatment with LENVIMA. Tell your healthcare provider right away if you have any of the following symptoms:
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark “tea colored” urine
  - light-colored bowel movements (stools)
- **increased protein in your urine (proteinuria).** Proteinuria is a common side effect of LENVIMA and can be serious. Your healthcare provider should check your urine for protein before and during your treatment with LENVIMA. If you develop protein in your urine, your healthcare provider may decrease your dose of LENVIMA or stop your treatment.
- **diarrhea.** Diarrhea is a common side effect of LENVIMA and can be serious. If you get diarrhea, ask your healthcare provider about what medicines you can take to treat your diarrhea. It is important to drink more water when you get diarrhea. Tell your healthcare provider or go to the emergency room, if you are unable to drink enough liquids and your diarrhea is not able to be controlled.
- **kidney problems.** Kidney failure has happened with LENVIMA treatment. Your healthcare provider should do regular blood tests to check your kidneys.
- **an opening in the wall of your stomach or intestines (perforation) or an abnormal connection between two parts of your gastrointestinal tract (fistula).** Get emergency medical help right away if you have severe stomach (abdomen) pain.
- **changes in the electrical activity of your heart called QT prolongation.** QT prolongation can cause irregular heartbeats that can be life threatening. Your healthcare provider will do blood tests during your treatment with LENVIMA to check the levels of potassium, magnesium, and calcium in your blood, and check the electrical activity of your heart with an ECG.
- **low levels of blood calcium (hypocalcemia).** Your healthcare provider will check your blood calcium levels during treatment with LENVIMA.
- **a condition called Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** Call your healthcare provider right away if you get: severe headache, seizures, weakness, confusion, or blindness or change in vision.
- **bleeding.** LENVIMA may cause serious bleeding problems that may lead to death. Tell your healthcare provider if you have any signs or symptoms of bleeding during treatment with LENVIMA, including:
  - severe and persistent nose bleeds
  - vomiting blood
  - red or black (looks like tar) stools
  - coughing up blood or blood clots
  - heavy or new onset vaginal bleeding
- **change in thyroid hormone levels**. You may have changes in your thyroid hormone levels when taking LENVIMA. Your healthcare provider may need to change your dose of thyroid medicine while you are taking LENVIMA. Your healthcare provider should check your thyroid hormone levels every month during treatment with LENVIMA.

The most common side effects of LENVIMA in people treated for thyroid cancer include:

- tiredness
- joint and muscle pain
- weight loss
- mouth sores
- vomiting
- stomach (abdomen) pain
- decreased appetite
- nausea
- headache
- rash, redness, itching, or peeling of your skin on your hands and feet
- hoarseness

The most common side effects of LENVIMA in people treated for kidney cancer include:

- tiredness
- decreased appetite
- nausea
- swelling in your arms and legs
- stomach (abdomen) pain
- rash
- bleeding
- joint and muscle pain
- vomiting
- mouth sores
- cough
- trouble breathing
- weight loss

LENVIMA may cause fertility problems in males and females. Talk to your healthcare provider if this is a concern for you.
These are not all the possible side effects of LENVIMA.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LENVIMA?

- Store LENVIMA at room temperature, between 68°F to 77°F (20°C to 25°C).

Keep LENVIMA and all medicines out of the reach of children.

General information about the safe and effective use of LENVIMA.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LENVIMA for a condition for which it was not prescribed. Do not give LENVIMA to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about LENVIMA that is written for health professionals.

What are the ingredients in LENVIMA?
Active ingredient: lenvatinib
Inactive ingredients: calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, hydroxypropylcellulose (type H), and talc.
The capsule shell contains: titanium dioxide, ferric oxide yellow, and ferric oxide red. The printing ink contains shellac, black iron oxide, potassium hydroxide, and propylene glycol.
Distributed by: Eisai Inc., Woodcliff Lake, NJ 07677
LENVIMA® is a registered trademark of Eisai R&D Management Co., Ltd. and is licensed to Eisai Inc.
For more information, call 1-877-873-4724 or go to www.LENVIMA.com.
This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 08/2016

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

LENVIMA 4 mg hard capsules
LENVIMA 10 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

LENVIMA 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.

LENVIMA 4 mg hard capsules
A yellowish-red body and yellowish-red cap, approximately 14.3 mm in length, marked in black ink with "C" on the cap, and "LENV 4 mg" on the body.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LENVIMA is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).

