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

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

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

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

Table 1 Adverse reactions requiring dose modification of lenvatinib

Adverse reaction	Severity	Action	Dose reduce and resume lenvatinib
Hypertension	Grade 3 (despite optimal antihypertensive therapy)	Interrupt	Resolves to Grade 0, 1 or 2. See detailed guidance in Table 3 in section 4.4.
	Grade 4	Discontinue	Do not resume
Proteinuria	≥ 2 gm / 24 hours	Interrupt	Resolves to less than 2 gm / 24 hours.
Nephrotic syndrome	-------	Discontinue	Do not resume
Renal impairment or failure	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume
Cardiac dysfunction	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume
PRES/RPLS	Any grade	Interrupt	Consider resuming at reduced dose if resolves to Grade 0-1.
Hepatotoxicity	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume
Arterial thromboembolisms	Any grade	Discontinue	Do not resume
Haemorrhage	Grade 3	Interrupt	Resolves to Grade 0-1.
	Grade 4	Discontinue	Do not resume
GI perforation or fistula	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume
Non-GI fistula	Grade 4	Discontinue	Do not resume
QT interval prolongation	>500 ms	Interrupt	Resolves to <480 ms or baseline
Diarrhoea	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4 (despite medical management)	Discontinue	Do not resume

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

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

Dose level	Daily dose	Number of capsules

Recommended daily dose	18 mg orally once daily	One 10 mg capsule plus two 4 mg capsules
First dose reduction	14 mg orally once daily	One 10 mg capsule plus one 4 mg capsule
Second dose reduction	10 mg orally once daily	One 10 mg capsule
Third dose reduction	8 mg orally once daily	Two 4 mg capsules
[a] Limited data are available for doses below 8 mg		

Special populations

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

All patients other than those with severe hepatic or renal impairment (see below) should initiate treatment at the recommended dose of 18 mg of lenvatinib with 5 mg of everolimus taken once daily, following which the dose should be further adjusted on the basis of individual tolerability.

Patients with hypertension

Blood pressure should be well controlled prior to treatment with lenvatinib, and should be regularly monitored during treatment (see section 4.4). Refer also to section 4.8, Other special populations.

Patients with hepatic impairment

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

Patients with renal impairment

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

Elderly population

No adjustment of starting dose is required on the basis of age. Limited data are available on use in patients aged ≥75 years (see also section 4.8, Other special populations).

Paediatric population

Lenvatinib should not be used in children younger than 2 years of age because of safety concerns identified in animal studies (see section 5.3). The safety and efficacy of lenvatinib in children aged 2 to <18 years have not yet been established (see section 5.1). No data are available.

Race

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

Body weight below 60 kg

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

Patients with high ECOG performance status

Patients with an ECOG (Eastern Cooperative Oncology Group) performance status of 2 or higher were excluded from the RCC study (see section 5.1). Benefit-risk in these patients has not been evaluated.

Method of administration

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

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

same amount of water or apple juice (one tablespoon) must be added to the glass and swirled a few times. The additional liquid must be swallowed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Hypertension

Hypertension has been reported in patients treated with lenvatinib, usually occurring early in the course of treatment (see section 4.8, Description of selected adverse reactions). Blood pressure (BP) should be well controlled prior to treatment with lenvatinib and, if patients are known to be hypertensive, they should be on a stable dose of antihypertensive therapy for at least 1 week prior to treatment with lenvatinib. Serious complications of poorly controlled hypertension, including aortic dissection, have been reported. The early detection and effective management of hypertension are important to minimise the need for lenvatinib dose interruptions and reductions. Antihypertensive agents should be started as soon as elevated BP is confirmed. BP should be monitored after 1 week of treatment with lenvatinib, then every 2 weeks for the first 2 months, and monthly thereafter. The choice of antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice. For previously normotensive subjects, monotherapy with one of the classes of antihypertensive should be started when elevated BP is observed. For those patients already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added. When necessary, manage hypertension as recommended in Table 3.

Table 3 Recommended management of hypertension

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

Aneurysms and artery dissections

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

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). Cases of nephrotic syndrome have been reported in patients using lenvatinib. Lenvatinib should be discontinued in the event of nephrotic syndrome.

Renal failure and impairment

Renal impairment and renal failure have been reported in patients treated with lenvatinib (see section 4.8, Description of selected adverse reactions). The primary risk factor identified was dehydration and/or hypovolemia due to gastrointestinal toxicity. Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or renal failure. Caution should be taken in patients receiving agents acting on the renin-angiotensin aldosterone system given a potentially higher risk for acute renal failure with the combination treatment. Dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

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

Cardiac dysfunction

Cardiac failure (<1%) and decreased left ventricular ejection fraction have been reported in patients treated with lenvatinib (see section 4.8, Description of selected adverse reactions). Patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

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

PRES, also known as RPLS, has been reported in patients treated with lenvatinib (<1%; see section 4.8, Description of selected adverse reactions). PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control blood pressure (see section 4.4, Hypertension). In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

Hepatotoxicity

Liver-related adverse reactions most commonly reported in patients treated with lenvatinib included increases in alanine aminotransferase, increases in aspartate aminotransferase, and increases in blood bilirubin. Hepatic failure and acute hepatitis (<1%; see section 4.8, Description of selected adverse reactions) have been reported in patients treated with lenvatinib. The hepatic failure cases were generally reported in patients with progressive liver metastases. Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

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

Arterial thromboembolisms

Arterial thromboembolisms (cerebrovascular accident, transient ischaemic attack, and myocardial infarction) have been reported in patients treated with lenvatinib (see section 4.8, Description of selected adverse reactions). Lenvatinib has not been studied in patients who have had an arterial thromboembolism within the previous 6 months, and therefore should be used with caution in such patients. A treatment decision should be made based upon an assessment of the individual patient's benefit/risk. Lenvatinib should be discontinued following an arterial thrombotic event.

Haemorrhage

Serious tumour related bleeds, including fatal haemorrhagic events have occurred in clinical trials and have been reported in post-marketing experience (see section 4.8, Description of selected adverse reactions). In post-marketing surveillance, serious and fatal carotid artery haemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than in DTC or other tumour types. The degree of tumour invasion/infiltration of major blood vessels (e.g. carotid artery) should be considered because of the potential risk of severe haemorrhage associated with tumour shrinkage/necrosis following lenvatinib therapy. Some cases of bleeding have occurred secondarily to tumour shrinkage and fistula formation, e.g. tracheo-oesophageal fistulae. Cases of fatal intracranial haemorrhage have been reported in some patients with or without brain metastases. Bleeding in sites other than the brain (e.g. trachea, intra-abdominal, lung) has also been reported.

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

Gastrointestinal perforation and fistula formation

Gastrointestinal perforation or fistulae have been reported in patients treated with lenvatinib (see section 4.8). In most cases, gastrointestinal perforation and fistulae occurred in patients with risk factors such as prior surgery or radiotherapy. In the case of a gastrointestinal perforation or fistula, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

Non-Gastrointestinal fistula

Patients may be at increased risk for the development of fistulae when treated with lenvatinib. Cases of fistula formation or enlargement that involve other areas of the body than stomach or intestines were observed in clinical

trials and in post-marketing experience (e.g. tracheal, tracheo-oesophageal, oesophageal, cutaneous, female genital tract fistulae). In addition, pneumothorax has been reported with and without clear evidence of a bronchopleural fistula. Some reports of fistula and pneumothorax occurred in association with tumour regression or necrosis. Prior surgery and radiotherapy may be contributing risk factors. Lung metastases may also increase the risk of pneumothorax. Lenvatinib should not be started in patients with fistulae to avoid worsening and lenvatinib should be permanently discontinued in patients with oesophageal or tracheobronchial tract involvement and any Grade 4 fistula (see section 4.2); limited information is available on the use of dose interruption or reduction in management of other events, but worsening was observed in some cases and caution should be taken. Lenvatinib may adversely affect the wound healing process as do other agents of the same class.

QT interval prolongation

QT/QTc interval prolongation has been reported at a higher incidence in patients treated with lenvatinib than in patients treated with placebo (see section 4.8, Description of selected adverse reactions). Electrocardiograms should be monitored in all patients with a special attention for those with congenital long QT syndrome, congestive heart failure, bradyarrhythmics, and those taking medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics. Lenvatinib should be withheld in the event of development of QT interval prolongation greater than 500 ms. Lenvatinib should be resumed at a reduced dose when QTc prolongation is resolved to < 480 ms or baseline.

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

Impairment of thyroid stimulating hormone suppression / Thyroid dysfunction

Hypothyroidism has been reported in patients treated with lenvatinib (see section 4.8, Description of selected adverse reactions). Thyroid function should be monitored before initiation of, and periodically throughout, treatment with lenvatinib. Hypothyroidism should be treated according to standard medical practice to maintain euthyroid state.

Lenvatinib impairs exogenous thyroid suppression (see section 4.8, Description of selected adverse reactions). Thyroid stimulating hormone (TSH) levels should be monitored on a regular basis and thyroid hormone administration should be adjusted to reach appropriate TSH levels, according to the patient's therapeutic target.

Diarrhoea

Diarrhoea has been reported frequently in patients treated with lenvatinib, usually occurring early in the course of treatment (see section 4.8, Description of selected adverse reactions). Prompt medical management of diarrhoea should be instituted in order to prevent dehydration. Lenvatinib should be discontinued in the event of persistence of Grade 4 diarrhoea despite medical management.

Wound Healing Complications

No formal studies of the effect of lenvatinib on wound healing have been conducted. Impaired wound healing has been reported in patients receiving lenvatinib. Temporary interruption of lenvatinib should be considered in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of lenvatinib following a major surgical procedure. Therefore, the decision to resume lenvatinib following a major surgical procedure should be based on clinical judgment of adequate wound healing.

Osteonecrosis of the jaw (ONJ)

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

Invasive dental procedures are an identified risk factor. Prior to treatment with lenvatinib, a dental examination and appropriate preventive dentistry should be considered. In patients who have previously received or are receiving intravenous bisphosphonates, invasive dental procedures should be avoided if possible (see section 4.8).

Special populations

Limited data are available for patients of ethnic origin other than Caucasian or Asian, and in patients aged ≥75 years. Lenvatinib should be used with caution in such patients, given the reduced tolerability of lenvatinib in Asian and elderly patients (see section 4.8, Other special populations).

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

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on lenvatinib

Chemotherapeutic agents

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

Effect of lenvatinib on other medicinal products

CYP3A4 substrates

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

Oral contraceptives

It is currently unknown whether lenvatinib may reduce the effectiveness of hormonal contraceptives, and therefore women using oral hormonal contraceptives should add a barrier method (see section 4.6).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in females

Women of childbearing potential should avoid becoming pregnant and use highly effective contraception while on treatment with lenvatinib and for at least one month after finishing treatment. It is currently unknown whether lenvatinib may reduce the effectiveness of hormonal contraceptives, and therefore women using oral hormonal contraceptives should add a barrier method.

Pregnancy

There are no data on the use of lenvatinib in pregnant women. Lenvatinib was embryotoxic and teratogenic when administered to rats and rabbits (see section 5.3).

Lenvatinib should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus.

Breast-feeding

It is not known whether lenvatinib is excreted in human milk. Lenvatinib and its metabolites are excreted in rat milk (see section 5.3).

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

Fertility

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

4.7 Effects on ability to drive and use machines

Lenvatinib has a minor influence on the ability to drive and use machines, due to undesirable effects such as fatigue and dizziness. Patients who experience these symptoms should use caution when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

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

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

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

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

Tabulated list of adverse reactions for RCC and DTC studies

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

Adverse reactions observed in clinical trials and reported from post-marketing use of lenvatinib are listed in Table 4.

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 treated with lenvatinib

System Organ Class (MedDRA terminology*)	Very Common	Common	Uncommon	Not known
Infections and infestation	Urinary tract infection		Perineal abscess	
Blood and lymphatic disorders	Thrombocytopenia[a]	Lymphopenia[a]	Splenic infarction	
Endocrine disorders	Hypothyroidism** Blood thyroid stimulating hormone increased‡**			
Metabolism and nutrition disorders	Hypocalcaemia‡ Hypercholesterolaemia[b]** Hypokalaemia Decreased appetite Weight decreased	Dehydration Hypomagnesaemia[b]		
Psychiatric disorders	Insomnia			
Nervous system disorders	Dizziness Headache Dysgeusia	Cerebrovascular accident	Posterior reversible encephalopathy syndrome Monoparesis Transient ischaemic attack	
Cardiac disorders		Myocardial infarction[c,†] Cardiac failure Electrocardiogram QT prolonged Ejection fraction decreased		
Vascular disorders	Haemorrhage[d, †,‡] Hypertension[e,‡]			Aneurysms and artery dissections

	Hypotension			
Respiratory, thoracic and mediastinal disorders	Dysphonia	Pulmonary embolism[†,]	Pneumothorax	
Gastrointestinal disorders	Diarrhoea[‡**] Gastrointestinal and abdominal pains[f] Vomiting Nausea Oral inflammation[g] Oral pain[h] Constipation Dyspepsia Dry mouth	Anal fistula Flatulence Lipase increased Amylase increased	Pancreatitis	
Hepatobiliary disorders		Aspartate aminotransferase increased[‡] Hypoalbuminaemia[‡] Alanine aminotransferase increased[‡] Blood alkaline phosphatase increased Hepatic function abnormal Gamma-glutamyltransferase increased[k] Blood bilirubin increased[‡] Cholecystitis	Hepatocellular damage/hepatitis[i]	
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome Palmar erythema Rash Alopecia	Hyperkeratosis		
Musculoskeletal and connective tissue disorders	Back pain Arthralgia Myalgia Pain in extremity Musculoskeletal pain		Osteonecrosis of the jaw	
Renal and urinary disorders	Proteinuria[‡]	Renal failure [j, †, ‡] Renal impairment[‡] Blood creatinine increased Blood urea increased	Nephrotic syndrome	
General disorders and administration site conditions	Fatigue Asthenia	Malaise	Impaired healing***	Non-gastrointestinal fistula[k]

	Oedema peripheral			

*: Medical Dictionary for Regulatory Activities (MedDRA) version 17.1. Preferred terms have been reassigned to the SOC most relevant to the target organ.

**: These adverse reactions occur more frequently with combination therapy compared to lenvatinib monotherapy.

***: Identified from post-marketing use of lenvatinib

†: Includes cases with a fatal outcome.

‡: See section 4.8 Description of selected adverse reactions for further characterisation.

The following terms have been combined:

a: Thrombocytopenia includes thrombocytopenia and decreased platelet count. Lymphopenia includes lymphopenia and decreased lymphocyte count.

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

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

d: Haemorrhage includes: epistaxis, haemoptysis, haematuria, contusion, haematochezia, gingival bleeding, petechiae, pulmonary haemorrhage, rectal haemorrhage, blood urine present, haematoma, vaginal haemorrhage, conjunctival haemorrhage, haemorrhoidal haemorrhage, intracranial tumour haemorrhage, laryngeal haemorrhage, ecchymosis, increased tendency to bruise, post procedural haemorrhage, purpura, skin haemorrhage, aneurysm ruptured, arterial haemorrhage, eye haemorrhage, gastric haemorrhage, gastroduodenitis haemorrhagic, gastrointestinal haemorrhage, haematemesis, haemorrhage, haemorrhagic stroke, melaena, metrorrhagia, nail bed bleeding, haemothorax, postmenopausal haemorrhage, proctitis haemorrhagic, renal haematoma, splenic haemorrhage, splinter haemorrhages, subarachnoid haemorrhage, tracheal haemorrhage, tumour haemorrhage.

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

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

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

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

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

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

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

Description of selected adverse reactions

Hypertension (see section 4.4)

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

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

Proteinuria (see section 4.4)

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

In the DTC study (see Lenvima SmPC), proteinuria was reported in 33.7% of lenvatinib-treated patients and 3.1% of patients in the placebo-treated group. The median time to onset was 6.7 weeks. Grade 3 reactions occurred in 10.7% of lenvatinib-treated patients and none in placebo-treated patients. The majority of cases had an outcome of

recovered or resolved following dose interruption or reduction, which occurred in 16.9% and 10.7% of patients, respectively. Proteinuria led to permanent treatment discontinuation in 0.8% of patients.

Renal failure and impairment (see section 4.4)

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

In the DTC study (see Lenvima SmPC), 5.0% of patients developed renal failure and 1.9% developed renal impairment, (3.1% of patients had a Grade ≥ 3 event of renal failure or impairment). In the placebo group 0.8% of patients developed renal failure or impairment (0.8% were Grade ≥ 3).

Cardiac dysfunction (see section 4.4)

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

In the DTC study (see Lenvima SmPC), decreased ejection fraction/cardiac failure was reported in 6.5% of patients (1.5% were Grade ≥ 3) in the lenvatinib treated group, and 2.3% in the placebo group (none were Grade ≥ 3).

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

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

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

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

Hepatotoxicity (see section 4.4)

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

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

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

Arterial thromboembolisms (see section 4.4)

In the RCC study (see section 5.1), 1.6% of patients in the lenvatinib plus everolimus-treated group reported arterial thromboembolic events. The time to onset was 69.6 weeks. In the everolimus group, 6.0% of patients reported an arterial thromboembolism (4.0% were Grade ≥ 3). In the DTC study (see Lenvima SmPC), arterial thromboembolic events were reported in 5.4% of lenvatinib-treated patients and 2.3% of patients in the placebo group.

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

Haemorrhage (see section 4.4)

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

one case of fatal cerebral haemorrhage in the lenvatinib plus everolimus-treated group and one case of fatal intracranial haemorrhage in the lenvatinib-treated group.

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

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

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

Hypocalcaemia (see section 4.4, QT interval prolongation)

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

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

Gastrointestinal perforation and fistula formation (see section 4.4)

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

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

Non-Gastrointestinal fistulae (see section 4.4)

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

QT interval prolongation (see section 4.4)

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

In the DTC study (see Lenvima SmPC), QT/QTc interval prolongation was reported in 8.8% of lenvatinib-treated patients and 1.5% of patients in the placebo group. The incidence of QT interval prolongation of greater than 500 ms was 2% in the lenvatinib-treated patients compared to no reports in the placebo group.

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

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

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

Diarrhoea (see section 4.4)

In the RCC study (see section 5.1), diarrhoea was reported in 80.6% of patients in the lenvatinib plus everolimus-treated group (21.0% were Grade ≥ 3) and in 34.0% of patients in the everolimus-treated group (2.0% were Grade ≥

3). The median time to onset was 4.1 weeks (any grade) and 8.1 weeks (Grade ≥ 3) in the lenvatinib plus everolimus-treated group. Diarrhoea was the most frequent cause of dose interruption/reduction and recurred despite dose reduction. Diarrhoea resulted in discontinuation in one patient.

In the DTC study (see Lenvima SmPC), diarrhoea was reported in 67.4% of patients in the lenvatinib-treated group (9.2% were Grade ≥ 3) and in 16.8% of patients in the placebo group (none were Grade ≥ 3).

Paediatric population

See section 4.2 for information on paediatric use.

Other special populations

Elderly

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

Gender

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

Ethnic origin

There are limited data on Asian patients with RCC. However, in DTC Asian patients had a higher incidence than Caucasian patients of peripheral oedema, hypertension, fatigue, PPE, proteinuria, stomatitis, thrombocytopenia, and myalgia; while Caucasian patients had a higher incidence of diarrhoea, weight decreased, nausea, vomiting, constipation, asthenia, abdominal pain, pain in extremity, and dry mouth.

Baseline hypertension

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

Baseline diabetes

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

Hepatic impairment

There are limited data on patients with hepatic impairment in RCC. However in DTC, patients with baseline hepatic impairment had a higher incidence of hypertension and PPE, and a higher incidence of Grade 3 or 4 hypertension, asthenia, fatigue, and hypocalcaemia compared with patients with normal hepatic function.

Renal impairment

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

Patients with body weight <60 kg

There are limited data on patients with body weight <60 kg in RCC. However in DTC patients with low body weight (<60 kg) had a higher incidence of PPE, proteinuria, of Grade 3 or 4 hypocalcaemia and hyponatraemia, and a trend towards a higher incidence of Grade 3 or 4 decreased appetite.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme: https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The highest doses of lenvatinib studied clinically were 32 mg and 40 mg per day. Accidental medication errors resulting in single doses of 40 to 48 mg have also occurred in clinical trials. The most frequently observed adverse drug reactions at these doses were hypertension, nausea, diarrhea, fatigue, stomatitis, proteinuria, headache, and aggravation of PPE. There have also been reports of overdose with lenvatinib involving single administrations of 6 to 10 times the recommended daily dose. These cases were associated with adverse reactions consistent with the known safety profile of lenvatinib (i.e., renal and cardiac failure), or were without adverse reactions.

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

Mechanism of action

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFRα, KIT, and RET. The combination of lenvatinib and everolimus showed increased antiangiogenic and antitumour activity as demonstrated by decreased human endothelial cell proliferation, tube formation, and VEGF signalling in vitro and tumour volume in mouse xenograft models of human renal cell cancer greater than each drug alone.