4.2 Posology and method of administration

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

Posology

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

If a patient misses a dose, and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration.

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

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

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

For lenvatinib related toxicities (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.

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

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

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.

Table 1 Adverse reactions requiring dose modification of lenvatinib

Adverse reaction	Severity	Action	Dose reduce and resume lenvatinib
	Grade 4	Discontinue	Do not resume
GI perforation or fistula	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume
Non-GI fistula	Grade 4	Discontinue	Do not resume
QT interval prolongation	>500 ms	Interrupt	Resolves to <480 ms or baseline
Diarrhoea	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4 (despite medical management)	Discontinue	Do not resume

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

Table 2 Dose modifications from recommended lenvatinib daily dose[a]

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

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

Special populations

Patients of age ≥75 years, of Asian race, with comorbidities (such as hypertension, and hepatic or renal impairment), or body weight below 60 kg appear to have reduced tolerability to lenvatinib (see section 4.8, Other special populations). All patients other than those with severe hepatic or renal impairment (see below) should initiate treatment at the recommended 24 mg dose, following which the dose should be further adjusted on the basis of individual tolerability.

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 adjustment of starting dose is required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. In patients with severe (Child-Pugh C) hepatic impairment, the recommended starting dose is 14 mg taken once daily. Further dose adjustments may be necessary on the basis of individual tolerability. 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 14 mg taken once daily. Further dose adjustments may be necessary based on individual tolerability. Patients with end-stage renal disease were not studied, therefore the use of lenvatinib in these patients is not recommended. 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).

Method of administration

Lenvatinib is for oral use. The capsules should be taken at about the same time each day, with or without food (see section 5.2). The capsules should be swallowed whole with water. Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.

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 antihypertensives should be started when elevated BP is observed. For those patients already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added. When necessary, manage hypertension as recommended in Table 3.

Table 3Recommended management of hypertension

Blood Pressure (BP) level	**Recommended action**
Systolic BP ≥140 mmHg up to <160 mmHg or diastolic BP ≥90 mmHg up to <100 mmHg	Continue lenvatinib and initiate antihypertensive therapy, if not already receiving OR Continue lenvatinib and increase the dose of the current antihypertensive therapy or initiate additional antihypertensive therapy
Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg despite optimal antihypertensive therapy	1. Withhold lenvatinib 2. When systolic BP ≤150 mmHg, diastolic BP ≤95 mmHg, and patient has been on a stable dose of antihypertensive therapy for at least 48 hours, resume lenvatinib at a reduced dose (see section 4.2)
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue lenvatinib and institute appropriate medical management.

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. 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 fistula to avoid worsening and lenvatinib should be permanently discontinued in patients with oesophageal or tracheobronchial tract involvement and any Grade 4 fistula (see section 4.2); limited information is available on the use of dose interruption or reduction in management of other events, but worsening was observed in some cases and caution should be taken. Lenvatinib may adversely affect the wound healing process as 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, bradyarrhythmias, and those taking medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics. Lenvatinib should be withheld in the event of development of QT interval prolongation greater than 500 ms. Lenvatinib should be resumed at a reduced dose when QTc prolongation is resolved to < 480 ms or baseline.

Electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia increase the risk of QT prolongation, therefore electrolyte abnormalities should be monitored and corrected in all patients before starting treatment. 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

No data is available that can be used to exclude the risk that lenvatinib could be an inducer of CYP3A4 or Pgp in the gastrointestinal tract. This could potentially lead to decreased exposure to oral CYP3A4/Pgp substrates. This should be considered if co-administering oral CYP3A4/Pgp 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

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 most frequently reported adverse reactions (occurring in ≥30% of patients) are hypertension (68.6%), diarrhoea (62.8%), decreased appetite (51.5%), weight decreased (49.1%), fatigue (45.8%), nausea (44.5%), proteinuria 36.9%), stomatitis (35.8%), vomiting (34.5%), dysphonia (34.1%), headache (34.1%), and palmar-plantar erythrodysaesthesia syndrome (PPE) (32.7%). Hypertension and proteinuria tend to occur early during lenvatinib treatment (see sections 4.4 and 4.8, Description of selected adverse reactions). The majority of Grade 3 to 4 adverse reactions occurred during the first 6 months of treatment except for diarrhoea, which occurred throughout treatment, and weight loss, which tended to be cumulative over time.