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

The mechanism of action for hypothyroidism is not fully elucidated.

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

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

Clinical efficacy and safety

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

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

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

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

The lenvatinib plus everolimus arm showed a statistically significant and clinically meaningful improvement in PFS compared with the everolimus arm (see Table 5 and Figure 1). Based on the results of a post-hoc exploratory analysis in a limited number of patients per subgroup, the positive effect on PFS was seen regardless of which prior VEGF-targeted therapy was used: sunitinib (Hazard ratio [HR] = 0.356 [95% CI: 0.188, 0.674] or other therapies (HR = 0.350 [95% CI: 0.148, 0.828]). The lenvatinib arm also showed an improvement in PFS compared with the

everolimus arm. Overall survival was longer in the lenvatinib plus everolimus arm (see Table 5 and Figure 2). The study was not powered for the OS analysis.

The treatment effect of the combination on PFS and ORR was also supported by a post-hoc retrospective independent blinded review of scans. The lenvatinib plus everolimus arm showed a statistically significant and clinically meaningful improvement in PFS compared with the everolimus arm. Results for ORR were consistent with that of the investigators' assessments, 35.3% in the lenvatinib plus everolimus arm, with one complete response and 17 partial responses; no subject had an objective response in the everolimus arm (P < 0.0001) in favour of the lenvatinib plus everolimus arm.

Table 5 Efficacy results in renal cell carcinoma

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

Tumour assessment was based on RECIST 1.1 criteria. Data cut-off date = 13 Jun 2014

Percentages are based on the total number of subjects in the Full Analysis Set within relevant treatment group.

CI = confidence interval, NE = not estimable

[a]Point estimates are based on Kaplan-Meier method and 95% CIs are based on the Greenwood formula using log-log transformation.

[b]Stratified hazard ratio is based on a stratified Cox regression model including treatment as a covariate factor and haemoglobin and corrected serum calcium as strata. The Efron method was used for correction for tied events.

[c]Data cut-off date = 31 Jul 2015

Figure 1: Kaplan-Meier Plot of Progression-Free Survival

(Investigator Assessment)

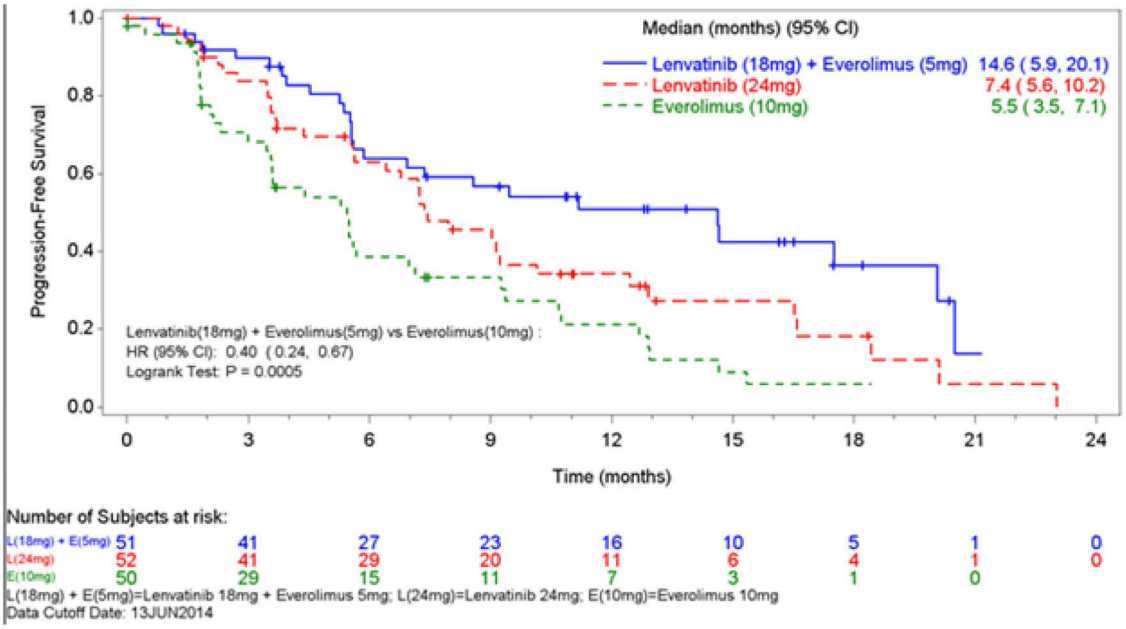
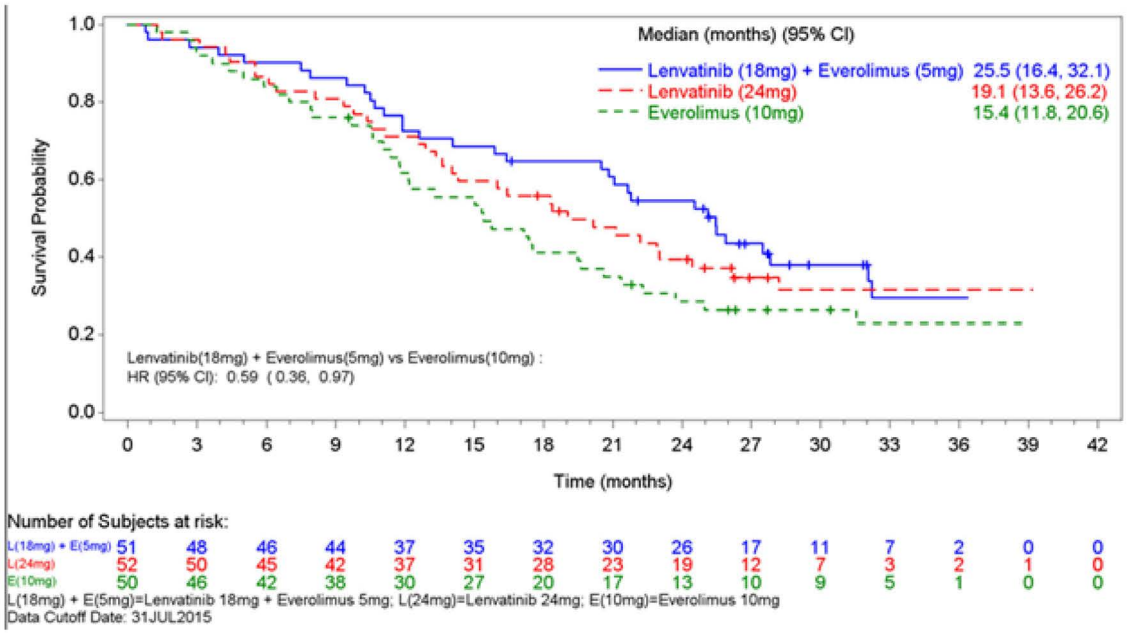


Figure 2: Kaplan-Meier Plot of Overall Survival



Paediatric population

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

5.2 Pharmacokinetic properties

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

Absorption

Lenvatinib is rapidly absorbed after oral administration with t_{max} typically observed from 1 to 4 hours postdose. Food does not affect the extent of absorption, but slows the rate of absorption. When administered with food to healthy subjects, peak plasma concentrations are delayed by 2 hours. Absolute bioavailability has not been determined in humans; however, data from a mass-balance study suggests that it is in the order of 85%.

Distribution

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

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

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

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

Biotransformation

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

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

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

Data from a human mass balance/excretion study indicate lenvatinib is extensively metabolised in humans. The main metabolic pathways in humans were identified as oxidation by aldehyde oxidase, demethylation via CYP3A4, glutathione conjugation with elimination of the O-aryl group (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

Please see distribution section.

Elimination

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

Following administration of radiolabelled lenvatinib to 6 patients with solid tumours, approximately two-thirds and one-fourth of the radiolabel were eliminated in the faeces and urine, respectively. The M3 metabolite was the predominant analyte in excreta (~17% of the dose), followed by M2' (~11% of the dose) and M2 (~4.4 of the dose).

Linearity/non-linearity

Dose proportionality and accumulation

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

Lenvatinib displays minimimal accumulation at steady state. Over this range, the median accumulation index (Rac) ranged from 0.96 (20 mg) to 1.54 (6.4 mg).

Special populations

Hepatic impairment

The pharmacokinetics of lenvatinib following a single 10-mg dose were evaluated in 6 subjects each with mild and moderate hepatic impairment (Child-Pugh A and Child-Pugh B, respectively). A 5-mg dose was evaluated in 6 subjects with severe hepatic impairment (Child-Pugh C). Eight healthy, demographically matched subjects served as controls and received a 10-mg dose. The median half-life was comparable in subjects with mild, moderate, and severe hepatic impairment as well as those with normal hepatic function and ranged from 26 hours to 31 hours. The percentage of the dose of lenvatinib excreted in urine was low in all cohorts (<2.16% across treatment cohorts).

Lenvatinib exposure, based on dose-adjusted AUC0-t and AUC0-inf data, was 119%, 107%, and 180% of normal for subjects with mild, moderate, and severe hepatic impairment, respectively. It has been determined that plasma

protein binding in plasma from hepatically impaired subjects was similar to the respective matched healthy subjects and no concentration dependency was observed. See section 4.2 for dosing recommendation.

Renal impairment

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

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

4 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, 60, or 90hard capsules.Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

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

7. Marketing authorisation holder

Eisai GmbH

Edmund-Rumpler-Straße 3

60549 Frankfurt am Main

Germany

E-mail: medinfo_de@eisai.net

8. Marketing authorisation number(s)

Kisplyx 4 mg hard capsules

EU/1/16/1128/001

EU/1/16/1128/003

EU/1/16/1128/004

Kisplyx 10 mg hard capsules

EU/1/16/1128/002

EU/1/16/1128/005

EU/1/16/1128/006

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 25 August 2016

10. Date of revision of the text

12/2020

KISP 0020/2020

Company Contact Details

Eisai Ltd

Address

European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN

Telephone

+44 (0)845 676 1400

Out of Hours Telephone

+44 (0)208 600 1400

WWW

http://www.eisai.eu

Medical Information e-mail

EUMedInfo@eisai.net

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LENVIMA safely and effectively. See full prescribing information for LENVIMA.

LENVIMA® (lenvatinib) capsules, for oral use
Initial U.S. Approval: 2015

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.5)	11/2020
Warnings and Precautions (5.14)	2/2020
Warnings and Precautions (5.15)	12/2020

----------INDICATIONS AND USAGE----------

LENVIMA is a kinase inhibitor that is indicated:

- For the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC). (1.1)
- In combination with everolimus, for the treatment of patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy. (1.2)
- For the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC). (1.3)
- In combination with pembrolizumab, for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial. (1.4)

----------DOSAGE AND ADMINISTRATION----------

- DTC: The recommended dosage is 24 mg orally once daily. (2.2)
- RCC: The recommended dosage is 18 mg orally once daily with everolimus 5 mg orally once daily. (2.3)
- HCC: The recommended dosage is based on actual body weight:
  - 12 mg orally once daily for patients greater than or equal to 60 kg
  - 8 mg orally once daily for patients less than 60 kg. (2.4)
- Endometrial Carcinoma: The recommended dosage is 20 mg orally once daily in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks. (2.5)
- Modify the recommended daily dose for certain patients with renal or hepatic impairment. (2.7, 2.8)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 4 mg and 10 mg. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypertension: Control blood pressure prior to treatment and monitor during treatment. Withhold for Grade 3 hypertension despite optimal antihypertensive therapy. Discontinue for Grade 4 hypertension. (2.6, 5.1)
- Cardiac Dysfunction: Monitor for clinical symptoms or signs of cardiac dysfunction. Withhold or discontinue for Grade 3 cardiac dysfunction. Discontinue for Grade 4 cardiac dysfunction. (2.6, 5.2)
- Arterial Thromboembolic Events: Discontinue following an arterial thromboembolic event. (2.6, 5.3)
- Hepatotoxicity: Monitor liver function prior to treatment and periodically during treatment. Withhold or discontinue for Grade 3 or 4 hepatotoxicity. Discontinue for hepatic failure. (2.6, 5.4)
- Renal Failure or Impairment: Withhold or discontinue for Grade 3 or 4 renal failure or impairment. (2.6, 5.5)
- Proteinuria: Monitor for proteinuria prior to treatment and periodically during treatment. Withhold for 2 or more grams of proteinuria per 24 hours. Discontinue for nephrotic syndrome. (2.6, 5.6)
- Diarrhea: May be severe and recurrent. Promptly initiate management for severe diarrhea. Withhold or discontinue based on severity. (2.6, 5.7)
- Fistula Formation and Gastrointestinal Perforation: Discontinue in patients who develop Grade 3 or 4 fistula or any Grade gastrointestinal perforation. (2.6, 5.8)
- QT Interval Prolongation: Monitor and correct electrolyte abnormalities. Withhold for QT interval greater than 500 ms or for 60 ms or greater increase in baseline QT interval. (2.6, 5.9)
- Hypocalcemia: Monitor blood calcium levels at least monthly and replace calcium as necessary. Withhold or discontinue based on severity. (2.6, 5.10)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Withhold for RPLS until fully resolved or discontinue. (2.6, 5.11)
- Hemorrhagic Events: Withhold or discontinue based on severity. (2.6, 5.12)
- Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction: Monitor thyroid function prior to treatment and monthly during treatment. (5.13)
- Impaired Wound Healing: Withhold LENVIMA for at least 1 week before elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of LENVIMA after resolution of wound healing complications has not been established. (5.14)
- Osteonecrosis of the Jaw: Consider preventive dentistry prior to treatment with LENVIMA. Avoid invasive dental procedures, if possible, particularly in patients at higher risk. (5.15)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.16, 8.1, 8.3)

----------ADVERSE REACTIONS----------

- In DTC, the most common adverse reactions (incidence ≥30%) for LENVIMA are hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, decreased weight, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, and dysphonia. (6.1)
- In RCC, the most common adverse reactions (incidence ≥30%) for LENVIMA and everolimus are diarrhea, fatigue, arthralgia/myalgia, decreased appetite, vomiting, nausea, stomatitis/oral inflammation, hypertension, peripheral edema, cough, abdominal pain, dyspnea, rash, decreased weight, hemorrhagic events, and proteinuria. (6.1)
- In HCC, the most common adverse reactions (incidence ≥20%) for LENVIMA are hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic events, hypothyroidism, and nausea. (6.1)
- In Endometrial Carcinoma, the most common adverse reactions (incidence ≥20%) for LENVIMA and pembrolizumab are fatigue, hypertension, musculoskeletal pain, diarrhea, decreased appetite, hypothyroidism, nausea, stomatitis, vomiting, decreased weight, abdominal pain, headache, constipation, urinary tract infection, dysphonia, hemorrhagic events, hypomagnesemia, palmar-plantar erythrodysesthesia, dyspnea, cough, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-877-873-4724 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
- 1.1 Differentiated Thyroid Cancer
- 1.2 Renal Cell Carcinoma
- 1.3 Hepatocellular Carcinoma
- 1.4 Endometrial Carcinoma

2 DOSAGE AND ADMINISTRATION
- 2.1 Important Dosage Information
- 2.2 Recommended Dosage for Differentiated Thyroid Cancer (DTC)
- 2.3 Recommended Dosage for Renal Cell Carcinoma (RCC)
- 2.4 Recommended Dosage for Hepatocellular Carcinoma (HCC)
- 2.5 Recommended Dosage for Endometrial Carcinoma
- 2.6 Dosage Modifications for Adverse Reactions
- 2.7 Dosage Modifications for Severe Renal Impairment
- 2.8 Dosage Modifications for Severe Hepatic Impairment
- 2.9 Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Hypertension
- 5.2 Cardiac Dysfunction
- 5.3 Arterial Thromboembolic Events
- 5.4 Hepatotoxicity
- 5.5 Renal Failure or Impairment
- 5.6 Proteinuria
- 5.7 Diarrhea
- 5.8 Fistula Formation and Gastrointestinal Perforation
- 5.9 QT Interval Prolongation
- 5.10 Hypocalcemia
- 5.11 Reversible Posterior Leukoencephalopathy Syndrome
- 5.12 Hemorrhagic Events
- 5.13 Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction
- 5.14 Impaired Wound Healing
- 5.15 Osteonecrosis of the Jaw (ONJ)
- 5.16 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS
- 7.1 Drugs That Prolong the QT Interval

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
- 14.1 Differentiated Thyroid Cancer
- 14.2 Renal Cell Carcinoma
- 14.3 Hepatocellular Carcinoma
- 14.4 Endometrial Carcinoma (EC)

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Differentiated Thyroid Cancer

LENVIMA is indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC).

1.2 Renal Cell Carcinoma

LENVIMA is indicated in combination with everolimus for the treatment of patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy.

1.3 Hepatocellular Carcinoma

LENVIMA is indicated for the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC).

1.4 Endometrial Carcinoma

LENVIMA, in combination with pembrolizumab, is indicated for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.4)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage Information

- Reduce the dose for certain patients with renal or hepatic impairment *[see Dosage and Administration (2.7, 2.8)]*.
- Take LENVIMA once daily, with or without food, at the same time each day *[see Clinical Pharmacology (12.3)]*. If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration.

2.2 Recommended Dosage for Differentiated Thyroid Cancer (DTC)

The recommended dosage of LENVIMA is 24 mg orally once daily until disease progression or until unacceptable toxicity.

2.3 Recommended Dosage for Renal Cell Carcinoma (RCC)

The recommended dosage of LENVIMA is 18 mg in combination with 5 mg everolimus orally once daily until disease progression or until unacceptable toxicity.

Refer to everolimus prescribing information for recommended everolimus dosing information.

2.4 Recommended Dosage for Hepatocellular Carcinoma (HCC)

The recommended dosage of LENVIMA is based on actual body weight:

- 12 mg for patients greater than or equal to 60 kg or
- 8 mg for patients less than 60 kg.

Take LENVIMA orally once daily until disease progression or until unacceptable toxicity.

2.5 Recommended Dosage for Endometrial Carcinoma

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

Refer to the pembrolizumab prescribing information for other pembrolizumab dosing information.

2.6 Dosage Modifications for Adverse Reactions

Recommendations for LENVIMA dose interruption, reduction and discontinuation for adverse reactions are listed in Table 1. Table 2 lists the recommended dosage reductions of LENVIMA for adverse reactions.

Table 1. Recommended Dosage Modifications for LENVIMA for Adverse Reactions

Adverse Reaction	Severity [a]	Dosage Modifications for LENVIMA
Hypertension *[see Warnings and Precautions (5.1)]*	Grade 3	• Withhold for Grade 3 that persists despite optimal antihypertensive therapy. • Resume at reduced dose when hypertension is controlled at less than or equal to Grade 2.
	Grade 4	• Permanently discontinue.
Cardiac Dysfunction *[see Warnings and Precautions (5.2)]*	Grade 3	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at a reduced dose or discontinue depending on the severity and persistence of adverse reaction.
	Grade 4	• Permanently discontinue.
Arterial Thromboembolic Event *[see Warnings and Precautions (5.3)]*	Any Grade	• Permanently discontinue.
Hepatotoxicity *[see Warnings and Precautions (5.4)]*	Grade 3 or 4	• Withhold until improves to Grade 0 to 1 or baseline. • Either resume at a reduced dose or discontinue depending on severity and persistence of hepatotoxicity. • Permanently discontinue for hepatic failure.
Renal Failure or Impairment *[see Warnings and Precautions (5.5)]*	Grade 3 or 4	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at a reduced dose or discontinue depending on severity and persistence of renal impairment.

Table 1. Recommended Dosage Modifications for LENVIMA for Adverse Reactions		
Adverse Reaction	**Severity** [a]	**Dosage Modifications for LENVIMA**
Proteinuria *[see Warnings and Precautions (5.6)]*	2 g or greater proteinuria in 24 hours	• Withhold until less than or equal to 2 grams of proteinuria per 24 hours. • Resume at a reduced dose. • Permanently discontinue for nephrotic syndrome.
Gastrointestinal Perforation *[see Warnings and Precautions (5.8)]*	Any Grade	• Permanently discontinue.
Fistula Formation *[see Warnings and Precautions (5.8)]*	Grade 3 or 4	• Permanently discontinue.
QT Prolongation *[see Warnings and Precautions (5.9)]*	Greater than 500 ms or greater than 60 ms increase from baseline	• Withhold until improves to less than or equal to 480 ms or baseline. • Resume at a reduced dose.
Reversible Posterior Leukoencephalopathy Syndrome *[see Warnings and Precautions (5.11)]*	Any Grade	• Withhold until fully resolved. • Resume at a reduced dose or discontinue depending on severity and persistence of neurologic symptoms.
Other Adverse Reactions *[see Warnings and Precautions (5.7, 5.10, 5.12)]*	Persistent or intolerable Grade 2 or 3 adverse reaction Grade 4 laboratory abnormality	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at reduced dose.
	Grade 4 adverse reaction	• Permanently discontinue.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Table 2: Recommended Dosage Reductions of LENVIMA for Adverse Reactions			
Indication	**First Dosage Reduction To**	**Second Dosage Reduction To**	**Third Dosage Reduction To**
DTC	20 mg once daily	14 mg once daily	10 mg once daily
RCC	14 mg once daily	10 mg once daily	8 mg once daily
Endometrial Carcinoma	14 mg once daily	10 mg once daily	8 mg once daily
HCC			
• Actual weight 60 kg or greater	8 mg once daily	4 mg once daily	4 mg every other day
• Actual weight less than 60 kg	4 mg once daily	4 mg every other day	Discontinue

When administering LENVIMA in combination with everolimus for the treatment of renal cell carcinoma, reduce the LENVIMA dose first and then the everolimus dose for adverse reactions of both LENVIMA and everolimus. Refer to the everolimus prescribing information for additional dose modification information.