The most important serious adverse reactions were renal failure and impairment (2.4%), arterial thromboembolisms (3.9%), cardiac failure (0.7%), intracranial tumour haemorrhage (0.7%), PRES / RPLS (0.2%), hepatic failure (0.2%), and arterial thromboembolisms (cerebrovascular accident (1.1%), transient ischaemic attack (0.7%), and myocardial infarction (0.9%).

In 452 patients with RAI-refractory DTC, dose reduction and discontinuation were the actions taken for an adverse reaction in 63.1% and 19.5% of patients, respectively. Adverse reactions that most commonly led to dose reductions (in ≥5% of patients) were hypertension, proteinuria, diarrhoea, fatigue, PPE, weight decreased, and decreased appetite. Adverse reactions that most commonly led to discontinuation of lenvatinib were proteinuria, asthenia, hypertension, cerebrovascular accident, diarrhoea, and pulmonary embolism.

Tabulated list of adverse reactions

Table 4 shows the frequency categories of adverse reactions observed in clinical trials.

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‡ Hypokalaemia Weight decreased Decreased appetite	Dehydration Hypomagnesaemia[b] Hypercholesterolaemia[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			

System Organ Class (MedDRA terminology*)	**Very Common**	**Common**	**Uncommon**	**Not known**
Respiratory, thoracic and mediastinal disorders	Dysphonia	Pulmonary embolism[†,]		
Gastrointestinal disorders	Diarrhoea Gastrointestinal and abdominal pains[f] Vomiting Nausea Oral inflammation[g] Oral pain[h] Constipation Dyspepsia Dry mouth	Anal fistula Flatulence Lipase increased Amylase increased	Pancreatitis	
Hepatobiliary disorders		Aspartate aminotransferase increased[‡] Hypoalbuminaemia[‡] Alanine aminotransferase increased[‡] Blood alkaline phosphatase increased Hepatic function abnormal Gamma-glutamyltransferase increased Blood bilirubin increased[‡] Cholecystitis	Hepatocellular damage/hepatitis[i]	
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome Rash Alopecia	Hyperkeratosis		
Musculoskeletal and connective tissue disorders	Back pain Arthralgia Myalgia Pain in extremity Musculoskeletal pain			
Renal and urinary disorders	Proteinuria[‡]	Renal failure cases[j, †] Renal impairment Blood creatinine increased Blood urea increased		

System Organ Class (MedDRA terminology*)	Very Common	Common	Uncommon	Not known
General disorders and administration site conditions	Fatigue Asthenia Oedema peripheral	Malaise		Non-gastrointestinal fistula[k]

*: Medical Dictionary for Regulatory Activities (MedDRA) version 16.1. Preferred terms have been reassigned to the SOC most relevant to the target organ.
†: 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 platelet count decreased. Lymphopenia includes lymphopenia and lymphocyte count decreased.
b: Hypomagnesaemia includes hypomagnesaemia and blood magnesium decreased. Hypercholesterolaemia includes hypercholesterolaemia and blood cholesterol increased.
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, pleural haemorrhage, postmenopausal haemorrhage, proctitis haemorrhagic, renal haematoma, splenic haemorrhage, splinter haemorrhages, subarachnoid haemorrhage, tracheal haemorrhage, tumour haemorrhage.
e: Hypertension includes: hypertension, hypertensive crisis, blood pressure diastolic increased, and blood pressure increased.
f: Gastrointestinal and abdominal pain includes: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, and gastrointestinal pain.
g: Oral inflammation includes: aphthous stomatitis, 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 cases includes: acute prerenal failure, renal failure, renal failure acute, 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 pivotal Phase 3 SELECT trial (see section 5.1), 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 pivotal Phase 3 SELECT trial (see section 5.1), proteinuria was reported in 33.7% of lenvatinib-treated patients and 3.1% of patients in the placebo-treated group. The median time to onset was 6.7 weeks. Grade 3 reactions occurred in 10.7% of lenvatinib-treated patients and none in placebo-treated patients. The majority of cases had an outcome of recovered or resolved following dose interruption or reduction, which occurred in 16.9% and 10.7% of patients, respectively. Proteinuria led to permanent treatment discontinuation in 0.8% of patients.