When administering LENVIMA in combination with pembrolizumab for the treatment of endometrial carcinoma, interrupt one or both drugs or dose reduce LENVIMA as appropriate. No dose reductions are recommended for pembrolizumab. Withhold or discontinue pembrolizumab in accordance with the instructions in the pembrolizumab prescribing information.

2.7 Dosage Modifications for Severe Renal Impairment

The recommended dosage of LENVIMA for patients with DTC, RCC, or endometrial carcinoma and severe renal impairment (creatinine clearance less than 30 mL/min calculated by Cockcroft-Gault equation using actual body weight) is *[see Warnings and Precautions (5.5), Use in Specific Populations (8.6)]*:

- Differentiated thyroid cancer: 14 mg orally once daily
- Renal cell carcinoma: 10 mg orally once daily
- Endometrial carcinoma: 10 mg orally once daily

2.8 Dosage Modifications for Severe Hepatic Impairment

The recommended dosage of LENVIMA for patients with DTC, RCC, or endometrial carcinoma and severe hepatic impairment (Child-Pugh C) is *[see Warnings and Precautions (5.4), Use in Specific Populations (8.7)]*:

- Differentiated thyroid cancer: 14 mg taken orally once daily
- Renal cell carcinoma: 10 mg taken orally once daily
- Endometrial carcinoma: 10 mg orally once daily

2.9 Preparation and Administration

LENVIMA capsules can be swallowed whole or dissolved in a small glass of liquid. To dissolve in liquid, put capsules into 1 tablespoon of water or apple juice without breaking or crushing the capsules. Leave the capsules in the water or apple juice for at least 10 minutes. Stir for at least 3 minutes. After drinking the mixture, add 1 tablespoon of water or apple juice to the glass, swirl the contents a few times and swallow the water or apple juice.

3 DOSAGE FORMS AND STRENGTHS

Capsules:

- 4 mg: yellowish-red body and yellowish-red cap, marked in black ink with "Є" on cap and "LENV 4 mg" on body.
- 10 mg: yellow body and yellowish-red cap, marked in black ink with "Є" on cap and "LENV 10 mg" on body.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension

Hypertension occurred in 73% of patients in SELECT (DTC) receiving LENVIMA 24 mg orally once daily and in 45% of patients in REFLECT (HCC) receiving LENVIMA 8 mg or 12 mg orally once daily. The median time to onset of new or worsening hypertension was 16 days in SELECT and 26 days in REFLECT. Grade 3 hypertension occurred in 44% of patients in SELECT and in 24% in REFLECT. Grade 4 hypertension occurred <1% in SELECT and Grade 4 hypertension was not reported in REFLECT.

In patients receiving LENVIMA 18 mg orally once daily with everolimus in Study 205 (RCC), hypertension was reported in 42% of patients and the median time to onset of new or worsening hypertension was 35 days. Grade 3 hypertension occurred in 13% of patients. Systolic blood pressure ≥160 mmHg occurred in 29% of patients and diastolic blood pressure ≥100 mmHg occurred in 21% *[see Adverse Reactions (6.1)]*.

Serious complications of poorly controlled hypertension have been reported.

Control blood pressure prior to initiating LENVIMA. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at a reduced dose when hypertension is controlled or permanently discontinue LENVIMA based on severity *[see Dosage and Administration (2.6)]*.

5.2 Cardiac Dysfunction

Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, RCC or HCC, Grade 3 or higher cardiac dysfunction (including cardiomyopathy, left or right ventricular dysfunction, congestive heart failure, cardiac failure, ventricular hypokinesia, or decrease in left or right ventricular ejection fraction of more than 20% from baseline) occurred in 3% of LENVIMA-treated patients.

Monitor patients for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity *[see Dosage and Administration (2.6)]*.

5.3 Arterial Thromboembolic Events

Among patients receiving LENVIMA or LENVIMA with everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in Study 205 (RCC), 2% of patients in REFLECT (HCC) and 5% of patients in SELECT (DTC). Grade 3 to 5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials *[see Adverse Reactions (6.1)]*.

Permanently discontinue LENVIMA following an arterial thrombotic event *[see Dosage and Administration (2.6)]*. The safety of resuming LENVIMA after an arterial thromboembolic event has not been established and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

5.4 Hepatotoxicity

Across clinical studies enrolling 1327 LENVIMA-treated patients with malignancies other than HCC, serious hepatic adverse reactions occurred in 1.4% of patients. Fatal events, including hepatic failure, acute hepatitis and hepatorenal syndrome, occurred in 0.5% of patients.

In REFLECT (HCC), hepatic encephalopathy (including hepatic encephalopathy, encephalopathy, metabolic encephalopathy, and hepatic coma) occurred in 8% of LENVIMA-treated patients and 3% of sorafenib-treated patients. Grade 3 to 5 hepatic encephalopathy occurred in 5% of LENVIMA-treated patients and 2% of sorafenib-treated patients. Grade 3 to 5 hepatic failure occurred in 3% of LENVIMA-treated patients and 3% of sorafenib-treated patients. Two percent of patients discontinued LENVIMA and 0.2% discontinued sorafenib due to hepatic encephalopathy and 1% of patients discontinued lenvatinib or sorafenib due to hepatic failure *[see Adverse Reactions (6.1)]*.

Monitor liver function prior to initiating LENVIMA, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Monitor patients with HCC closely for signs of hepatic failure, including hepatic encephalopathy. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity *[see Dosage and Administration (2.6)]*.

5.5 Renal Failure or Impairment

Serious including fatal renal failure or impairment can occur with LENVIMA. Renal impairment occurred in 14% of patients receiving LENVIMA in SELECT (DTC) and in 7% of patients receiving LENVIMA in REFLECT (HCC). Grade 3 to 5 renal failure or impairment occurred in 3% (DTC) and 2% (HCC) of patients, including 1 fatality in each study.

In Study 205 (RCC), renal impairment or renal failure occurred in 18% of patients receiving LENVIMA with everolimus, including Grade 3 in 10% of patients *[see Adverse Reactions (6.1)]*.

Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA for renal failure or impairment based on severity *[see Dosage and Administration (2.6)]*.

5.6 Proteinuria

Proteinuria occurred in 34% of LENVIMA-treated patients in SELECT (DTC) and in 26% of LENVIMA-treated patients in REFLECT (HCC). Grade 3 proteinuria occurred in 11% and 6% in SELECT and REFLECT, respectively. In Study 205 (RCC), proteinuria occurred in

31% of patients receiving LENVIMA with everolimus and 14% of patients receiving everolimus. Grade 3 proteinuria occurred in 8% of patients receiving LENVIMA with everolimus compared to 2% of patients receiving everolimus *[see Adverse Reactions (6.1)]*.

Monitor for proteinuria prior to initiating LENVIMA and periodically during treatment. If urine dipstick proteinuria greater than or equal to 2+ is detected, obtain a 24-hour urine protein. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity *[see Dosage and Administration (2.6)]*.

5.7 Diarrhea

Of the 737 patients treated with LENVIMA in SELECT (DTC) and REFLECT (HCC), diarrhea occurred in 49% of patients, including Grade 3 in 6%.

In Study 205 (RCC), diarrhea occurred in 81% of patients receiving LENVIMA with everolimus, including Grade 3 in 19%. Diarrhea was the most frequent cause of dose interruption/reduction and diarrhea recurred despite dose reduction *[see Adverse Reactions (6.1)]*.

Promptly initiate management of diarrhea. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity *[see Dosage and Administration (2.6)]*.

5.8 Fistula Formation and Gastrointestinal Perforation

Of 799 patients treated with LENVIMA or LENVIMA with everolimus in SELECT (DTC), Study 205 (RCC) and REFLECT (HCC), fistula or gastrointestinal perforation occurred in 2%.

Permanently discontinue LENVIMA in patients who develop gastrointestinal perforation of any severity or Grade 3 or 4 fistula *[see Dosage and Administration (2.6)]*.

5.9 QT Interval Prolongation

In SELECT (DTC), QT/QTc interval prolongation occurred in 9% of LENVIMA-treated patients and QT interval prolongation of >500 ms occurred in 2%. In Study 205 (RCC), QTc interval increases of >60 ms occurred in 11% of patients receiving LENVIMA with everolimus and QTc interval >500 ms occurred in 6%. In REFLECT (HCC), QTc interval increases of >60 ms occurred in 8% of LENVIMA-treated patients and QTc interval >500 ms occurred in 2%.

Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Withhold and resume at reduced dose of LENVIMA upon recovery based on severity *[see Dosage and Administration (2.6)]*.

5.10 Hypocalcemia

In SELECT (DTC), Grade 3 to 4 hypocalcemia occurred in 9% of patients receiving LENVIMA. In 65% of cases, hypocalcemia improved or resolved following calcium supplementation, with or without dose interruption or dose reduction.

In Study 205 (RCC), Grade 3 to 4 hypocalcemia occurred in 6% of patients treated with LENVIMA with everolimus. In REFLECT (HCC), Grade 3 hypocalcemia occurred in 0.8% of LENVIMA-treated patients *[see Adverse Reactions (6.1)]*.

Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue LENVIMA depending on severity *[see Dosage and Administration (2.6)]*.

5.11 Reversible Posterior Leukoencephalopathy Syndrome

Across clinical studies of 1823 patients who received LENVIMA as a single agent *[see Adverse Reaction (6.1)]*, reversible posterior leukoencephalopathy syndrome (RPLS) occurred in 0.3%.

Confirm the diagnosis of RPLS with magnetic resonance imaging. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA depending on severity and persistence of neurologic symptoms *[see Dosage and Administration (2.6)]*.

5.12 Hemorrhagic Events

Serious including fatal hemorrhagic events can occur with LENVIMA. Across SELECT (DTC), Study 205 (RCC) and REFLECT (HCC), hemorrhagic events of any grade occurred in 29% of the 799 patients treated with LENVIMA as a single agent or in combination with everolimus. The most frequently reported hemorrhagic events (all grades and occurring in at least 5% of patients) were epistaxis and hematuria.

In SELECT, Grade 3 to 5 hemorrhage occurred in 2% of patients receiving LENVIMA, including 1 fatal intracranial hemorrhage among 16 patients who received LENVIMA and had CNS metastases at baseline. In Study 205, Grade 3 to 5 hemorrhage occurred in 8% of patients receiving LENVIMA with everolimus, including 1 fatal cerebral hemorrhage. In REFLECT, Grade 3 to 5 hemorrhage occurred in 5% of patients receiving LENVIMA, including 7 fatal hemorrhagic events *[see Adverse Reactions (6.1)]*.

Serious tumor related bleeds, including fatal hemorrhagic events, occurred in patients treated with LENVIMA in clinical trials and in the post-marketing setting. In post-marketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than in other tumor types. The safety and effectiveness of LENVIMA in patients with ATC have not been demonstrated in clinical trials.

Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (e.g. carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue LENVIMA based on the severity *[see Dosage and Administration (2.6)]*.

5.13 Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction

LENVIMA impairs exogenous thyroid suppression. In SELECT (DTC), 88% of all patients had a baseline thyroid stimulating hormone (TSH) level ≤0.5 mU/L. In those patients with a normal TSH at baseline, elevation of TSH level >0.5 mU/L was observed post baseline in 57% of LENVIMA-treated patients.

Grade 1 or 2 hypothyroidism occurred in 24% of patients receiving LENVIMA with everolimus in Study 205 (RCC) and in 21% of patients receiving LENVIMA in REFLECT (HCC). In those patients with a normal or low TSH at baseline, an elevation of TSH was observed post baseline in 70% of patients receiving LENVIMA in REFLECT and 60% of patients receiving LENVIMA with everolimus in Study 205 *[see Adverse Reactions (6.1)]*.

Monitor thyroid function prior to initiating LENVIMA and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

5.14 Impaired Wound Healing

Impaired wound healing has been reported in patients who received LENVIMA *[see Adverse Reactions (6.2)]*.

Withhold LENVIMA for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of LENVIMA after resolution of wound healing complications has not been established.

5.15 Osteonecrosis of the Jaw

Osteonecrosis of the Jaw (ONJ) has been reported in patients receiving LENVIMA *[see Adverse Reactions (6.1)]*. Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease or invasive dental procedures, may increase the risk of ONJ.

Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA treatment. Advise patients regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk. Withhold LENVIMA for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold LENVIMA if ONJ develops and restart based on clinical judgement of adequate resolution.

5.16 Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended clinical doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 30 days after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Hypertension *[see Warnings and Precautions (5.1)]*
- Cardiac Dysfunction *[see Warnings and Precautions (5.2)]*
- Arterial Thromboembolic Events *[see Warnings and Precautions (5.3)]*
- Hepatotoxicity *[see Warnings and Precautions (5.4)]*
- Renal Failure and Impairment *[see Warnings and Precautions (5.5)]*
- Proteinuria *[see Warnings and Precautions (5.6)]*
- Diarrhea *[see Warnings and Precautions (5.7)]*
- Fistula Formation and Gastrointestinal Perforation *[see Warnings and Precautions (5.8)]*

- QT Interval Prolongation *[see Warnings and Precautions (5.9)]*
- Hypocalcemia *[see Warnings and Precautions (5.10)]*
- Reversible Posterior Leukoencephalopathy Syndrome *[see Warnings and Precautions (5.11)]*
- Hemorrhagic Events *[see Warnings and Precautions (5.12)]*
- Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction *[see Warnings and Precautions (5.13)]*
- Impaired Wound Healing *[see Warnings and Precautions (5.14)]*
- Osteonecrosis of the Jaw (ONJ) *[see Warnings and Precautions (5.15)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the Warnings and Precautions reflect exposure to LENVIMA as a single agent in 261 patients with DTC (SELECT) and 476 patients with HCC (REFLECT), LENVIMA with pembrolizumab in 94 patients with endometrial carcinoma (Study 111), and LENVIMA with everolimus in 62 patients with RCC (Study 205). Safety data obtained in 1823 patients with advanced solid tumors who received LENVIMA as a single agent across multiple clinical studies was used to further characterize the risks of serious adverse reactions. Among the 1823 patients who received LENVIMA as a single agent, the median age was 61 years (20 to 89 years), the dose range was 0.2 mg to 32 mg daily, and the median duration of exposure was 5.6 months.

The data below reflect exposure to LENVIMA in 893 patients enrolled in randomized, active-controlled trials (REFLECT; Study 205), a randomized, placebo-controlled trial (SELECT) and a single arm trial (Study 111). The median duration of exposure to LENVIMA across these four studies ranged from 6 to 16 months. The demographic and exposure data for each clinical trial population are described in the subsections below.

Differentiated Thyroid Cancer

The safety of LENVIMA was evaluated in SELECT, in which patients with radioactive iodine-refractory differentiated thyroid cancer were randomized (2:1) to LENVIMA (n=261) or placebo (n=131) *[see Clinical Studies (14.1)]*. The median treatment duration was 16.1 months for LENVIMA. Among 261 patients who received LENVIMA, median age was 64 years, 52% were females, 80% were White, 18% were Asian, and 2% were Black; and 4% were Hispanic/Latino.

The most common adverse reactions observed in LENVIMA-treated patients (≥30%) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, decreased weight, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia (PPE) syndrome, abdominal pain, and dysphonia. The most common serious adverse reactions (at least 2%) were pneumonia (4%), hypertension (3%), and dehydration (3%).

Adverse reactions led to dose reductions in 68% of patients receiving LENVIMA; 18% of patients discontinued LENVIMA for adverse reactions. The most common adverse reactions

(at least 10%) resulting in dose reductions of LENVIMA were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions (at least 1%) resulting in discontinuation of LENVIMA were hypertension (1%) and asthenia (1%).

Table 3 presents adverse reactions occurring at a higher rate in LENVIMA-treated patients than patients receiving placebo in the double-blind phase of the study.

Table 3: Adverse Reactions Occurring in Patients with a Between-Group Difference of ≥5% in All Grades or ≥2% in Grades 3 and 4 in SELECT (DTC)

	LENVIMA 24 mg N=261		Placebo N=131	
Adverse Reaction	**All Grades (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Vascular				
Hypertension[a]	73	44	16	4
Hypotension	9	2	2	0
Gastrointestinal				
Diarrhea	67	9	17	0
Nausea	47	2	25	1
Stomatitis[b]	41	5	8	0
Vomiting	36	2	15	0
Abdominal pain[c]	31	2	11	1
Constipation	29	0.4	15	1
Oral pain[d]	25	1	2	0
Dry mouth	17	0.4	8	0
Dyspepsia	13	0.4	4	0
General				
Fatigue[e]	67	11	35	4
Edema peripheral	21	0.4	8	0
Musculoskeletal and Connective Tissue				
Arthralgia/Myalgia[f]	62	5	28	3
Metabolism and Nutrition				
Decreased appetite	54	7	18	1
Decreased weight	51	13	15	1
Dehydration	9	2	2	1
Nervous System				
Headache	38	3	11	1
Dysgeusia	18	0	3	0
Dizziness	15	0.4	9	0
Renal and Urinary				
Proteinuria	34	11	3	0
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	32	3	1	0
Rash[g]	21	0.4	3	0
Alopecia	12	0	5	0
Hyperkeratosis	7	0	2	0
Respiratory, Thoracic and Mediastinal				
Dysphonia	31	1	5	0
Cough	24	0	18	0
Epistaxis	12	0	1	0
Psychiatric				

Table 3: Adverse Reactions Occurring in Patients with a Between-Group Difference of ≥5% in All Grades or ≥2% in Grades 3 and 4 in SELECT (DTC)				
	LENVIMA 24 mg N=261		Placebo N=131	
Adverse Reaction	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Insomnia	12	0	3	0
Infections				
Urinary tract infection	11	1	5	0
Dental and oral infections[h]	10	1	1	0
Cardiac				
Electrocardiogram QT prolonged	9	2	2	0

a Includes hypertension, hypertensive crisis, increased blood pressure diastolic, and increased blood pressure
b Includes aphthous stomatitis, stomatitis, glossitis, mouth ulceration, and mucosal inflammation
c Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal pain
d Includes oral pain, glossodynia, and oropharyngeal pain
e Includes asthenia, fatigue, and malaise
f Includes musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia
g Includes macular rash, maculo-papular rash, generalized rash, and rash
h Includes gingivitis, oral infection, parotitis, pericoronitis, periodontitis, sialoadenitis, tooth abscess, and tooth infection

Clinically important adverse reactions occurring more frequently in LENVIMA-treated patients than patients receiving placebo, but with an incidence of <5% were pulmonary embolism (3%, including fatal reports vs 2%, respectively) and osteonecrosis of the jaw (0.4% vs 0%, respectively).

Laboratory abnormalities with a difference of ≥2% in Grade 3 – 4 events and at a higher incidence in the LENVIMA arm are presented in Table 4.

Table 4: Laboratory Abnormalities with a Difference of ≥2% in Grade 3 - 4 Events and at a Higher Incidence in the LENVIMA Arm[a, b] in SELECT (DTC)		
Laboratory Abnormality	LENVIMA 24 mg	Placebo
	Grades 3-4 (%)	Grades 3-4 (%)
Chemistry		
Hypocalcemia	9	2
Hypokalemia	6	1
Increased aspartate aminotransferase (AST)	5	0
Increased alanine aminotransferase (ALT)	4	0
Increased lipase	4	1
Increased creatinine	3	0
Hematology		
Thrombocytopenia	2	0

a With at least 1 grade increase from baseline
b Laboratory Abnormality percentage is based on the number of patients who had both baseline and at least one post baseline laboratory measurement for each parameter. LENVIMA (n = 253 to 258), Placebo (n = 129 to 131)

The following laboratory abnormalities (all Grades) occurred in >5% of LENVIMA-treated patients and at a rate that was two-fold or higher than in patients who received placebo: hypoalbuminemia, increased alkaline phosphatase, hypomagnesemia, hypoglycemia,

hyperbilirubinemia, hypercalcemia, hypercholesterolemia, increased serum amylase, and hyperkalemia.

Renal Cell Carcinoma

The safety of LENVIMA was evaluated in Study 205, in which patients with unresectable advanced or metastatic renal cell carcinoma (RCC) were randomized (1:1:1) to LENVIMA 18 mg orally once daily with everolimus 5 mg orally once daily (n=51), LENVIMA 24 mg orally once daily (n=52), or everolimus 10 mg orally once daily (n=50) *[see Clinical Studies (14.2)]*. This data also includes patients on the dose escalation portion of the study who received LENVIMA with everolimus (n=11). The median treatment duration was 8.1 months for LENVIMA with everolimus. Among 62 patients who received LENVIMA with everolimus, the median age was 61 years, 71% were men, and 98% were White.

The most common adverse reactions observed in the LENVIMA with everolimus-treated group (≥30%) were, in order of decreasing frequency, diarrhea, fatigue, arthralgia/myalgia, decreased appetite, vomiting, nausea, stomatitis/oral inflammation, hypertension, peripheral edema, cough, abdominal pain, dyspnea, rash, decreased weight, hemorrhagic events, and proteinuria. The most common serious adverse reactions (≥5%) were renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%).

Adverse reactions led to dose reductions or interruption in 89% of patients receiving LENVIMA with everolimus. The most common adverse reactions (≥5%) resulting in dose reductions in the LENVIMA with everolimus-treated group were diarrhea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%).

Treatment discontinuation due to an adverse reaction occurred in 29% of patients in the LENVIMA with everolimus-treated group.

Table 5 presents the adverse reactions in >15% of patients in the LENVIMA with everolimus arm. Study 205 was not designed to demonstrate a statistically significant difference in adverse reaction rates for LENVIMA in combination with everolimus, as compared to everolimus for any specific adverse reaction listed in Table 5.

Table 5: Adverse Reactions Occurring in >15% of Patients in the LENVIMA with Everolimus Arm in Study 205 (RCC)

	LENVIMA 18 mg with Everolimus 5 mg N=62		Everolimus 10 mg N=50	
Adverse Reactions	**Grade 1-4 (%)**	**Grade 3-4 (%)**	**Grade 1-4 (%)**	**Grade 3-4 (%)**
Endocrine				
Hypothyroidism	24	0	2	0
Gastrointestinal				
Diarrhea	81	19	34	2
Vomiting	48	7	12	0
Nausea	45	5	16	0
Stomatitis/Oral inflammation[a]	44	2	50	4
Abdominal pain[b]	37	3	8	0
Oral pain[c]	23	2	4	0
Dyspepsia/Gastro-esophageal	21	0	12	0

Table 5: Adverse Reactions Occurring in >15% of Patients in the LENVIMA with Everolimus Arm in Study 205 (RCC)

	LENVIMA 18 mg with Everolimus 5 mg N=62		Everolimus 10 mg N=50	
Adverse Reactions	**Grade 1-4 (%)**	**Grade 3-4 (%)**	**Grade 1-4 (%)**	**Grade 3-4 (%)**
reflux				
Constipation	16	0	18	0
General				
Fatigue[d]	73	18	40	2
Peripheral edema	42	2	20	0
Pyrexia/Increased body temperature	21	2	10	2
Metabolism and Nutrition				
Decreased appetite	53	5	18	0
Decreased weight	34	3	8	0
Musculoskeletal and Connective Tissue				
Arthralgia/Myalgia[e]	55	5	32	0
Musculoskeletal chest pain	18	2	4	0
Nervous System				
Headache	19	2	10	2
Psychiatric				
Insomnia	16	2	2	0
Renal and Urinary				
Proteinuria/Urine protein present	31	8	14	2
Renal failure event[f]	18	10	12	2
Respiratory, Thoracic and Mediastinal				
Cough	37	0	30	0
Dyspnea/Exertional dyspnea	35	5	28	8
Dysphonia	18	0	4	0
Skin and Subcutaneous Tissue				
Rash[g]	35	0	40	0
Vascular				
Hypertension/Increased blood pressure	42	13	10	2
Hemorrhagic events[h]	32	6	26	2

a Includes aphthous stomatitis, gingival inflammation, glossitis, and mouth ulceration
b Includes abdominal discomfort, gastrointestinal pain, lower abdominal pain, and upper abdominal pain
c Includes gingival pain, glossodynia, and oropharyngeal pain
d Includes asthenia, fatigue, lethargy and malaise
e Includes arthralgia, back pain, extremity pain, musculoskeletal pain, and myalgia
f Includes blood creatinine increased, blood urea increased, creatinine renal clearance decreased, nephropathy toxic, renal failure, renal failure acute, and renal impairment
g Includes erythema, erythematous rash, genital rash, macular rash, maculo-papular rash, papular rash, pruritic rash, pustular rash, and septic rash
h Includes hemorrhagic diarrhea, epistaxis, gastric hemorrhage, hemarthrosis, hematoma, hematuria, hemoptysis, lip hemorrhage, renal hematoma, and scrotal hematocele

In Table 6, Grade 3-4 laboratory abnormalities occurring in ≥3% of patients in the LENVIMA with everolimus arm are presented.

Table 6: Grade 3-4 Laboratory Abnormalities Occurring in ≥3% of Patients in the LENVIMA with Everolimus Arm[a,b] in Study 205 (RCC)

Laboratory Abnormality	LENVIMA 18 mg with Everolimus 5 mg	Everolimus 10 mg
	Grades 3-4 (%)	Grades 3-4 (%)
Chemistry		
Hypertriglyceridemia	18	18
Increased lipase	13	12
Hypercholesterolemia	11	0
Hyponatremia	11	6
Hypophosphatemia	11	6
Hyperkalemia	6	2
Hypocalcemia	6	2
Hypokalemia	6	2
Increased aspartate aminotransferase (AST)	3	0
Increased alanine aminotransferase (ALT)	3	2
Increased alkaline phosphatase	3	0
Hyperglycemia	3	16
Increased creatine kinase	3	4
Hematology		
Lymphopenia	10	20
Anemia	8	16
Thrombocytopenia	5	0

a With at least 1 grade increase from baseline

b Laboratory Abnormality percentage is based on the number of patients who had both baseline and at least one post baseline laboratory measurement for each parameter. LENVIMA with Everolimus (n = 62), Everolimus (n = 50).

Hepatocellular Carcinoma

The safety of LENVIMA was evaluated in REFLECT, which randomized (1:1) patients with unresectable hepatocellular carcinoma (HCC) to LENVIMA (n=476) or sorafenib (n=475) *[see Clinical Studies (14.3)]*. The dose of LENVIMA was 12 mg orally once daily for patients with a baseline body weight of ≥60 kg and 8 mg orally once daily for patients with a baseline body weight of <60 kg. The dose of sorafenib was 400 mg orally twice daily. Duration of treatment was ≥6 months in 49% and 32% of patients in the LENVIMA and sorafenib groups, respectively. Among the 476 patients who received LENVIMA in REFLECT, the median age was 63 years, 85% were men, 28% were White and 70% were Asian.

The most common adverse reactions observed in the LENVIMA-treated patients (≥20%) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic events, hypothyroidism, and nausea.

The most common serious adverse reactions (≥2%) in LENVIMA-treated patients were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%).

Adverse reactions led to dose reduction or interruption in 62% of patients receiving LENVIMA. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of LENVIMA were fatigue (9%), decreased appetite (8%), diarrhea (8%), proteinuria (7%), hypertension (6%), and palmar-plantar erythrodysesthesia syndrome (5%).

Treatment discontinuation due to adverse reactions occurred in 20% of patients in the LENVIMA-treated group. The most common adverse reactions (≥1%) resulting in discontinuation of LENVIMA were fatigue (1%), hepatic encephalopathy (2%), hyperbilirubinemia (1%), and hepatic failure (1%).

Table 7 summarizes the adverse reactions that occurred in ≥10% of patients receiving LENVIMA in REFLECT. REFLECT was not designed to demonstrate a statistically significant reduction in adverse reaction rates for LENVIMA, as compared to sorafenib, for any specified adverse reaction listed in Table 7.

Table 7: Adverse Reactions Occurring in ≥10% of Patients in the LENVIMA Arm in REFLECT (HCC)

Adverse Reaction	LENVIMA 8 mg/12 mg N=476		Sorafenib 800 mg N=475	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Endocrine				
Hypothyroidism[a]	21	0	3	0
Gastrointestinal				
Diarrhea	39	4	46	4
Abdominal pain[b]	30	3	28	4
Nausea	20	1	14	1
Vomiting	16	1	8	1
Constipation	16	1	11	0
Ascites[c]	15	4	11	3
Stomatitis[d]	11	0.4	14	1
General				
Fatigue[e]	44	7	36	6
Pyrexia[f]	15	0	14	0.2
Peripheral edema	14	1	7	0.2
Metabolism and Nutrition				
Decreased appetite	34	5	27	1
Decreased weight	31	8	22	3
Musculoskeletal and Connective Tissue				
Arthralgia/Myalgia[g]	31	1	20	2
Nervous System				
Headache	10	1	8	0
Renal and Urinary				
Proteinuria[h]	26	6	12	2
Respiratory, Thoracic and Mediastinal				
Dysphonia	24	0.2	12	0

Table 7: Adverse Reactions Occurring in ≥10% of Patients in the LENVIMA Arm in REFLECT (HCC)				
Adverse Reaction	**LENVIMA 8 mg/12 mg N=476**		**Sorafenib 800 mg N=475**	
	Grade 1-4 (%)	**Grade 3-4 (%)**	**Grade 1-4 (%)**	**Grade 3-4 (%)**
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia syndrome	27	3	52	11
Rash[i]	14	0	24	2
Vascular				
Hypertension[j]	45	24	31	15
Hemorrhagic events[k]	23	4	15	4

a Includes hypothyroidism, blood thyroid stimulating hormone increased.
b Includes abdominal discomfort, abdominal pain, abdominal tenderness, epigastric discomfort, gastrointestinal pain, lower abdominal pain, and upper abdominal pain
c Includes ascites and malignant ascites
d Includes aphthous ulcer, gingival erosion, gingival ulceration, glossitis, mouth ulceration, oral mucosal blistering, and stomatitis
e Includes asthenia, fatigue, lethargy and malaise
f Includes increased body temperature, pyrexia
g Includes arthralgia, back pain, extremity pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, and myalgia
h Includes proteinuria, increased urine protein, protein urine present
i Includes erythema, erythematous rash, exfoliative rash, genital rash, macular rash, maculo-papular rash, papular rash, pruritic rash, pustular rash and rash
j Includes increased diastolic blood pressure, increased blood pressure, hypertension and orthostatic hypertension
k Includes all hemorrhage terms. Hemorrhage terms that occurred in 5 or more subjects in either treatment group include: epistaxis, hematuria, gingival bleeding, hemoptysis, esophageal varices hemorrhage, hemorrhoidal hemorrhage, mouth hemorrhage, rectal hemorrhage and upper gastrointestinal hemorrhage

In Table 8, Grade 3-4 laboratory abnormalities occurring in ≥2% of patients in the LENVIMA arm in REFLECT (HCC) are presented.

Table 8: Grade 3-4 Laboratory Abnormalities Occurring in ≥2% of Patients in the LENVIMA Arm[a,b] in REFLECT (HCC)		
Laboratory Abnormality	**Lenvatinib (%)**	**Sorafenib (%)**
Chemistry		
Increased GGT	17	20
Hyponatremia	15	9
Hyperbilirubinemia	13	10
Increased aspartate aminotransferase (AST)	12	18
Increased alanine aminotransferase (ALT)	8	9
Increased alkaline phosphatase	7	5
Increased lipase	6	17
Hypokalemia	3	4
Hyperkalemia	3	2
Decreased albumin	3	1
Increased creatinine	2	2

Table 8: Grade 3-4 Laboratory Abnormalities Occurring in ≥2% of Patients in the LENVIMA Arm[a,b] in REFLECT (HCC)		
Laboratory Abnormality	**Lenvatinib (%)**	**Sorafenib (%)**
Hematology		
Thrombocytopenia	10	8
Lymphopenia	8	9
Neutropenia	7	3
Anemia	4	5

a With at least 1 grade increase from baseline
b Laboratory Abnormality percentage is based on the number of patients who had both baseline and at least one post baseline laboratory measurement for each parameter. LENVIMA (n=278 to 470) and sorafenib (n=260 to 473)

Endometrial Carcinoma

The safety of LENVIMA (20 mg orally once daily) in combination with pembrolizumab (200 mg intravenously every 3 weeks) was evaluated in Study 111, a single-arm, multicenter, open-label trial in 94 patients with endometrial carcinoma whose tumors had progressed following one line of systemic therapy and were not MSI-H or dMMR *[see Clinical Studies (14.4)]*. The median duration of study treatment was 7 months (range: 0.03 to 37.8 months). Pembrolizumab was continued for a maximum of 24 months; however, treatment with LENVIMA could be continued beyond 24 months.

Fatal adverse reactions occurred in 3% of patients treated with LENVIMA and pembrolizumab, including gastrointestinal perforation, RPLS with intraventricular hemorrhage, and intracranial hemorrhage.

Serious adverse reactions occurred in 52% of patients receiving LENVIMA and pembrolizumab. Serious adverse reactions in ≥3% of patients were hypertension (9%), abdominal pain (6%), musculoskeletal pain (5%), hemorrhage (4%), fatigue (4%), nausea (4%), confusional state (4%), pleural effusion (4%), adrenal insufficiency (3%), colitis (3%), dyspnea (3%), and pyrexia (3%).

Permanent discontinuation due to adverse reaction (Grade 1-4) occurred in 21% of patients who received LENVIMA and pembrolizumab. The most common adverse reactions (>2%) resulting in discontinuation of LENVIMA were gastrointestinal perforation or fistula (2%), muscular weakness (2%), and pancreatitis (2%).

Adverse reactions led to dose reduction or interruption in 88% of patients receiving LENVIMA. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of LENVIMA were fatigue (32%), hypertension (26%), diarrhea (18%), nausea (13%), palmar-plantar erythrodysesthesia (13%), vomiting (13%), decreased appetite (12%), musculoskeletal pain (11%), stomatitis (9%), abdominal pain (7%), hemorrhages (7%), renal impairment (6%), decreased weight (6%), rash (5%), headache (5%), increased lipase (5%), and proteinuria (5%).

Table 9 presents the adverse reactions in ≥20% of patients with LENVIMA in combination with pembrolizumab.

Table 9: Adverse Reactions in ≥20% of Patients on LENVIMA plus Pembrolizumab in Study 111

	LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=94	
Adverse Reactions	**All Grades (%)**	**Grade 3-4 (%)**
General		
Fatigue[a]	65	17
Musculoskeletal and Connective Tissue		
Musculoskeletal pain[b]	65	3
Vascular		
Hypertension[c]	65	38
Hemorrhagic events[d]	28	4
Gastrointestinal		
Diarrhea[e]	64	4
Nausea	48	5
Stomatitis[f]	43	0
Vomiting	39	0
Abdominal pain[g]	33	6
Constipation	32	0
Metabolism		
Decreased appetite[h]	52	0
Hypomagnesaemia	27	3
Endocrine		
Hypothyroidism[i]	51	1
Investigations		
Decreased weight	36	3
Nervous System		
Headache	33	1
Infections		
Urinary tract infection[j]	31	4
Respiratory, Thoracic and Mediastinal		
Dysphonia	29	0
Dyspnea[k]	24	2
Cough	21	0
Skin and Subcutaneous Tissue		
Palmar-plantar erythrodysesthesia syndrome	26	3
Rash[l]	21	3

Table 9: Adverse Reactions in ≥20% of Patients on LENVIMA plus Pembrolizumab in Study 111		
	LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=94	
Adverse Reactions	**All Grades (%)**	**Grade 3-4 (%)**

a Includes asthenia, fatigue, and malaise
b Includes arthralgia, arthritis, back pain, breast pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity
c Includes essential hypertension, hypertension, and hypertensive encephalopathy
d Includes catheter site bruise, contusion, epistaxis, gastrointestinal hemorrhage, hematemesis, hematuria, hemorrhage intracranial, injection site hemorrhage, intraventricular hemorrhage, large intestinal hemorrhage, metrorrhagia, mouth hemorrhage, uterine hemorrhage, and vaginal hemorrhage
e Includes diarrhea, gastroenteritis, gastrointestinal viral infection, and viral diarrhea
f Includes glossitis, mouth ulceration, oral discomfort, oral mucosal blistering, oropharyngeal pain, and stomatitis
g Includes abdominal discomfort, abdominal pain, lower abdominal pain, and upper abdominal pain
h Includes decreased appetite and early satiety
i Includes increased blood thyroid stimulating hormone and hypothyroidism
j Includes cystitis and urinary tract infection
k Includes dyspnea and exertional dyspnea
l Includes rash, rash generalized, rash macular, and rash maculo-papular

Table 10 presents, laboratory abnormalities in ≥20% (All Grades) or ≥3% (Grades 3-4) of patients with LENVIMA in combination with pembrolizumab.

Table 10: Laboratory Abnormalities in ≥20% (All Grades) or ≥3% (Grades 3-4) of Patients on LENVIMA plus Pembrolizumab in Study 111		
	LENVIMA 20 mg plus Pembrolizumab 200 mg	
Laboratory Abnormality[a]	**All Grades %[b]**	**Grade 3-4 %[b]**
Chemistry		
Increased creatinine	80	7
Hypertriglyceridemia	58	4
Hyperglycemia	53	1
Hypercholesteremia	49	6
Hypoalbuminemia	48	0
Hypomagnesemia	47	2
Increased aspartate aminotransferase	43	4
Hyponatremia	42	13
Increased lipase	42	18
Increased alanine aminotransferase	35	3
Increased alkaline phosphatase	32	1
Hypokalemia	27	5
Increased amylase	19	6
Hypocalcemia	14	3
Hypermagnesemia	4	3
Hematology		
Thrombocytopenia	48	0
Leukopenia	38	2
Lymphopenia	36	7

Table 10: Laboratory Abnormalities in ≥20% (All Grades) or ≥3% (Grades 3-4) of Patients on LENVIMA plus Pembrolizumab in Study 111		
	LENVIMA 20 mg plus Pembrolizumab 200 mg	
Laboratory Abnormality[a]	All Grades %[b]	Grade 3-4 %[b]
Anemia	35	1
Increased INR	21	3
Neutropenia	12	3
a With at least 1 grade increase from baseline b Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post baseline laboratory measurement for each parameter (range: 71 to 92 patients)		

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of LENVIMA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal: pancreatitis, increased amylase

General: impaired wound healing

Hepatobiliary: cholecystitis

Renal and Urinary: nephrotic syndrome

Vascular: arterial (including aortic) aneurysms, dissections, and rupture

7 DRUG INTERACTIONS

7.1 Drugs That Prolong the QT Interval

LENVIMA has been reported to prolong the QT/QTc interval. Avoid coadministration of LENVIMA with medicinal products with a known potential to prolong the QT/QTc interval *[see Warnings and Precautions (5.9)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended human doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits *(see Data)*. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryofetal development study, daily oral administration of lenvatinib mesylate at doses ≥0.3 mg/kg [approximately 0.14 times the recommended clinical dose of 24 mg based on body surface area (BSA)] to pregnant rats during organogenesis resulted in dose-related decreases in mean fetal body weight, delayed fetal ossifications, and dose-related increases in fetal external (parietal edema and tail abnormalities), visceral, and skeletal anomalies. Greater than 80% postimplantation loss was observed at 1.0 mg/kg/day (approximately 0.5 times the recommended clinical dose of 24 mg based on BSA).

Daily oral administration of lenvatinib mesylate to pregnant rabbits during organogenesis resulted in fetal external (short tail), visceral (retroesophageal subclavian artery), and skeletal anomalies at doses greater than or equal to 0.03 mg/kg (approximately 0.03 times the recommended clinical dose of 24 mg based on BSA). At the 0.03 mg/kg dose, increased post-implantation loss, including 1 fetal death, was also observed. Lenvatinib was abortifacient in rabbits, resulting in late abortions in approximately one-third of the rabbits treated at a dose level of 0.5 mg/kg/day (approximately 0.5 times the recommended clinical dose of 24 mg based on BSA).

8.2 Lactation

Risk Summary

It is not known whether LENVIMA is present in human milk; however, lenvatinib and its metabolites are excreted in rat milk at concentrations higher than those in maternal plasma *(see Data)*. Because of the potential for serious adverse reactions in breastfed infants, advise women to discontinue breastfeeding during treatment with LENVIMA and for at least 1 week after the last dose.

Data

Animal Data

Following administration of radiolabeled lenvatinib to lactating Sprague Dawley rats, lenvatinib-related radioactivity was approximately 2 times higher [based on area under the curve (AUC)] in milk compared to maternal plasma.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating LENVIMA *[see Use in Specific Populations (8.1)]*.

Contraception

Based on its mechanism of action, LENVIMA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 30 days after the last dose.

Infertility

LENVIMA may impair fertility in males and females of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of LENVIMA in pediatric patients have not been established.