Renal failure and impairment (see section 4.4)
In the pivotal Phase 3 SELECT trial (see section 5.1), 5.0% of patients developed renal failure and 1.9% developed renal impairment (3.1% of patients had a Grade ≥ 3 event of renal failure or impairment). In the placebo group 0.8% of patients developed renal failure or impairment (0.8% were Grade ≥ 3).

Cardiac dysfunction (see section 4.4)
In the pivotal Phase 3 SELECT trial (see section 5.1), decreased ejection fraction/cardiac failure was reported in 6.5% of patients (1.5% were Grade ≥ 3) in the lenvatinib treated group, and 2.3% in the placebo group (none were Grade ≥ 3).

Posterior reversible encephalopathy syndrome (PRES) / Reversible posterior leucoencephalopathy syndrome (RPLS) (see section 4.4)
In the pivotal Phase 3 SELECT trial (see section 5.1), there was 1 event of PRES (Grade 2) in the lenvatinib-treated group and no reports in the placebo group.

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

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

Arterial thromboembolisms (see section 4.4)
In the pivotal Phase 3 SELECT trial (see section 5.1), arterial thromboembolic events were reported in 5.4% of lenvatinib-treated patients and 2.3% of patients in the placebo group.

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

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

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

Gastrointestinal perforation and fistula formation (see section 4.4)
In the pivotal Phase 3 SELECT trial (see section 5.1), events of gastrointestinal perforation or fistula were reported in 1.9% of lenvatinib-treated patients and 0.8% of patients in the placebo group.

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

Blood thyroid stimulating hormone increased (see section 4.4 Impairment of thyroid stimulating hormone suppression / Thyroid dysfunction)
In the pivotal Phase 3 SELECT trial (see section 5.1), 88% of all patients had a baseline TSH level less than or equal to 0.5 mU/L. In those patients with a normal TSH at baseline, elevation of TSH level above 0.5 mU/L was observed post baseline in 57% of lenvatinib-treated patients as compared with 14% of placebo-treated patients.

Diarrhoea (see section 4.4)
In the pivotal Phase 3 SELECT trial (see section 5.1), diarrhoea was reported in 67.4% of patients in the lenvatinib-treated group (9.2% were Grade ≥ 3) and in 16.8% of patients in the placebo group (none were Grade ≥ 3).

Paediatric population

Clinical data are not yet available in this population (see section 4.2).

Other special populations

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

Gender
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
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
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).

Hepatic impairment
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
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.

Patients with body weight <60 kg
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.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01XE29

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

Mechanism of action

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFRα, KIT, and RET.

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.

Clinical efficacy

Radioiodine-refractory differentiated thyroid cancer
The SELECT study was a multicentre, randomised, double-blind, placebo-controlled trial that was conducted in 392 patients with radioiodine-refractory differentiated thyroid cancer with independent, centrally reviewed, radiographic evidence of disease progression within 12 months (+1 month

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

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

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

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

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

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

Table 5 Efficacy results

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

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

a: Independent radiologic review.