Juvenile Animal Data

Daily oral administration of lenvatinib mesylate to juvenile rats for 8 weeks starting on postnatal day 21 (approximately equal to a human pediatric age of 2 years) resulted in growth retardation (decreased body weight gain, decreased food consumption, and decreases in the width and/or length of the femur and tibia) and secondary delays in physical development and reproductive organ immaturity at doses greater than or equal to 2 mg/kg (approximately 1.2 to 5 times the human exposure based on AUC at the recommended clinical dose of 24 mg). Decreased length of the femur and tibia persisted following 4 weeks of recovery. In general, the toxicologic profile of lenvatinib was similar between juvenile and adult rats, though toxicities including broken teeth at all dose levels and mortality at the 10 mg/kg/day dose level (attributed to primary duodenal lesions) occurred at earlier treatment time-points in juvenile rats.

8.5 Geriatric Use

Of the 261 patients with differentiated thyroid cancer (DTC) who received LENVIMA in SELECT, 45% were ≥65 years of age and 11% were ≥75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Of the 62 patients with renal cell carcinoma (RCC) who received LENVIMA with everolimus in Study 205, 36% were ≥65 years of age. Conclusions are limited due to the small sample size, but there appeared to be no overall differences in safety or effectiveness between these subjects and younger subjects.

Of the 476 patients with hepatocellular carcinoma (HCC) who received LENVIMA in REFLECT, 44% were ≥65 years of age and 12% were ≥75 years of age. No overall differences in safety or effectiveness were observed between patients ≥65 and younger subjects. Patients ≥75 years of age showed reduced tolerability to LENVIMA.

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild (CLcr 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment. Lenvatinib concentrations may increase in patients with DTC, RCC, or endometrial carcinoma and severe (CLcr 15-29 mL/min) renal impairment. Reduce the dose of lenvatinib for patients with RCC, DTC, or endometrial carcinoma and severe renal impairment *[see Dosage and Administration (2.6)]*. There is no recommended dose of LENVIMA for patients with HCC and severe renal impairment. LENVIMA has not been studied in patients with end stage renal disease *[see Warnings and Precautions (5.5), Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with HCC and mild hepatic impairment (Child-Pugh A). There is no recommended dose for patients with HCC with moderate or severe hepatic impairment.

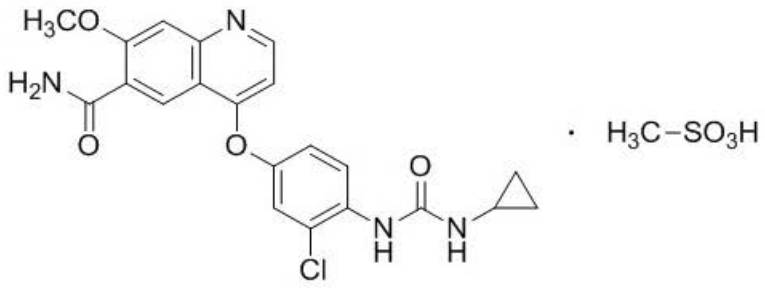
No dose adjustment is recommended for patients with DTC, RCC, or endometrial carcinoma and mild or moderate hepatic impairment (Child-Pugh A or B). Lenvatinib concentrations may increase in patients with DTC, RCC, or endometrial carcinoma and severe hepatic impairment (Child-Pugh C). Reduce the dose of lenvatinib for patients with DTC, RCC, or endometrial carcinoma and severe hepatic impairment *[see Dosage and Administration (2.6), Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable *[see Clinical Pharmacology (12.3)]*. Death due to multiorgan dysfunction occurred in a patient who received a single dose of LENVIMA 120 mg orally.

11 DESCRIPTION

LENVIMA, a kinase inhibitor, is the mesylate salt of lenvatinib. Its chemical name is 4-[3-chloro-4-(*N*'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate. The molecular formula is $C_{21}H_{19}ClN_4O_4 \cdot CH_4O_3S$, and the molecular weight of the mesylate salt is 522.96. The chemical structure of lenvatinib mesylate is:



Lenvatinib mesylate is a white to pale reddish yellow powder. It is slightly soluble in water and practically insoluble in ethanol (dehydrated). The dissociation constant (pKa value) of lenvatinib mesylate is 5.05 at 25°C. The partition coefficient (log P value) is 3.3.

LENVIMA capsules for oral administration contain 4 mg or 10 mg of lenvatinib, equivalent to 4.90 mg or 12.25 mg of lenvatinib mesylate, respectively. The inactive ingredients are: calcium carbonate, hydroxypropyl cellulose, low-substituted hydroxypropylcellulose, mannitol, microcrystalline cellulose, and talc.

In addition, the capsule shell contains ferric oxide red, ferric oxide yellow, hypromellose, and titanium dioxide. The printing ink contains black iron oxide, potassium hydroxide, propylene glycol, and shellac.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lenvatinib is a kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET. Lenvatinib also exhibited antiproliferative activity in hepatocellular carcinoma cell lines dependent on activated FGFR signaling with a concurrent inhibition of FGF-receptor substrate 2α (FRS2α) phosphorylation.

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

The combination of lenvatinib and everolimus showed increased antiangiogenic and antitumor activity as demonstrated by decreases in human endothelial cell proliferation, tube formation, and VEGF signaling in vitro, and by decreases in tumor volume in mouse xenograft models of human renal cell cancer that were greater than those with either drug alone.

12.3 Pharmacokinetics

In patients with solid tumors administered single and multiple doses of LENVIMA once daily, the maximum lenvatinib plasma concentration (C_{max}) and the area under the concentration-time curve (AUC) increased proportionally over the dose range of 3.2 mg (0.1 times the recommended clinical dose of 24 mg) to 32 mg (1.33 times the recommended clinical dose of 24 mg) with a median accumulation index of 0.96 (20 mg) to 1.54 (6.4 mg).

Absorption

The time to peak plasma concentration (T_{max}) typically occurred from 1 to 4 hours post-dose.

Food Effect

Administration with a high fat meal (approximately 900 calories of which approximately 55% were from fat, 15% from protein, and 30% from carbohydrates) did not affect the extent of absorption, but decreased the rate of absorption and delayed the median T_{max} from 2 hours to 4 hours.

Distribution

In vitro binding of lenvatinib to human plasma proteins ranged from 98% to 99% at concentrations of 0.3 to 30 μg/mL. The blood-to-plasma concentration ratio ranged from 0.59 to 0.61 at concentrations of 0.1 to 10 μg/mL in vitro.

Elimination

The terminal elimination half-life of lenvatinib was approximately 28 hours.

Metabolism

The main metabolic pathways for lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes.

Excretion

Ten days after a single administration of radiolabeled lenvatinib, approximately 64% and 25% of the radiolabel were eliminated in the feces and urine, respectively.

Specific Populations

Age, sex, and race did not have a significant effect on apparent oral clearance (CL/F).

Patients with Renal Impairment

The pharmacokinetics of lenvatinib following a single 24 mg dose were evaluated in subjects with mild (CLcr 60-89 mL/min), moderate (CLcr 30-59 mL/min), or severe (CLcr <30 mL/min) renal impairment, and compared to healthy subjects. Subjects with end stage renal disease were not studied. The $AUC_{0\text{-}inf}$ for subjects with renal impairment were similar compared to those for healthy subjects.

Patients with Hepatic Impairment

The pharmacokinetics of lenvatinib following a single 10 mg dose were evaluated in subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. The pharmacokinetics of a single 5 mg dose were evaluated in subjects with severe (Child-Pugh C) hepatic impairment. Compared to subjects with normal hepatic function, the dose-adjusted $AUC_{0\text{-}inf}$ of lenvatinib for subjects with mild, moderate, and severe hepatic impairment were 119%, 107%, and 180%, respectively.

Apparent oral clearance of lenvatinib in patients with HCC and mild hepatic impairment was similar to patients with HCC and moderate hepatic impairment.

Tumor

Patients with HCC in REFLECT had a 13% lower lenvatinib CL/F than patients with other cancer types.

Body Weight

Lenvatinib exposures in patients with HCC in REFLECT were comparable between those weighing <60 kg who received a starting dose of 8 mg and those ≥60 kg who received a starting dose of 12 mg.

Drug Interaction Studies

Effect of Other Drugs on Lenvatinib

CYP3A, P-gp, and BCRP Inhibitors: Ketoconazole (400 mg daily for 18 days) increased lenvatinib (administered as a single 5 mg dose on Day 5) AUC by 15% and C_{max} by 19%.

P-gp Inhibitor: Rifampicin (600 mg as a single dose) increased lenvatinib (24 mg as a single dose) AUC by 31% and C_{max} by 33%.

CYP3A and P-gp Inducers: Rifampicin (600 mg daily for 21 days) decreased lenvatinib (24 mg as a single dose on Day 15) AUC by 18%. The C_{max} was unchanged.

In Vitro Studies with Transporters: Lenvatinib is a substrate of P-gp and BCRP but not a substrate for organic anion transporter (OAT) 1, OAT3, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, multidrug and toxin extrusion (MATE) 1, MATE2-K, or the bile salt export pump (BSEP).

Effect of Lenvatinib on Other Drugs

Clinical Studies with Substrates of CYP3A4 or CYP2C8: There is no projected significant drug-drug interaction risk between lenvatinib and midazolam (a CYP3A4 substrate) or repaglinide (a CYP2C8 substrate).

In Vitro Studies with Substrates of CYP or UDP-glucuronosyltransferase (UGT): Lenvatinib inhibits CYP2C8, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Lenvatinib does not inhibit CYP2A6 and CYP2E1. Lenvatinib induces CYP3A, but it does not induce CYP1A1, CYP1A2, CYP2B6, and CYP2C9.

Lenvatinib inhibits UGT1A1, UGT1A4, and UGT1A9 in vitro, but likely only inhibits UGT1A1 in vivo in the gastrointestinal tract based on the expression of the enzyme in tissues. Lenvatinib does not inhibit UGT1A6, UGT2B7 or aldehyde oxidase. Lenvatinib does not induce UGT1A1, UGT1A4, UGT1A6, UGT1A9, or UGT2B7.

In Vitro Studies with Substrates of Transporters:

Lenvatinib does not have the potential to inhibit MATE1, MATE2-K, OCT1, OCT2, OAT1, OAT3, BSEP, OATP1B1, or OATP1B3 in vivo.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with lenvatinib. Lenvatinib mesylate was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay. Lenvatinib was not clastogenic in the in vitro mouse lymphoma thymidine kinase assay or the in vivo rat micronucleus assay.

No specific studies with lenvatinib have been conducted in animals to evaluate the effect on fertility; however, results from general toxicology studies in rats, monkeys, and dogs suggest there is a potential for lenvatinib to impair fertility. Male dogs exhibited testicular hypocellularity of the seminiferous epithelium and desquamated seminiferous epithelial cells in the epididymides at lenvatinib exposures approximately 0.02 to 0.09 times the AUC at the recommended clinical dose of 24 mg once daily. Follicular atresia of the ovaries was observed in monkeys and rats at exposures 0.2 to 0.8 times and 10 to 44 times the AUC at the recommended clinical dose of 24 mg once daily, respectively. In addition, in monkeys, a decreased incidence of menstruation was reported at lenvatinib exposures lower than those observed in humans at the recommended clinical dose of 24 mg once daily.

14 CLINICAL STUDIES

14.1 Differentiated Thyroid Cancer

A multicenter, randomized (2:1), double-blind, placebo-controlled study (SELECT; NCT01321554) was conducted in 392 patients with locally recurrent or metastatic radioactive iodine-refractory differentiated thyroid cancer and radiographic evidence of disease progression within 12 months prior to randomization, confirmed by independent radiologic review. Radioactive iodine (RAI)-refractory was defined as 1 or more measurable lesions with no iodine uptake on RAI scan, iodine uptake with progression within 12 months of RAI therapy, or having received cumulative RAI activity >600 mCi (22 GBq) with the last dose administered at least 6 months prior to study entry. Patients were randomized to receive LENVIMA 24 mg once daily (n=261) or placebo (n=131) until disease progression. Randomization was stratified by geographic region, prior VEGF/VEGFR-targeted therapy, and age. The major efficacy outcome measure was progression-free survival (PFS) as determined by blinded independent radiologic review using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Independent review confirmation of disease progression was required prior to discontinuing patients from the randomization phase of the study. Other efficacy outcome measures included objective response rate (ORR) and overall survival (OS).

Patients in the placebo arm could receive lenvatinib following independent review confirmation of disease progression.

Of the 392 patients randomized, 51% were male, the median age was 63 years, 40% were 65 years or older, 79% were White, 54% had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, and 24% had received 1 prior VEGF/VEGFR-targeted therapy. Metastases were present in 99% of the patients: lungs in 89%, lymph nodes in 52%, bone in 39%, liver in 18%, and brain in 4%. The histological diagnoses were papillary thyroid cancer (66%) and follicular thyroid cancer (34%); of those with follicular histology, 44% had Hürthle cell and 11% had clear cell subtypes. In the LENVIMA arm, 67% of patients did not demonstrate iodine uptake on any RAI scan compared to 77% in the placebo arm. Additionally, 59% of patients on the LENVIMA arm and 61% of patients on placebo arm progressed, according to RECIST 1.1, within 12 months of prior I 131 therapy; 19.2% of patients on the LENVIMA arm and 17.6% of patients on placebo arm received prior cumulative activity of >600 mCi or 22 GBq I 131, with the last dose administered at least 6 months prior to study entry. The median cumulative RAI activity administered prior to study entry was 350 mCi (12.95 GBq).

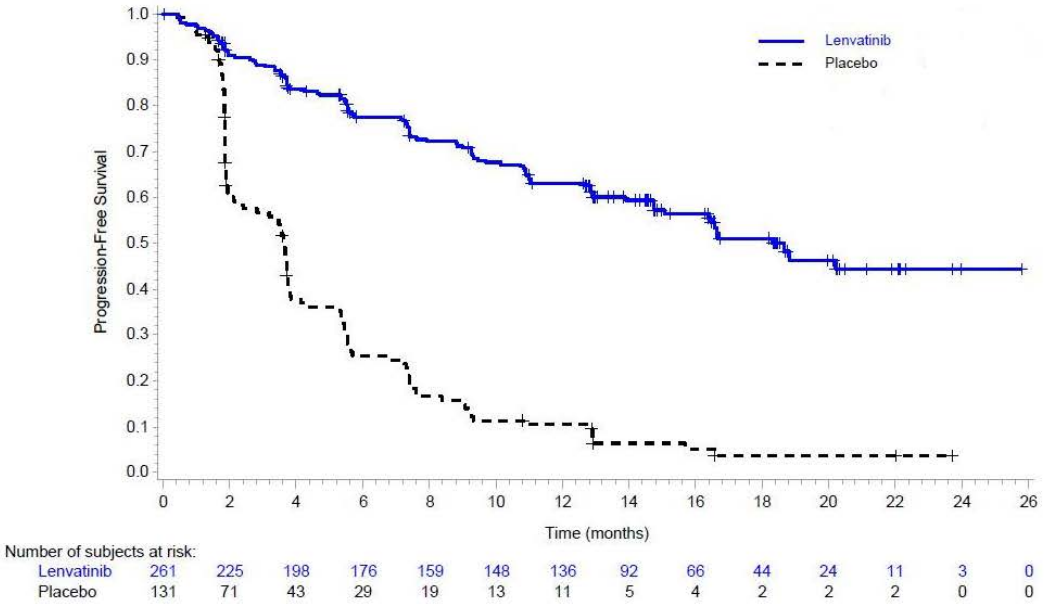
A statistically significant prolongation in PFS was demonstrated in LENVIMA-treated patients compared to those receiving placebo (Table 11 and Figure 1). Upon confirmation of progression, 83% of patients that were randomly assigned to placebo crossed over to receive open-label LENVIMA.

Table 11: Efficacy Results in Differentiated Thyroid Cancer in SELECT

	LENVIMA N=261	**Placebo N=131**
Progression-Free Survival (PFS)[a]		
Number of events (%)	107 (41)	113 (86)
Progressive disease	93 (36)	109 (83)
Death	14 (5)	4 (3)
Median PFS in months (95% CI)	18.3 (15.1, NE)	3.6 (2.2, 3.7)
Hazard ratio (95% CI)[b]	0.21 (0.16, 0.28)	
P-value[c]	<0.001	
Objective Response Rate[a]		
Objective response rate	65%	2%
(95% CI)	(59%, 71%)	(0%, 4%)
Complete response	2%	0%
Partial response	63%	2%
P-value[d]	<0.001	
Overall Survival (OS)[e]		
Number of deaths (%)	71 (27)	47 (36)
Median OS in months (95% CI)	NE (22.1, NE)	NE (20.3, NE)
Hazard ratio (95% CI)[b]	0.73 (0.50, 1.07)	
P-value[b]	0.10	

a Independent radiologic review
b Estimated with Cox proportional hazard model stratified by region (Europe vs North America vs other), age group (≤65 years vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs 1)
c Log-rank test stratified by region (Europe vs North America vs other), age group (≤65 years vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs 1)
d Cochran-Mantel-Haenszel chi-square test
e NE = Not estimable

Figure 1: Kaplan-Meier Curves for Progression-Free Survival in SELECT



14.2 Renal Cell Carcinoma

The efficacy was evaluated in a multicenter, randomized (1:1:1) study (Study 205: NCT01136733), in which 153 patients with advanced or metastatic renal cell carcinoma who have previously received anti-angiogenic therapy received LENVIMA 18 mg orally once daily with everolimus 5 mg orally once daily, LENVIMA 24 mg orally once daily, or everolimus 10 mg orally once daily. Patients were required to have histological confirmation of clear cell RCC and ECOG PS of 0 or 1. Patients were stratified by hemoglobin level (≤ or >13 g/dL for males and ≤ or >11.5 g/dL for females) and corrected serum calcium (≥10 mg/dL vs. <10 mg/dL). The major efficacy outcome measure was investigator-assessed PFS evaluated according to RECIST 1.1.

Of the 101 patients randomized to the LENVIMA with everolimus arm or everolimus arm, 72% were male, the median age was 60 years, 31% were older than 65 years, and 96% were White. Metastases were present in 95% of the patients and unresectable advanced disease was present in 5%. All patients had a baseline ECOG PS of either 0 (54%) or 1 (46%) with similar distribution across these two treatment arms. Memorial Sloan Kettering Cancer Center (MSKCC) favorable, intermediate and poor risk categories were observed respectively, in 24%, 37%, and 39% of patients in the LENVIMA with everolimus arm, and 24%, 38%, and 38% of patients in the everolimus arm.

Efficacy results from Study 205 are summarized in Table 12 and Figures 2 and 3. The treatment effect of the combination on PFS was supported by a retrospective independent review of radiographs with an observed hazard ratio (HR) of 0.43 (95% CI: 0.24, 0.75) compared with the everolimus arm.