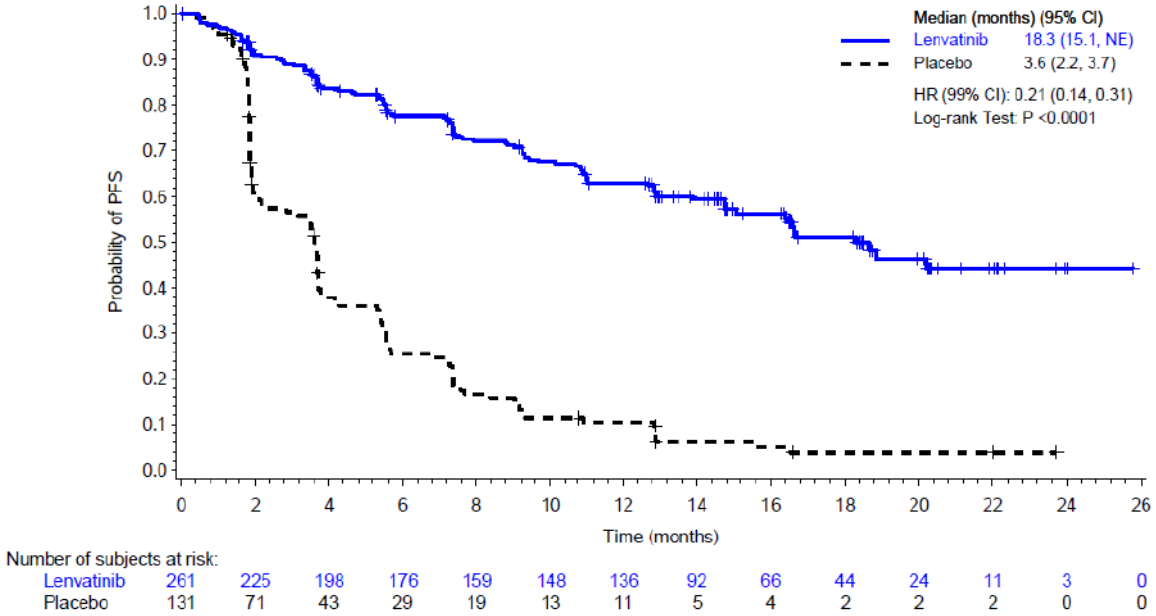
b: Stratified by region (Europe vs. North America vs. Other), age group (≤65 year vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs. 1).

c: Estimated with Cox proportional hazard model.

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

e: Not adjusted for crossover effect.

Figure 1 Kaplan-Meier Plot of Progression-Free Survival



CI, confidence interval; NE, not estimable.

QT interval prolongation

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

Paediatric population

The European Medicines Agency (EMA) has deferred the obligation to submit the results of a study with lenvatinib in one or more subsets of the paediatric population in the treatment of radioiodine-refractory differentiated thyroid cancer.

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%. Lenvatinib exhibited good oral bioavailability in dogs (70.4%) and monkeys (78.4%).

Distribution

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

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

Lenvatinib is a substrate for P-gp and BCRP. Lenvatinib is not a substrate for OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, or the BSEP.

In patients, the median apparent volume of distribution (Vz/F) of the first dose ranged from 50.5 L to 92 L and was generally consistent across the dose groups from 3.2 mg to 32 mg. The analogous median apparent volume of distribution at steady-state (Vz/Fss) was also generally consistent and ranged from 43.2 L to 121 L.

Biotransformation

In vitro, cytochrome P450 3A4 was demonstrated as the predominant (>80%) isoform involved in the P450-mediated metabolism of lenvatinib. However, *in vivo* data indicated that non-P450-mediated pathways contributed to a significant portion of the overall metabolism of lenvatinib. Consequently, *in vivo,* inducers and inhibitors of CYP 3A4 had a minimal effect on lenvatinib exposure (see section 4.5).

In human liver microsomes, the demethylated form of lenvatinib (M2) was identified as the main metabolite. M2' and M3', the major metabolites in human faeces, were formed from M2 and lenvatinib, respectively, by aldehyde oxidase.

In plasma samples collected up to 24 hours after administration, lenvatinib constituted 97% of the radioactivity in plasma radiochromatograms while the M2 metabolite accounted for an additional 2.5%. Based on $AUC_{(0-inf)}$, lenvatinib accounted for 60% and 64% of the total radioactivity in plasma and blood, respectively.

Data from a human mass balance/excretion study indicate lenvatinib is extensively metabolised in humans. The main metabolic pathways in humans were identified as oxidation by aldehyde oxidase, demethylation via CYP3A4, glutathione conjugation with elimination of the O-aryl group (chlorophenyl moiety), and combinations of these pathways followed by further biotransformations (e.g., glucuronidation, hydrolysis of the glutathione moiety, degradation of the cysteine moiety, and intramolecular rearrangement of the cysteinylglycine and cysteine conjugates with subsequent dimerisation). These *in vivo* metabolic routes align with the data provided in the *in vitro* studies using human biomaterials.

In vitro transporter studies

For the following transporters, clinically relevant inhibition was excluded based on a cutoff of $IC_{50} > 50 \times C_{max,unbound}$.

Lenvatinib showed minimal or no inhibitory activities toward P-gp-mediated and BCRP-mediated transport activities. Similarly, no induction of P-gp mRNA expression was observed .

Lenvatinib showed minimal or no inhibitory effect on OATP1B3. In human liver cytosol, lenvatinib did not inhibit aldehyde oxidase activity.

Elimination

Plasma concentrations decline bi-exponentially following C_{max}. The mean terminal exponential half-life of lenvatinib is approximately 28 hours.

Following administration of radiolabelled lenvatinib to 6 patients with solid tumours, approximately two-thirds and one-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 AUC_{0-t} and AUC_{0-inf} data, was 119%, 107%, and 180% of normal for subjects with mild, moderate, and severe hepatic impairment, respectively. It 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

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

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1002/001
EU/1/15/1002/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 May 2015

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
European Knowledge Centre, Mosquito Way, Hatfield, Herfordshire, 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 marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

LENVIMA 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/1/15/1002/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

LENVIMA 4 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

LENVIMA 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

LENVIMA 10 mg hard capsules
lenvatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 10 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/1/15/1002/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

LENVIMA 10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

LENVIMA 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

LENVIMA 4 mg hard capsules
LENVIMA 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 LENVIMA is and what it is used for
2. What you need to know before you take LENVIMA
3. How to take LENVIMA
4. Possible side effects
5. How to store LENVIMA
6. Contents of the pack and other information

1. What LENVIMA is and what it is used for

What LENVIMA is
LENVIMA is a medicine that contains the active substance lenvatinib. It is used to treat progressive or advanced thyroid cancer in adults when radioactive iodine treatment has not helped to stop the disease.

How LENVIMA works
LENVIMA 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 LENVIMA 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 LENVIMA

Do not take LENVIMA 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 LENVIMA if you:
- have high blood pressure
- are a woman able to become pregnant (see the section below on Contraception, pregnancy and breast-feeding)
- have a history of heart problems or strokes
- have liver or kidney problems
- have had recent surgery or radiotherapy
- are over 75 years

- 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 LENVIMA, 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 LENVIMA. You may need to have additional treatment with other medicines, to take a lower dose of LENVIMA, or to take extra care due to an increased risk of side effects.

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

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

Other medicines and LENVIMA
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.
- If you could become pregnant, use highly effective contraception while taking this medicine, and for at least one month after you finish treatment. Because it is not known if LENVIMA can reduce the effect of the oral contraceptive pill, if this is your normal method of contraception you should ensure you also add a barrier method such as the cap or condoms if you have sex during treatment of LENVIMA.
- Do not take LENVIMA 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 LENVIMA, tell your doctor immediately. Your doctor will help you decide whether the treatment should be continued.
- Do not breast-feed if you are taking LENVIMA. This is because the medicine passes into breast milk and may seriously harm your breastfed baby.

Driving and using machines
LENVIMA 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 LENVIMA

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 dose of LENVIMA is usually 24 mg once a day (2 capsules of 10 mg and 1 capsule of 4 mg).
- If you have severe liver or kidney problems the recommended dose is 14 mg once a day (1 capsule of 10 mg and 1 capsule of 4 mg).
- Your doctor may reduce your dose if you have problems with side effects.

Taking this medicine
- You can take the capsules with or without food.
- Swallow the capsules whole with water.
- Take the capsules at about the same time each day.

- Caregivers should not open the capsules to avoid exposure to the contents of the capsule.

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

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

If you forget to take LENVIMA
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 on 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 sick 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
- changes in urine tests for protein (high) 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) and calcium levels (low)
- 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
- underactive thyroid (tiredness, weight gain, constipation, feeling cold, dry skin)
- heart problems or blood clots in the lungs (difficulty breathing, chest pain) or other organs
- feeling unwell
- inflammation of the gallbladder
- stroke
- anal fistula (a small channel that forms between the anus and the surrounding skin)
- changes in blood test results for liver, kidney, white blood cells (low), blood sodium and magnesium (low), cholesterol (high) and thyroid stimulating hormone (high)
- changes in blood test results for kidney function and kidney failure
- increase in lipase and amylase (enzymes involved in digestion)

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
- inflammation of the pancreas

Not Known (the following side effects have been reported since the marketing of LENVIMA 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 an organ to the skin and 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 LENVIMA

- 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 on each 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 LENVIMA contains

- The active substance is lenvatinib.
  - LENVIMA 4 mg hard capsules: - Each hard capsule contains 4 mg of lenvatinib (as mesilate).
  - LENVIMA 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 LENVIMA looks like and contents of the pack

- The 4 mg capsule is 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.
- The 10 mg capsule is 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.
- The capsules come in blisters of polyamide/aluminium/PVC with a push through aluminium foil lidding in cartons of 30 capsules.