Table 12: Efficacy Results in Renal Cell Carcinoma Per Investigator Assessment in Study 205

	LENVIMA 18 mg with Everolimus 5 mg N=51	Everolimus 10 mg N=50
Progression-Free Survival (PFS)[a]		
Number of events, n (%)	26 (51)	37 (74)
Progressive disease	21 (41)	35 (70)
Death	5 (10)	2 (4)
Median PFS in months (95% CI)	14.6 (5.9, 20.1)	5.5 (3.5, 7.1)
Hazard Ratio (95% CI)[b] LENVIMA with Everolimus vs Everolimus	0.37 (0.22, 0.62)	-
Overall Survival (OS)[c]		
Number of deaths, n (%)	32 (63)	37 (74)
Median OS in months (95% CI)	25.5 (16.4, 32.1)	15.4 (11.8, 20.6)
Hazard Ratio (95% CI)[b] LENVIMA with Everolimus vs Everolimus	0.67 (0.42, 1.08)	-
Objective Response Rate (Confirmed)		
Objective response rate, n (%)	19 (37)	3 (6)
(95% CI)	(24, 52)	(1, 17)
Number of complete responses, n (%)	1 (2)	0
Number of partial responses (%)	18 (35)	3 (6)

Tumor assessments were based on RECIST v1.1 criteria for progression but only confirmed responses are included for ORR. Data cutoff date = 13 Jun 2014

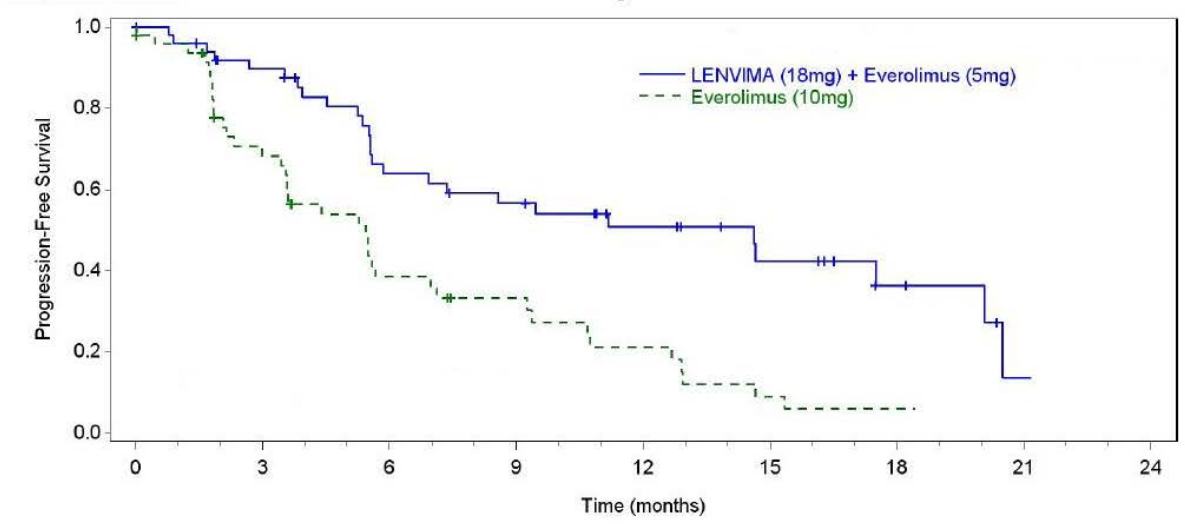
CI = confidence interval

a Point estimates are based on Kaplan-Meier method and 95% CIs are based on the Greenwood formula using log-log transformation.

b Hazard ratio is based on a stratified Cox regression model including treatment as a covariate factor and hemoglobin and corrected serum calcium as strata.

c Data cutoff date = 31 Jul 2015

Figure 2: Kaplan-Meier Curves for Progression-Free Survival in Study 205

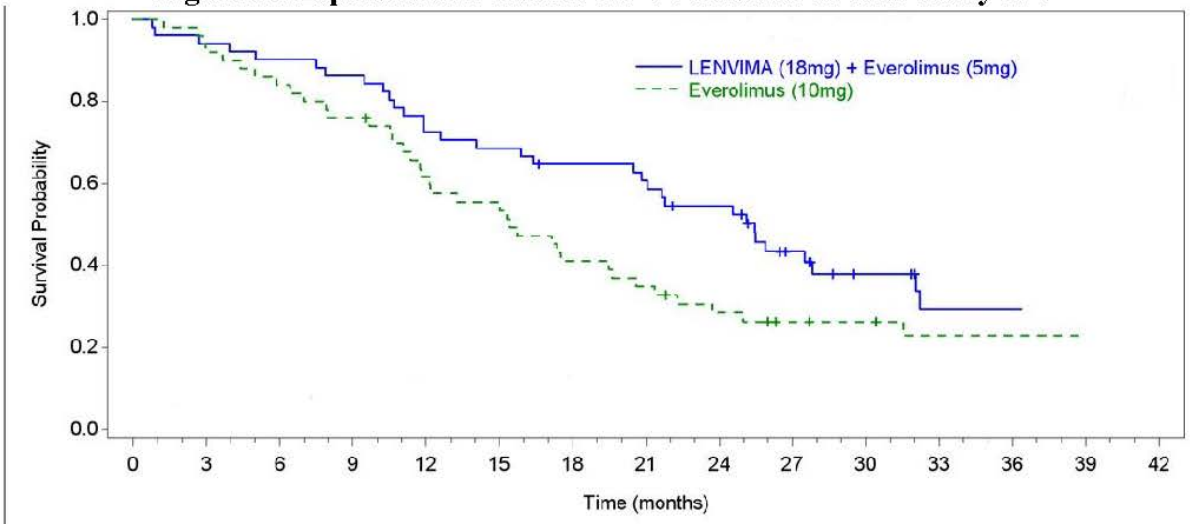


Number of Subjects at risk:

L(18mg) + E(5mg)	51	41	27	23	16	10	5	1	0
E(10mg)	50	29	15	11	7	3	1	0	

L(18mg) + E(5mg)=LENVIMA 18mg + Everolimus 5mg; E(10mg)=Everolimus 10mg
Data Cutoff Date: 13JUN2014

Figure 3: Kaplan-Meier Curves for Overall Survival in Study 205



Number of Subjects at risk:

L(18mg) + E(5mg)	51	48	46	44	37	35	32	30	26	17	11	7	2	0	0
E(10mg)	50	46	42	38	30	27	20	17	13	10	9	5	1	0	0

L(18mg) + E(5mg)=LENVIMA 18mg + Everolimus 5mg; E(10mg)=Everolimus 10mg
Data Cutoff Date: 31JUL2015

14.3 Hepatocellular Carcinoma

The efficacy of LENVIMA was evaluated in a randomized, open-label, multicenter, international study (REFLECT; NCT01761266) conducted in patients with previously untreated unresectable hepatocellular carcinoma (HCC). The study enrolled adults with Child-Pugh A and Barcelona Clinic Liver Cancer (BCLC) Stage C or B HCC who were ineligible for local liver-directed therapy; had an ECOG PS of 0 or 1; had received no prior systemic therapy for HCC; and had at least one measurable target lesion according to modified RECIST for HCC.

Patients were randomized (1:1) to receive LENVIMA (12 mg for baseline body weight ≥60 kg or 8 mg for baseline body weight <60 kg) orally once daily or sorafenib 400 mg orally twice daily until radiological disease progression or unacceptable toxicity. Randomization was stratified by region (Western vs Asia Pacific), presence of macroscopic portal vein invasion or extrahepatic spread (yes vs no), ECOG PS (0 vs 1), and body weight (<60 kg vs ≥60 kg). The major efficacy outcome measure was overall survival (OS). REFLECT was designed to show the non-inferiority of LENVIMA to sorafenib for OS. Additional efficacy outcome measures were progression-free survival (PFS) and objective response rate (ORR) according to modified RECIST for HCC.

A total of 954 patients were randomized, 478 to the LENVIMA arm and 476 to the sorafenib arm. The demographics of the study population were: median age of 62 years (range: 20 to 88 years); 84% male; 69% Asian and 29% White; 63% ECOG PS of 0; and 69% weighed ≥60 kg. Of the 590 (62%) patients with at least one site of documented distant metastatic disease, 52% had lung metastasis, 45% had lymph node metastasis, and 16% had bone metastasis.

Macroscopic portal vein invasion, extra-hepatic spread, or both were present in 70% of patients. HCC was categorized as Child-Pugh A and BCLC Stage C in 79% and Child-Pugh A and BCLC Stage B in 21% of patients. Seventy-five percent (75%) of patients had radiographic evidence of cirrhosis at baseline. Investigator-documented primary risk factors for the development of HCC were hepatitis B (50%), hepatitis C (23%), alcohol use (6%), other (7%), and unknown (14%).

REFLECT demonstrated that LENVIMA was non-inferior to sorafenib for OS. REFLECT did not demonstrate a statistically significant improvement in OS for patients randomized to LENVIMA as compared to those in the sorafenib arm. LENVIMA was statistically significantly superior to sorafenib for PFS and ORR. Efficacy results are summarized in Table 13 and Figure 4.

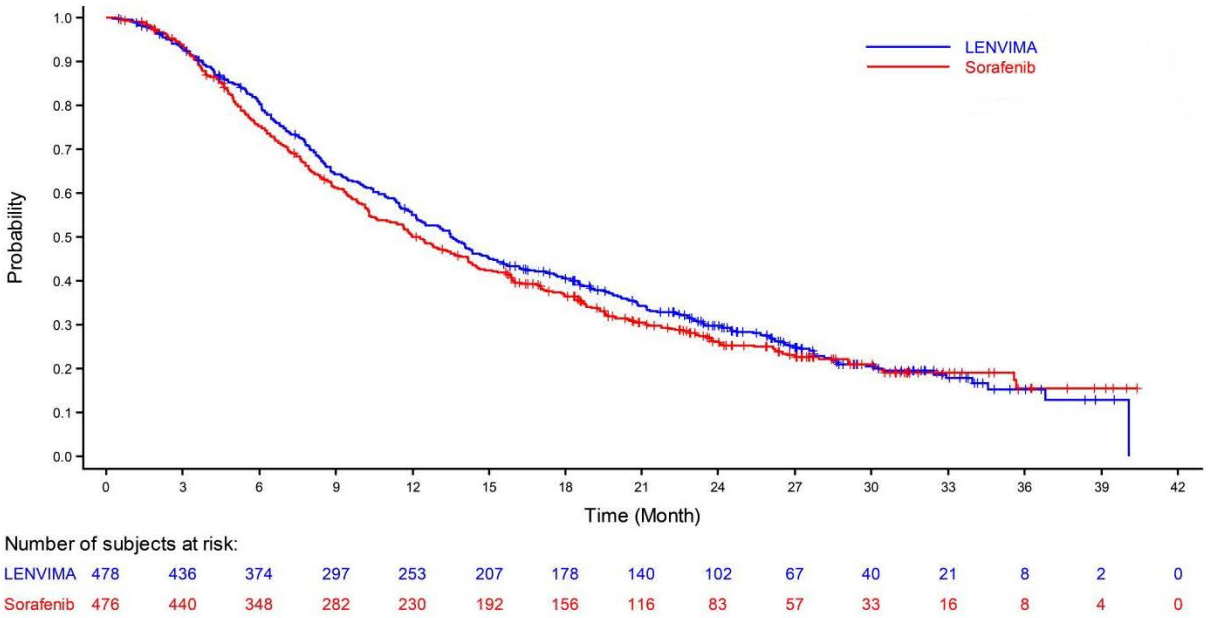
Table 13: Efficacy Results in Hepatocellular Carcinoma in REFLECT		
	LENVIMA N= 478	**Sorafenib N=476**
Overall Survival		
Number of deaths (%)	351 (73)	350 (74)
Median OS in months (95% CI)	13.6 (12.1, 14.9)	12.3 (10.4, 13.9)
Hazard Ratio (95% CI)[a]	0.92 (0.79, 1.06)	
Progression-Free Survival[b] (mRECIST)		
Number of Events (%)	311 (65)	323 (68)
Median PFS in months (95% CI)	7.3 (5.6, 7.5)	3.6 (3.6, 3.7)
Hazard Ratio (95% CI)	0.64 (0.55, 0.75)	
P-value	<0.001	
Objective Response Rate[b] (mRECIST)		
Objective response rate	41%	12%
Complete responses, n (%)	10 (2.1)	4 (0.8)
Partial responses, n (%)	184 (38.5)	55 (11.6)
95% CI	(36%, 45%)	(10%, 16%)
P-value	<0.001	
Progression-Free Survival[b] (RECIST 1.1)		
Number of Events (%)	307 (64)	320 (67)
Median PFS in months (95% CI)	7.3 (5.6, 7.5)	3.6 (3.6, 3.9)
Hazard Ratio (95% CI)	0.65 (0.56, 0.77)	
Objective Response Rate[b] (RECIST 1.1)		
Objective response rate	19%	7%
Complete responses, n (%)	2 (0.4)	1 (0.2)
Partial responses, n (%)	88 (18.4)	30 (6.3)
95% CI	(15%, 22%)	(4%, 9%)

CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HR = hazard ratio; OS = overall survival.

a Based on stratified Cox-model. Non-inferiority margin for HR (lenvatinib vs sorafenib) is 1.08.

b Per independent radiology review.

Figure 4: Kaplan-Meier Curves for Overall Survival in REFLECT



14.4 Endometrial Carcinoma (EC)

The efficacy of LENVIMA in combination with pembrolizumab was investigated in Study 111 (NCT02501096), a single-arm, multicenter, open-label, multi-cohort trial that enrolled 108 patients with metastatic endometrial carcinoma that had progressed following at least one prior systemic therapy in any setting. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients were treated with LENVIMA 20 mg orally once daily in combination with pembrolizumab 200 mg administered intravenously every 3 weeks until unacceptable toxicity or disease progression as determined by the investigator. The major efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) by independent radiologic review committee (IRC) using RECIST 1.1.

Administration of LENVIMA and pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. Pembrolizumab was continued for a maximum of 24 months; however, treatment with LENVIMA could be continued beyond 24 months. Assessment of tumor status was performed at baseline and then every 6 weeks until week 24, followed by every 9 weeks thereafter.

Among the 108 patients, 87% (n= 94) had tumors that were not MSI-H or dMMR; 10% (n=11) had tumors that were MSI-H or dMMR; and in 3% (n=3) the status was not known. Tumor MSI status was determined using a polymerase chain reaction (PCR) test. Tumor MMR status was determined using an immunohistochemistry (IHC) test. The baseline characteristics of the 94 patients with tumors that were not MSI-H or dMMR were: median age of 66 years with 62% 65 years or older; 86% White, 6% Black, 4% Asian, 3% other races; and ECOG PS of 0 (52%) or 1 (48%). All 94 of these patients received prior systemic therapy

for endometrial carcinoma: 51% had one, 38% had two, and 11% had three or more prior systemic therapies.
Efficacy results are summarized in Table 14.

Table 14: Efficacy Results per IRC in Endometrial Carcinoma that is not MSI-H or dMMR (Study 111)

	LENVIMA with pembrolizumab N=94*
Objective Response Rate (ORR)	
ORR (95% CI)	38.3% (29%, 49%)
Complete response, n (%)	10 (10.6%)
Partial response, n (%)	26 (27.7%)
Duration of Response	
Median in months (range)	NR (1.2+, 33.1+)†
Duration of response ≥6 months, n (%)	25 (69%)

Tumor assessments were based on RECIST 1.1 per independent radiologic review committee (IRC). All responses were confirmed.
*Median follow-up time of 18.7 months
† Based on patients (n=36) with a response by independent review
+ Censored at data cutoff
CI = confidence interval; NR= Not reached.

16 HOW SUPPLIED/STORAGE AND HANDLING

LENVIMA 4 mg capsules are supplied as hard hypromellose capsules with yellowish-red body and yellowish-red cap, marked in black ink with "Є" on the cap and "LENV 4 mg" on the body.

LENVIMA 10 mg capsules are supplied as hard hypromellose capsules with yellow body and yellowish-red cap, marked in black ink with "Є" on the cap and "LENV 10 mg" on the body.

LENVIMA capsules are supplied in cartons of 6 cards. Each card is a 5-day blister card as follows:

- NDC 62856-724-30: 24 mg, carton with 6 cards NDC 62856-724-05 (ten 10 mg capsules and five 4 mg capsules per card).
- NDC 62856-720-30: 20 mg, carton with 6 cards NDC 62856-720-05 (ten 10 mg capsules per card).
- NDC 62856-718-30: 18 mg, carton with 6 cards NDC 62856-718-05 (five 10 mg capsules and ten 4 mg capsules per card).
- NDC 62856-714-30: 14 mg, carton with 6 cards NDC 62856-714-05 (five 10 mg capsules and five 4 mg capsules per card).
- NDC 62856-712-30: 12 mg, carton with 6 cards NDC 62856-712-05 (fifteen 4 mg capsules per card).
- NDC 62856-710-30: 10 mg, carton with 6 cards NDC 62856-710-05 (five 10 mg capsules per card).
- NDC 62856-708-30: 8 mg, carton with 6 cards NDC 62856-708-05 (ten 4 mg capsules per card).
- NDC 62856-704-30: 4 mg, carton with 6 cards NDC 62856-704-05 (five 4 mg capsules per card).

Store at 25°C (77°F); excursions permitted to 15 – 30°C (59 – 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypertension

Advise patients to undergo regular blood pressure monitoring and to contact their health care provider if blood pressure is elevated *[see Warnings and Precautions (5.1)]*.

Cardiac Dysfunction

Advise patients that LENVIMA can cause cardiac dysfunction and to immediately contact their healthcare provider if they experience any clinical symptoms of cardiac dysfunction *[see Warnings and Precautions (5.2)]*.

Arterial Thrombotic Events

Advise patients to seek immediate medical attention for new onset chest pain or acute neurologic symptoms consistent with myocardial infarction or stroke *[see Warnings and Precautions (5.3)]*.

Hepatotoxicity

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

Proteinuria and Renal Failure/Impairment

Advise patients that they will need to undergo regular laboratory tests to monitor kidney function and protein in the urine *[see Warnings and Precautions (5.5, 5.6)]*.

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 (5.7)]*.

Fistula Formation and Gastrointestinal Perforation

Advise patients that LENVIMA can increase the risk of fistula formation or gastrointestinal perforation 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)]*.

Hypocalcemia

Advise patients of the risks of hypocalcemia, that they will need to undergo laboratory tests to monitor calcium levels, and the potential requirement for calcium supplementation *[see Warnings and Precautions (5.10)]*.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Advise patients of the signs and symptoms of RPLS and to contact their healthcare provider for new onset or worsening neurological function *[see Warnings and Precautions (5.11)]*.

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)]*.

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction

Advise patients that LENVIMA can cause hypothyroidism and that their thyroid function should be monitored regularly during treatment *[see Warnings and Precautions (5.13)]*.

Impaired Wound Healing

Advise patients that LENVIMA may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure *[see Warnings and Precautions (5.14)]*.

Osteonecrosis of the Jaw (ONJ)

Advise patients regarding good oral hygiene practices and to have preventive dentistry performed prior to treatment with LENVIMA and throughout treatment with LENVIMA. Inform patients being treated with LENVIMA, particularly those who are at high risk for ONJ, to avoid invasive dental procedures, if possible, and to inform their healthcare provider of any planned dental procedures *[see Warnings and Precautions (5.15)]*. Advise patients to immediately contact their healthcare provider for signs or symptoms associated with ONJ.

Embryo-Fetal 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 (5.16), Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 30 days after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women to discontinue breastfeeding during treatment with LENVIMA and for at least 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

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.

© 2020 Eisai Inc.

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 called everolimus to treat advanced renal cell carcinoma (RCC), a type of kidney cancer, after one course of treatment with another anti-cancer medicine.
- LENVIMA is used by itself as the first treatment for a type of liver cancer called hepatocellular carcinoma (HCC) when it cannot be removed by surgery.
- LENVIMA is used along with another medicine called pembrolizumab to treat advanced endometrial carcinoma, a type of uterine cancer:
  - that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), **and**
  - that has progressed after treatment with anti-cancer medicine, **and**
  - that cannot be treated with surgery or radiation.

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

Before you take LENVIMA, tell your healthcare provider about all of your medical conditions, including 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 liver or kidney problems
- have a history of a tear (perforation) in your stomach or intestine, or an abnormal connection between two or more body parts (fistula)
- have headaches, seizures, or vision problems
- have any bleeding problems
- plan to have surgery, a dental procedure, or have had a recent surgery. You should stop taking LENVIMA at least 1 week before planned surgery. See **"What are the possible side effects of LENVIMA?"**
- are pregnant or plan to become pregnant. LENVIMA can harm your unborn baby.
  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with LENVIMA.
  - You should use an effective method of birth control during treatment with LENVIMA and for at least 30 days 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 and for at least 1 week after the last dose.

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

Especially tell your healthcare provider if you are taking, or have taken, an osteoporosis medicine.

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.
- **heart problems.** LENVIMA can cause serious heart problems that may lead to death. 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)
  - feeling drowsy, confused or loss of consciousness
- **kidney problems.** Kidney failure, which can lead to death, has happened with LENVIMA treatment. Your healthcare provider should do regular blood tests to check your kidneys.
- **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.
- **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.
- **an opening in the wall of your stomach or intestines (perforation) or an abnormal connection between two or more body parts (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 before and during your treatment with LENVIMA to check the levels of potassium, magnesium, and calcium in your blood, and may 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 and may tell you to take a calcium supplement if your calcium levels are low.

- **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
  - blood in your urine
  - coughing up blood or blood clots
  - heavy or new onset vaginal bleeding
- **change in thyroid hormone levels**. Your healthcare provider should check your thyroid hormone levels before starting and every month during treatment with LENVIMA.
- **wound healing problems.** Wound healing problems have happened in some people who take LENVIMA. Tell your healthcare provider if you plan to have any surgery before or during treatment with LENVIMA.
  - You should stop taking LENVIMA at least 1 week before planned surgery.
  - Your healthcare provider should tell you when you may start taking LENVIMA again after surgery.
- **severe jaw bone problems (osteonecrosis).** Severe jaw bone problems have happened in some people who take LENVIMA. Certain risk factors such as taking a bisphosphonate medicine or the medicine denosumab, having dental disease, or an invasive dental procedure may increase your risk of getting jaw bone problems. Your healthcare provider should examine your mouth before you start and during treatment with LENVIMA. Tell your dentist that you are taking LENVIMA. It is important for you to practice good mouth care during treatment with LENVIMA. Tell your healthcare provider right away if you get signs or symptoms of jaw bone problems during treatment with LENVIMA, including jaw pain, toothache, or sores on your gums. Tell your healthcare provider if you plan to have any dental procedures before or during treatment with LENVIMA. You should avoid having invasive dental procedures if possible, during treatment with LENVIMA. Stopping your bisphosphonate medicine before an invasive dental procedure may help decrease your risk of getting these jaw problems.
  - You should stop taking LENVIMA at least 1 week before planned dental surgery or invasive dental procedures.
  - Your healthcare provider should tell you when you may start taking LENVIMA again after dental procedures.