Marketing Authorisation Holder
Eisai Europe Limited, European Knowledge Centre, Mosquito Way, Hatfield, Herts AL10 9SN, United Kingdom
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:

België/Belgique/Belgien
Eisai SA/NV
Tél/Tel: + 32 (0) 800 158 58

България
Eisai Europe Ltd.
Тел .: +44 (0)20 8600 1400
(Обединено кралство)

Česká republika
Eisai GesmbH organizačni složka
Tel.: + 420 242 485 839

Danmark
Eisai AB
Tlf: + 46 (0) 8 501 01 600
(Sverige)

Lietuva
Eisai Europe Ltd.
Tel. + 44 (0) 208 600 1400
(Jungtinė Karalystė)

Luxembourg/Luxemburg
Eisai SA/NV
Tél/Tel: + 32 (0) 800 158 58
(Belgique/Belgien)

Magyarország
Eisai Europe Ltd.
Tel.: + 44 (0) 20 8600 1400
(Egyesült Királyság)

Malta
Eisai Europe Ltd.
Tel: +44 (0) 20 8600 1400
(United Kingdom)

Deutschland
Eisai GmbH
Tel: + 49 (0) 69 66 58 50

Eesti
Eisai Europe Ltd.
Tel: + 44 (0) 208 600 1400
(Ühendkuningriik)

Ελλάδα
Eisai Europe Ltd.
Tel: + 44 (0) 208 600 1400
(Ηνωμένο Βασίλειο)

España
Eisai Farmacéutica, S.A.
Tel: + (34) 91 455 94 55

France
Eisai SAS
Tél: + (33) 1 47 67 00 05

Hrvatska
Eisai Europe Ltd.
Tel : + 44 (0) 20 8600 1400
(Velika Britanija)

Ireland
Eisai Europe Ltd.
Tel: + 44 (0) 208 600 1400
(United Kingdom)

Ísland
Eisai AB
Sími: + 46 (0) 8 501 01 600
(Svíþjóð)

Italia
Eisai S.r.l.
Tel: + 39 02 5181401

Κύπρος
Eisai Europe Ltd.
Τηλ: +44 (0) 20 8600 1400
(Ηνωμένο Βασίλειο)

Latvija
Eisai Europe Ltd.
Tel: +44 (0) 20 8600 1400
(Anglija)

Nederland
Eisai B.V.
Tél/Tel: + 31 (0) 900 575 3340

Norge
Eisai AB
Tlf: + 46 (0) 8 501 01 600
(Sverige)

Österreich
Eisai GesmbH
Tel: + 43 (0) 1 535 1980-0

Polska
Eisai Europe Ltd.
Tel.: + 44 (0) 208 600 1400
(Wielka Brytania)

Portugal
Eisai Farmacêutica, Unipessoal Lda
Tel: + 351 214 875 540

România
Eisai Europe Ltd.
Tel: +44 (0) 20 8600 1400
(Marea Britanie)

Slovenija
Eisai Europe Ltd.
Tel: +44 (0) 20 8600 1400
(Velika Britanija)

Slovenská republika
Eisai GesmbH organizační složka
Tel.: +420 242 485 839
(Česká republika)

Suomi/Finland
Eisai AB
Puh/Tel: + 46 (0) 8 501 01 600
(Ruotsi/Sverige)

Sverige
Eisai AB
Tel: + 46 (0) 8 501 01 600

United Kingdom
Eisai Europe Ltd.
Tel: + 44 (0) 208 600 1400

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.

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
Kisplyx 10 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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).

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 "C" on the cap, and "LENV 4 mg" on the body.

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

Table 1 Adverse reactions requiring dose modification of lenvatinib

Adverse reaction	Severity	Action	Dose reduce and resume lenvatinib
GI perforation or fistula	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume
Non-GI fistula	Grade 4	Discontinue	Do not resume
QT interval prolongation	>500 ms	Interrupt	Resolves to <480 ms or baseline
Diarrhoea	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4 (despite medical management)	Discontinue	Do not resume

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

Table 2 Dose modifications from recommended lenvatinib daily dose [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).