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

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

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

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

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

- tiredness
- decreased appetite
- joint and muscle pain
- weight loss
- rash, redness, itching, or peeling of your skin on your hands and feet
- hoarseness
- bleeding

- stomach (abdomen) pain
- change in thyroid hormone levels
- nausea

The most common side effects of LENVIMA when given with pembrolizumab in people treated for uterine cancer include:

- tiredness
- joint and muscle pain
- decreased appetite
- change in thyroid hormone levels
- nausea
- mouth sores
- vomiting
- weight loss
- stomach (abdomen) pain
- headache
- constipation
- urinary tract infection
- hoarseness
- bleeding
- low magnesium level
- rash, redness, itching, or peeling of your skin on your hands and feet
- trouble breathing
- cough
- rash

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).

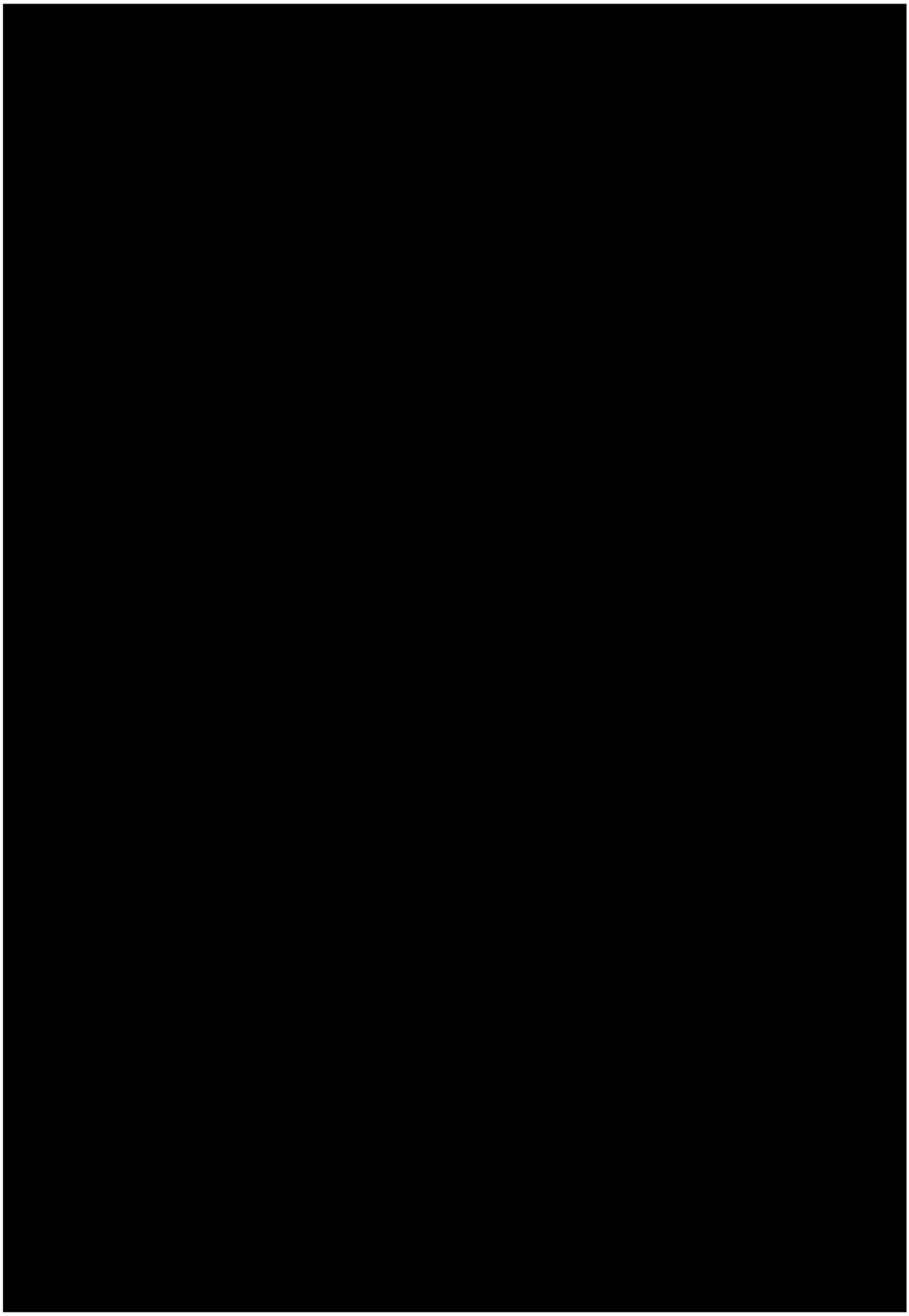
Keep LENVIMA and all medicines out of the reach of children.

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, hydroxypropyl cellulose, low-substituted hydroxypropylcellulose, mannitol, microcrystalline cellulose, and talc.
The capsule shell contains: ferric oxide red, ferric oxide yellow, hypromellose, and titanium dioxide. The printing ink contains black iron oxide, potassium hydroxide, propylene glycol, and shellac.

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: 12/2020



＊以下，P2～59は削除

1.7. 同種同効品一覧表

胸腺癌の効能・効果を有する既承認の医薬品はない。

最新の添付文書を参照すること。

日本標準商品分類番号
874291

貯　　法：室温保存
有効期間：3年

	カプセル 4mg	カプセル 10mg
承認番号	22700AMX00640000	22700AMX00641000
販売開始	2015年5月	2015年5月

抗悪性腫瘍剤
レンバチニブメシル酸塩製剤

劇薬，処方箋医薬品[注)]

レンビマ®カプセル4mg
レンビマ®カプセル10mg
Lenvima®capsules

（案）

注）注意－医師等の処方箋により使用すること

1. 警告

本剤は，緊急時に十分対応できる医療施設において，がん化学療法に十分な知識・経験を持つ医師のもとで，本剤の使用が適切と判断される症例についてのみ投与すること。また，治療開始に先立ち，患者又はその家族に本剤の有効性及び危険性を十分説明し，同意を得てから投与すること。

2. 禁忌（次の患者には投与しないこと）

2.1 本剤の成分に対し過敏症の既往歴のある患者
2.2 妊婦又は妊娠している可能性のある女性［9.5 参照］

3. 組成・性状

3.1 組成

販売名	レンビマカプセル4mg	レンビマカプセル10mg
有効成分	1カプセル中 レンバチニブメシル酸塩4.90mg（レンバチニブとして4mg）	1カプセル中 レンバチニブメシル酸塩12.25mg（レンバチニブとして10mg）
添加剤	結晶セルロース，タルク，沈降炭酸カルシウム，低置換度ヒドロキシプロピルセルロース，ヒドロキシプロピルセルロース，ヒプロメロース，D-マンニトール，ラウリル硫酸ナトリウム	結晶セルロース，タルク，沈降炭酸カルシウム，低置換度ヒドロキシプロピルセルロース，ヒドロキシプロピルセルロース，ヒプロメロース，D-マンニトール，ラウリル硫酸ナトリウム

3.2 製剤の性状

販売名	レンビマカプセル4mg	レンビマカプセル10mg
剤形	硬カプセル	硬カプセル
識別コード	ЄLENV 4mg	ЄLENV 10mg
外形		
全長（mm）	14.3	14.3
質量（mg）	137	137
号数	4	4
色	カプセル 上半分：黄赤色不透明 下半分：黄赤色不透明 内容物 白色の顆粒	カプセル 上半分：黄赤色不透明 下半分：黄色不透明 内容物 白色の顆粒

4. 効能又は効果

〈レンビマカプセル4mg〉
根治切除不能な甲状腺癌，切除不能な肝細胞癌，切除不能な胸腺癌
〈レンビマカプセル10mg〉
根治切除不能な甲状腺癌，切除不能な胸腺癌

5. 効能又は効果に関連する注意

〈根治切除不能な甲状腺癌〉
5.1 放射性ヨウ素による治療歴のない分化型甲状腺癌患者に対する本剤の有効性及び安全性は確立していない。
5.2 臨床試験に組み入れられた患者の病理組織型等について，「17. 臨床成績」の項の内容を熟知し，本剤の有効性及び安全性を十分に理解した上で，適応患者の選択を行うこと。［17.1.1，17.1.2参照］
〈切除不能な肝細胞癌〉
5.3 局所療法（経皮的エタノール注入療法，ラジオ波焼灼療法，マイクロ波凝固療法，肝動脈塞栓療法／肝動脈化学塞栓療法，放射線療法等）の適応となる肝細胞癌患者に対する本剤の有効性及び安全性は確立していない。
5.4 臨床試験に組み入れられた患者の肝機能障害の程度等について，「17. 臨床成績」の項の内容を熟知し，本剤の

有効性及び安全性を十分に理解した上で,適応患者の選択を行うこと。[17.1.3参照]

〈切除不能な胸腺癌〉

5.5 本剤の術前補助療法としての有効性及び安全性は確立していない。

5.6「17.臨床成績」の項の内容を熟知し,本剤の有効性及び安全性を十分に理解した上で,適応患者の選択を行うこと。[17.1.4参照]

6. 用法及び用量

	効能又は効果	用法及び用量
レンビマカプセル4mg レンビマカプセル10mg	根治切除不能な甲状腺癌 切除不能な胸腺癌	通常,成人にはレンバチニブとして1日1回24mgを経口投与する。なお,患者の状態により適宜減量する。
レンビマカプセル4mg	切除不能な肝細胞癌	通常,成人には体重にあわせてレンバチニブとして体重60kg以上の場合は12mg,体重60kg未満の場合は8mgを1日1回,経口投与する。なお,患者の状態により適宜減量する。

7. 用法及び用量に関連する注意

〈効能共通〉

7.1 本剤と他の抗悪性腫瘍剤との併用について,有効性及び安全性は確立していない。

〈根治切除不能な甲状腺癌,切除不能な胸腺癌〉

7.2 副作用があらわれた場合は,症状,重症度等に応じて以下の基準を考慮して,本剤を減量,休薬又は中止すること。減量して投与を継続する場合には,1日1回20mg,14mg,10mg,8mg又は4mgに減量すること。

減量,休薬及び中止基準

副作用	程度*	処置
高血圧 [8.1,9.1.1,11.1.1参照]	収縮期血圧140mmHg以上又は拡張期血圧90mmHg以上のとき	本剤の投与を継続し,降圧剤の投与を行う。
	降圧治療にも係らず,収縮期血圧160mmHg以上又は拡張期血圧100mmHg以上のとき	収縮期血圧150mmHg以下及び拡張期血圧95mmHg以下になるまで本剤を休薬し,降圧剤による治療を行う。 本剤の投与を再開する場合,1段階減量する。
	Grade 4の副作用が発現した場合	本剤の投与を中止する。
上記以外の副作用	忍容性がないGrade 2又はGrade 3の副作用が発現した場合	本剤の投与開始前の状態又はGrade 1以下に回復するまで休薬する（悪心・嘔吐・下痢に対しては休薬の前に適切な処置を行い,コントロールできない場合に本剤を休薬すること）。 本剤の投与を再開する場合,1段階減量する。
	Grade4 の副作用が発現した場合（生命を脅かさない臨床検査値異常の場合は,Grade 3の副作用と同じ処置とする）	本剤の投与を中止する。

*：GradeはCTCAE（Common Terminology Criteria for Adverse Events）version 4.0に準じる。

〈切除不能な肝細胞癌〉

7.3 臨床試験において,中等度（Child-Pughスコア7～8）の肝機能障害を有する肝細胞癌患者に対する最大耐用量は1日1回8mgであることが確認されている。[9.3.2参照]

7.4 副作用があらわれた場合は,症状,重症度等に応じて以下の基準を考慮して,本剤を減量,休薬又は中止すること。

減量段階基準

開始用量	1段階減量	2段階減量	3段階減量
12mgを1日1回投与	8mgを1日1回投与	4mgを1日1回投与	4mgを隔日投与
8mgを1日1回投与	4mgを1日1回投与	4mgを隔日投与	投与を中止する

減量,休薬及び中止基準

副作用	程度*	処置
高血圧 [8.1,9.1.1,11.1.1参照]	収縮期血圧140mmHg以上又は拡張期血圧90mmHg以上のとき	本剤の投与を継続し,降圧剤の投与を行う。
	降圧治療にも係らず,収縮期血圧160mmHg以上又は拡張期血圧100mmHg以上のとき	収縮期血圧150mmHg以下及び拡張期血圧95mmHg以下になるまで本剤を休薬し,降圧剤による治療を行う。 本剤の投与を再開する場合,1段階減量する。
	Grade 4の副作用が発現した場合	本剤の投与を中止する。

副作用	程度*	処置
血液毒性及び蛋白尿［8.2,8.3,11.1.7,11.1.13参照］	Grade 3の副作用が発現した場合（臨床的に意義がない臨床検査値異常の場合を除く）	本剤の投与開始前の状態又はGrade 2以下に回復するまで休薬する。本剤の投与を再開する場合，初回の副作用発現時は減量せず，2回目以降の副作用発現時は1段階減量する。
	Grade 4の副作用が発現した場合	本剤の投与開始前の状態又はGrade 2以下に回復するまで休薬する。本剤の投与を再開する場合，1段階減量する。
上記以外の副作用	忍容性がないGrade 2の副作用が発現した場合	本剤の投与開始前の状態若しくはGrade 1以下に回復するまで休薬する，又は本剤の投与量を1段階減量して投与を継続する（悪心・嘔吐・下痢・甲状腺機能低下に対しては休薬又は減量の前に適切な処置を行い，コントロールできない場合に本剤を休薬又は減量すること）。本剤の投与を再開する場合，1段階減量する。
	Grade 3の副作用が発現した場合（臨床的に意義がない臨床検査値異常の場合を除く）	本剤の投与開始前の状態はGrade 1以下に回復するまで休薬する（悪心・嘔吐・下痢・甲状腺機能低下に対しては休薬の前に適切な処置を行い，コントロールできない場合に本剤を休薬すること）。本剤の投与を再開する場合，1段階減量する。
	Grade 4の副作用が発現した場合（生命を脅かさない臨床検査値異常の場合は，Grade 3の副作用と同じ処置とする）	本剤の投与を中止する。

*：GradeはCTCAE version 4.0に準じる。

8. 重要な基本的注意

〈効能共通〉

8.1 血圧の上昇が認められることがあるので，本剤の投与開始前及び投与期間中は定期的に血圧測定を行うこと。［7.2,7.4,9.1.1,11.1.1参照］

8.2 蛋白尿があらわれることがあるので，本剤の投与開始前及び投与期間中は定期的に尿蛋白を観察すること。［7.4,11.1.7参照］

8.3 骨髄抑制があらわれることがあるので，定期的に血液学的検査を行うなど，患者の状態を十分に観察すること。［7.4,11.1.13参照］

8.4 肝障害があらわれることがあるので，本剤の投与期間中は定期的に肝機能検査，血中アンモニア値の測定を行うなど，患者の状態を十分に観察すること。［11.1.5参照］

8.5 心機能不全があらわれることがあるので，本剤の投与開始前及び投与期間中は定期的に心エコー，十二誘導心電図検査等の心機能検査を行うなど，患者の状態を十分に観察すること。［11.1.10参照］

8.6 創傷治癒を遅らせる可能性があるので，外科的処置が予定されている場合には，外科的処置の前に本剤の投与を中断すること。外科的処置後の投与再開は，患者の状態に応じて判断すること。［9.1.4,11.1.15参照］

8.7 疲労，無力症，めまい，筋痙縮等があらわれることがあるので，自動車の運転等，危険を伴う機械の操作に従事する際には注意するよう患者に十分に説明すること。

8.8 定期的に血清カルシウム濃度を測定すること。［11.1.14参照］

8.9 甲状腺機能低下があらわれることがあるので，本剤の投与開始前及び投与期間中は定期的に甲状腺機能検査を行うなど，患者の状態を十分に観察すること。［11.1.17参照］

〈根治切除不能な甲状腺癌〉

8.10 本剤投与前には頸動脈・静脈等への腫瘍浸潤を十分確認するとともに，本剤の投与期間中は患者の状態の観察や瘻孔形成の有無の確認を十分に行うこと。［9.1.5,11.1.2参照］

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 高血圧症の患者

高血圧が悪化するおそれがある。[7.2,7.4,8.1,11.1.1参照]

9.1.2 脳転移のある患者

転移部位からの出血があらわれるおそれがある。[11.1.2参照]

9.1.3 血栓塞栓症又はその既往歴のある患者

血栓塞栓症が悪化又は再発するおそれがある。[11.1.3,11.1.4参照]

9.1.4 外科的処置後,創傷が治癒していない患者

創傷治癒遅延があらわれることがある。[8.6,11.1.15参照]

9.1.5 頸動脈・静脈等への腫瘍浸潤のある患者

腫瘍縮小・壊死に伴う頸動脈露出,頸動脈出血,腫瘍出血があらわれることがある。なお,甲状腺未分化癌患者では,頸動脈・静脈への腫瘍浸潤例が多いので,特に注意すること。[8.10,11.1.2参照]

9.1.6 肺転移を有する患者

気胸が発現するおそれがある。[11.1.8参照]

9.3 肝機能障害患者

9.3.1 重度の肝機能障害のある患者

減量を考慮するとともに,患者の状態をより慎重に観察し,有害事象の発現に十分注意すること。本剤の血中濃度が上昇するとの報告がある。なお,重度の肝機能障害を有する肝細胞癌患者に対する臨床試験は実施していない。[16.6.2参照]

9.3.2 中等度の肝機能障害のある肝細胞癌患者

減量を考慮するとともに,患者の状態を慎重に観察し,有害事象の発現に十分注意すること。なお,中等度（Child-Pugh スコア 9）の肝機能障害を有する肝細胞癌患者に対する臨床試験は実施していない。[7.3参照]

9.4 生殖能を有する者

妊娠可能な女性に対しては,本剤投与中及び投与終了後一定期間は適切な避妊を行うよう指導すること。[9.5,15.2.1参照]

9.5 妊婦

妊婦又は妊娠している可能性のある女性には,投与しないこと。外国臨床試験において,本剤の投与終了後に妊娠が判明し,自然流産となったことが報告されている。ラット及びウサギにおいて胚毒性・催奇形性が報告されている。なお,ラットでは臨床曝露量以下で認められた。[2.2,9.4参照]

9.6 授乳婦

授乳しないことが望ましい。ラットにおいて乳汁中へ移行することが報告されている。

9.7 小児等

小児等を対象とした臨床試験は実施していない。幼若ラットを用いた反復投与毒性試験において,切歯の異形成及び骨の短小など成長を阻害する影響が認められ,成熟ラットに比較し,致死量での死亡がより早期にみられた。[15.2.2参照]

9.8 高齢者

患者の状態を十分に観察し,慎重に投与すること。一般に高齢者では生理機能が低下していることが多く,副作用があらわれやすい。

10. 相互作用

本剤はP糖蛋白（P-gp）及びCYP3Aの基質となる。[16.4参照]

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
P-gp阻害剤 ケトコナゾール イトラコナゾール リファンピシン アミオダロン クラリスロマイシン シクロスポリン キニジン ベラパミル等 [16.7.1参照]	本剤の血中濃度が上昇する可能性がある。	これらの薬剤が消化管のP-gp活性を阻害することによる。
CYP3A／P-gp誘導剤 リファンピシン フェニトイン カルバマゼピン セイヨウオトギリソウ（St. John' s Wort,セント・ジョーンズ・ワート）含有食品等 [16.7.2参照]	本剤の血中濃度が低下する可能性がある。	これらの薬剤がCYP3A及びP-gp等を誘導することによる。

11. 副作用

次の副作用があらわれることがあるので,観察を十分に行い,異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 高血圧

高血圧（56.0%）,高血圧クリーゼ（頻度不明）等があらわれることがある。必要に応じて降圧剤の投与を行うなど適切な処置を行うこと。重症,持続性あるいは通常の降圧治療でコントロールできない高血圧があらわれた場合には,減量,休薬又は投与を中止すること。また,高血圧クリーゼがあらわれた場合には投与を中止し,適切な処置を行うこと。[7.2,7.4,8.1,9.1.1参照]

11.1.2 出血（16.2%）

鼻出血,血尿,喀血,肺出血,消化管出血,脳出血,腫瘍出血等の出血があらわれることがある。また,甲状腺癌患者において,腫瘍縮小・壊死に伴う頸動脈露出,頸動脈出血,腫瘍出血があらわれることがある。頸動脈露出部位や皮膚瘻形成部位より大量出血した例が認められており,気管瘻や食道瘻を形成している場合には,喀血や吐血のおそれがある。重篤な出血があらわれた場合には,投与を中止し,適切な処置を行うこと。[8.10,9.1.2,9.1.5参照]

11.1.3 動脈血栓塞栓症（2.2%）
心筋梗塞,脳血管発作,脾臓梗塞等の動脈血栓塞栓症があらわれることがある。[9.1.3参照]

11.1.4 静脈血栓塞栓症（2.2%）
肺塞栓症,深部静脈血栓症,網膜静脈血栓症,門脈血栓症等の静脈血栓塞栓症があらわれることがある。[9.1.3 参照]

11.1.5 肝障害
AST,ALT 等の上昇を伴う肝障害（18.2%）,アルブミン低下（6.9%）,肝性脳症（2.3%）,肝不全（0.7%）等があらわれることがある。[8.4参照]

11.1.6 急性胆嚢炎（0.5%）
無石胆嚢炎を含む急性胆嚢炎があらわれることがあり,胆嚢穿孔に至った例も報告されている。

11.1.7 腎障害
蛋白尿（32.2%）,腎機能障害（1.3%）,腎不全（0.4%）,ネフローゼ症候群（0.2%）等があらわれることがある。[7.4,8.2参照]

11.1.8 消化管穿孔,瘻孔形成,気胸
腸管穿孔（0.1%）,痔瘻（0.1%）,腸膀胱瘻（0.1%）,気胸（0.2%）等があらわれることがある。[9.1.6 参照]

11.1.9 可逆性後白質脳症症候群（0.2%）
痙攣,頭痛,錯乱,視覚障害,皮質盲等が認められた場合には投与を中止し,血圧のコントロールを含め,適切な処置を行うこと。

11.1.10 心障害
心電図 QT 延長（5.1%）,駆出率減少（1.6%）,心房細動・粗動（0.5%）,心不全（0.4%）等があらわれることがある。[8.5参照]

11.1.11 手足症候群（33.3%）

11.1.12 感染症
気道感染（1.7%）,肺炎（1.8%）,敗血症（0.6%）等があらわれることがある。

11.1.13 骨髄抑制
血小板減少（20.1%）,白血球減少（9.1%）,好中球減少（9.0%）,リンパ球減少（3.6%）,貧血（4.3%）等があらわれることがある。感染症,出血傾向等の発現に留意すること。[7.4,8.3参照]

11.1.14 低カルシウム血症（3.2%）
副甲状腺機能低下症の既往歴がある患者で高発現したことが報告されている。観察を十分に行い,異常が認められた場合には,血清カルシウム濃度を確認し,カルシウム剤やビタミン D 製剤の投与等の適切な処置を行うこと。[8.8参照]

11.1.15 創傷治癒遅延
治癒不良（0.4%）,創離開（0.1%）があらわれることがある。創傷治癒遅延があらわれた場合には,創傷が治癒するまで本剤の投与を中止すること。[8.6,9.1.4 参照]

11.1.16 間質性肺疾患（0.4%）

11.1.17 甲状腺機能低下（18.7%）[8.9 参照]

11.2 その他の副作用

	30%以上	10～30%未満	5～10%未満	5%未満
消化器	下痢（42.1%）	悪心,口内炎,嘔吐,腹痛	口腔咽頭痛,口腔内乾燥,便秘,消化不良	嚥下障害,血中リパーゼの上昇,舌痛,血中アミラーゼの上昇,膵炎
全身症状	疲労	無力症,浮腫	発熱,疼痛	創傷
精神神経系		発声障害,頭痛	味覚異常,めまい	睡眠障害
代謝	食欲減退（37.6%）			脱水,血中コレステロールの上昇,血中カリウムの低下
筋骨格系		関節痛,筋肉痛		背部痛,筋痙縮,四肢痛
呼吸器				咳嗽
皮膚		発疹	脱毛症,皮膚病変,皮膚乾燥,皮膚炎	瘙痒症
その他		体重減少		CRP の上昇

14. 適用上の注意

14.1 薬剤交付時の注意

14.1.1 PTP 包装の薬剤は PTP シートから取り出して服用するよう指導すること。PTP シートの誤飲により,硬い鋭角部が食道粘膜へ刺入し,更には穿孔をおこして縦隔洞炎等の重篤な合併症を併発することがある。

14.1.2 本剤は湿気に不安定なため,服用直前に PTP シートから取り出すよう指導すること。

15. その他の注意

15.2 非臨床試験に基づく情報

15.2.1 反復投与毒性試験（ラット,イヌ及びサル）の病理組織学的検査において,精巣（精上皮細胞の減少）及び卵巣（卵胞閉鎖）の変化が認められており,生殖機能に障害を及ぼす可能性が示唆されている。[9.4参照]

15.2.2 反復投与毒性試験において,ラット及びサル（成長板が残存する場合）に骨端軟骨成長板の肥厚が認められた。[9.7参照]

15.2.3 ラット及びイヌを用いた反復投与毒性試験において,副腎の出血（イヌ）及び副腎皮質壊死（ラット）が認められた。

16. 薬物動態

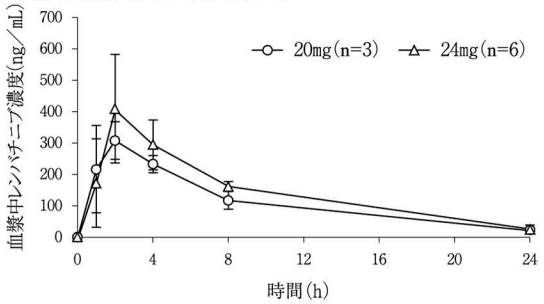
16.1 血中濃度

16.1.1 反復投与

(1) 固形がん患者

日本人固形がん患者 9 例に本剤 20mg[注)] 又は 24mg[注)] を 1 日 1 回経口投与したときの,初回投与時の血漿中レンバチニブ濃度推移を以下の図に示した。初回投与時及び 1 日 1 回反復投与した 15 日目の薬物動態パラメータを表に示

した。レンバチニブの C_{max} 及び AUC $_{(0\text{-}24h)}$ には用量比例性が認められた。反復投与 15 日後の薬物動態は，初回投与の結果から推測可能であり，C_{max} 及び AUC $_{(0\text{-}24h)}$ の累積係数の平均値は，20mg 投与群で 1.27 及び 1.44，24mg 投与群で 1.42 及び 1.32 であった[1]。



日本人固形がん患者に本剤を経口投与したときの血漿中レンバチニブ濃度（1 日目）　　（平均値±標準偏差）

日本人固形がん患者に本剤を反復経口投与したときの血漿中レンバチニブの薬物動態パラメータ

		C_{max} (ng／mL)	AUC $_{(0\text{-}24h)}$ (ng・h／mL)	t_{max}[c] (h)
20mg／日[注]	1 日目 (n=3)	309±60.1	2500±647	2 (2-2)
	15 日目 (n=3)	415±267	3690±1790	2 (2-2)
24mg／日[注]	1 日目 (n=6)	418±167	3150±352[a]	2 (2-4)
	15 日目 (n=6)	518±209	4140±1350[b]	2 (2-4)

平均値±標準偏差
a：n=4，b：n=5，c：中央値（最小値-最大値）

注）本剤の承認された用法及び用量は，「根治切除不能な甲状腺癌」，「切除不能な胸腺癌」は 24mg／日，「切除不能な肝細胞癌」は体重 60kg 以上の場合は 12mg／日，体重 60kg 未満の場合は 8mg／日である。

（2）肝細胞癌患者

国際共同第Ⅲ相試験において，日本人及び外国人肝細胞癌患者に開始用量として本剤 8mg（体重 60kg 未満）又は 12mg（体重 60kg 以上）を 1 日 1 回反復経口投与したときのレンバチニブの血漿中トラフ濃度を開始用量ごとに表に示した。開始用量 8mg とした場合と 12mg とした場合との間でレンバチニブの血漿中トラフ濃度に明確な差異は認められなかった。

国際共同第Ⅲ相試験におけるレンバチニブの血漿中トラフ濃度

測定時点	開始用量			
	8mg		12mg	
	N	C_{trough} (ng/mL)	N	C_{trough} (ng/mL)
第 1 サイクル第 15 日目	136	37.70±25.58	299	40.83±34.97
第 2 サイクル第 1 日目	128	36.80±33.01	275	37.30±28.19
第 3 サイクル第 1 日目	62	32.46±33.83	139	40.95±40.39
第 4 サイクル第 1 日目	65	29.74±28.01	136	38.25±36.82
第 5 サイクル第 1 日目	65	36.07±40.59	129	34.02±27.09
第 6 サイクル第 1 日目	59	38.73±50.49	128	32.94±25.89

平均値±標準偏差

16.2 吸収

16.2.1 食事の影響

外国人健康成人 16 例に本剤 10mg[注] をクロスオーバー法により，空腹時又は食後（高脂肪食）に単回経口投与した。空腹時と比較して，食後投与の C_{max} 及び AUC $_{(0\text{-}inf)}$ の臨床的に意味のある変化は認められなかった[2]。

注）本剤の承認された用法及び用量は，「根治切除不能な甲状腺癌」，「切除不能な胸腺癌」は 24mg／日，「切除不能な肝細胞癌」は体重 60kg 以上の場合は 12mg／日，体重 60kg 未満の場合は 8mg／日である。

16.3 分布

レンバチニブの蛋白結合率は 97.9～98.6%（*in vitro* 試験），96.6～98.2%（日本人固形がん患者）であった。主な結合蛋白はアルブミンであった[3),4)]。

16.4 代謝

本剤は主にアルデヒドオキシダーゼ，CYP3A により代謝され，グルタチオンが非酵素的に結合する[5)]（*in vitro* 試験）。

外国人固形がん患者 6 例に ^{14}C 標識-レンバチニブ 24mg を単回経口投与した結果，血漿中の放射能の大部分は未変化体であった[6)]。［10. 参照］

16.5 排泄

外国人固形がん患者 6 例に ^{14}C 標識-レンバチニブ 24mg を単回経口投与したとき，投与 10 日後までに投与した総放射能の 25%が尿中に，64%が糞中に回収された。また，尿及び糞中に排泄された未変化体は投与量のそれぞれ 0.38%及び 2.5%であった。未変化体の血漿中消失半減期は，約 35.4 時間であった[6)]。

16.6 特定の背景を有する患者

16.6.1 腎機能障害患者

レンバチニブ 24mg を外国人の腎機能が正常な被験者（クレアチニンクリアランス［CL_{cr}］：≥90mL／min，n＝8），軽度（CL_{cr}：60～89mL／min），中等度（CL_{cr}：30～59mL／min）及び重度（CL_{cr}：15～29mL／min）の腎機能障害を有する被験者（各 6 例）に単回投与した。

軽度，中等度及び重度の腎機能障害を有する被験者における C_{max} は健康被験者のそれぞれ 1.0，0.61 及び 0.87 倍であり，AUC $_{(0\text{-}inf)}$ は，健康被験者のそれぞれ 1.0，0.90 及び 1.2 倍であった[7)]。

16.6.2 肝機能障害患者

本剤 10mg を外国人の肝機能が正常な被験者（n＝8），軽度（Child-Pugh 分類 A）及び中等度（Child-Pugh 分類 B）の肝機能障害を有する被験者（各 6 例）に単回投与した。また，本剤 5mg を外国人の重度（Child-Pugh 分類 C）の肝機能障害を有する被験者（6 例）に単回投与した。

軽度，中等度及び重度の肝機能障害を有する被験者における投与量補正した C_{max} は健康被験者のそれぞれ 0.97，0.79 及び 1.1 倍であり，投与量補正した $AUC_{(0-inf)}$ は健康被験者のそれぞれ 1.2，1.1 及び 1.8 倍であった[8]。［9.3.1 参照］

16.7 薬物相互作用

16.7.1 ケトコナゾール

外国人健康成人 16 例に，レンバチニブをケトコナゾールと併用投与した際の C_{max} 及び $AUC_{(0-inf)}$ は，レンバチニブをプラセボと併用した場合と比べてそれぞれ 19%及び 15%上昇した[9]。［10.2 参照］

16.7.2 リファンピシン

外国人健康成人 15 例に，レンバチニブをリファンピシンと単回同時併用投与した際の C_{max} 及び $AUC_{(0-inf)}$ は，レンバチニブを単独投与した場合と比べてそれぞれ 33%及び 31%上昇した。リファンピシンの反復投与後に，レンバチニブをリファンピシンと同時併用投与した際の C_{max} 及び $AUC_{(0-inf)}$ は，レンバチニブをリファンピシンと単回同時併用投与した場合と比べてそれぞれ 24%及び 37%減少した[10]。［10.2 参照］

16.7.3 その他

レンバチニブは，乳癌耐性蛋白（BCRP）の基質となること，及び UGT1A1 を阻害すること（IC_{50} 値：10.6μmol／L）が示されている[5),11)]（*in vitro*）。

17. 臨床成績

17.1 有効性及び安全性に関する試験

〈根治切除不能な甲状腺癌〉

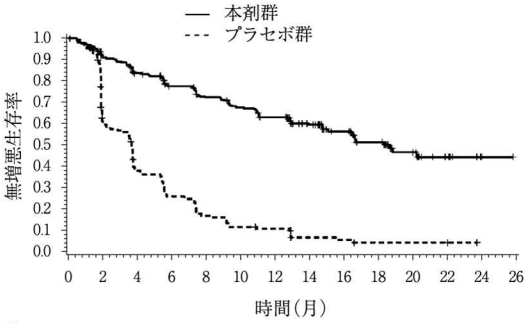
17.1.1 国際共同第Ⅲ相試験

放射性ヨウ素治療抵抗性・難治性（ヨウ素の取込みが認められない，放射性ヨウ素治療後 12 ヵ月以内に病勢の進行が認められた，又は累積線量が 600mCi［22GBq］を超える放射性ヨウ素治療を受けている）の分化型甲状腺癌患者（乳頭癌，濾胞癌，Hürthle 細胞癌，及び低分化癌）392 例（本剤群 261 例［日本人患者 30 例］，プラセボ群 131 例［日本人患者 10 例］）において，プラセボを比較対照として本剤 24mg を 1 日 1 回投与した場合の有効性と安全性を評価した。

なお，心不全の既往，心血管系疾患の既往，不整脈，出血性疾患，血栓性疾患又は活動性の喀血がある患者，抗凝固剤を投与されている患者，3 週間以内に大手術を受けた患者，及び QTc 間隔が 480ms 超の患者は除外された。主要評価項目である無増悪生存期間（PFS）の中央値は本剤投与群で 18.3 ヵ月，プラセボ群で 3.6 ヵ月であり，本剤はプラセボ群に対して PFS を有意に延長した（P＜0.0001；層別 Log Rank 検定，ハザード比：0.21，99%信頼区間：0.14，0.31）[12)]。

無作為化期において，本剤が投与された 261 例（日本人 30 例を含む）中 254 例（97.3%）に副作用が認められた。主な副作用は，高血圧 177 例（67.8%），下痢 159 例（60.9%），食欲減退 135 例（51.7%），体重減少 123 例（47.1%），悪心 107 例（41.0%），疲労 104 例（39.8%），口内炎 96 例（36.8%），蛋白尿 85 例（32.6%），手掌・足底発赤知覚不全症候群 83 例（31.8%）等であった。［5.2 参照］

無増悪生存期間のKaplan-Meier曲線



at risk数

本剤群：	261	225	198	176	159	148	136	92	66	44	24	11	3	0
プラセボ群：	131	71	43	29	19	13	11	5	4	2	2	2	0	0

17.1.2 国内第Ⅱ相試験

甲状腺癌（放射性ヨウ素治療抵抗性・難治性の分化型甲状腺癌［ヨウ素の取込みが認められない，放射性ヨウ素治療後 12 ヵ月以内に病勢の進行が認められた，又は累積線量が 600mCi［22GBq］を超える放射性ヨウ素治療を受けている］，切除不能の甲状腺髄様癌及び切除不能の甲状腺未分化癌）43 例に対し，本剤 24mg を 1 日 1 回投与した場合の安全性と有効性を評価した。主要評価項目を安全性とし，副次評価項目として有効性を評価した。有効性解析対象例はそれぞれ 23 例，8 例及び 11 例であった[13)]。

43 例中全例（100%）に副作用が認められた。主な副作用は，高血圧 37 例（86.0%），手掌・足底発赤知覚不全症候群 34 例（79.1%），食欲減退 33 例（76.7%），疲労 31 例（72.1%），蛋白尿 25 例（58.1%），口内炎 24 例（55.8%）及び下痢 22 例（51.2%）であった。［5.2 参照］

n（%）	分化型甲状腺癌（N=23）	甲状腺髄様癌（N=8）	甲状腺未分化癌（N=11）
完全奏効（CR）	0	0	0
部分奏効（PR）	16（69.6）	1（12.5）	3（27.3）
安定（SD）	7（30.4）	7（87.5）	7（63.6）
病勢進行（PD）	0	0	1（9.1）

〈切除不能な肝細胞癌〉

17.1.3 国際共同第Ⅲ相試験

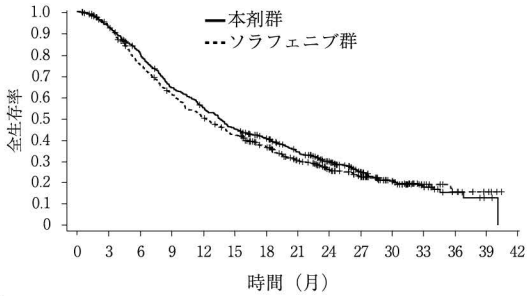
全身化学療法歴のない Child-Pugh 分類 A の切除不能な肝細胞癌患者 954 例（本剤群 478 例［日本人患者 81 例］，ソラフェニブ群 476 例［日本人患者 87 例］）において，ソ

ラフェニブを比較対照として本剤の有効性と安全性を評価した。本剤群では体重 60kg 以上の患者には本剤 12mg を 1 日 1 回,体重 60kg 未満の患者には本剤 8mg を 1 日 1 回投与した。

なお,局所療法（経皮的エタノール注入療法,ラジオ波焼灼療法,マイクロ波凝固療法,肝動脈塞栓療法／肝動脈化学塞栓療法,放射線療法等）の適応となる患者は除外された。主要評価項目である全生存期間（OS）において,ハザード比（95%信頼区間）は 0.92（0.79, 1.06）であり,95%信頼区間の上限が事前に規定した非劣性マージンの 1.08 を下回ったことから,本剤群のソラフェニブ群に対する非劣性が統計学的に検証された（OS の中央値：本剤群 13.6 ヵ月,ソラフェニブ群 12.3 ヵ月）[14]。

本剤が投与された 476 例（日本人 81 例を含む）中 447 例（93.9%）に副作用が認められた。主な副作用は,高血圧 189 例（39.7%）,下痢 143 例（30.0%）,手掌・足底発赤知覚不全症候群 126 例（26.5%）,食欲減退 122 例（25.6%）,蛋白尿 114 例（23.9%）,疲労 111 例（23.3%）,発声障害 104 例（21.8%）等であった。[5.4 参照]

全生存期間のKaplan-Meier曲線



at risk数

本剤群：	478	436	374	297	253	207	178	140	102	67	40	21	8	2	0
ソラフェニブ群：	476	440	348	282	230	192	156	116	83	57	33	16	8	4	0

〈切除不能な胸腺癌〉

17.1.4 国内第Ⅱ相試験

プラチナ製剤を含む化学（放射線）療法歴を有する切除不能な胸腺癌患者[注)] 42 例に対し,本剤 24mg を 1 日 1 回投与した場合の安全性と有効性を評価した。主要評価項目である奏効率（RECIST ガイドライン 1.1 版に基づく中央判定による CR 又は PR）は 38.1%（90%信頼区間：25.6, 52.0）であった。[15] また安全性評価対象 42 例中全例（100%）に副作用が認められた。主な副作用は,高血圧 37 例（88.1%）,蛋白尿 30 例（71.4%）,手掌・足底発赤知覚不全症候群 29 例（69.0%）,甲状腺機能低下症 27 例（64.3%）,血小板数減少 22 例（52.4%）及び下痢 21 例（50.0%）であった。[5.6 参照]

注）正岡-古賀分類Ⅲa～Ⅳb 又は術後再発の患者が臨床試験に組入れられた。

n（%）	切除不能な胸腺癌 （N=42）
完全奏効（CR）	0
部分奏効（PR）	16（38.1）
安定（SD）	24（57.1）
病勢進行（PD）	2（4.8）

18. 薬効薬理

18.1 作用機序

レンバチニブは,腫瘍血管新生及び腫瘍増殖等に関与する,血管内皮増殖因子（VEGF）受容体（VEGFR1-3）,線維芽細胞増殖因子（FGF）受容体（FGFR1-4）,血小板由来増殖因子受容体（PDGFR）α,幹細胞因子受容体（KIT）,Rearranged During Transfection がん原遺伝子（RET）等の受容体チロシンキナーゼを阻害した。また,レンバチニブは,VEGF 及び FGF によって誘導される血管内皮細胞の血管様管腔構造の形成を阻害した[16),17)]。

18.2 抗腫瘍効果

レンバチニブは,ヒト甲状腺乳頭癌由来細胞株（K1）,ヒト甲状腺濾胞癌由来細胞株（RO82-W-1）,ヒト甲状腺髄様癌由来細胞株（TT）,ヒト甲状腺未分化癌由来細胞株（8305C）,ヒト甲状腺由来扁平上皮癌由来細胞株（SW579）,ヒト肝細胞癌由来細胞株（Hep 3B2.1-7,LIXC-012 及び PLC/PRF/5）,肝細胞癌患者由来腫瘍組織片（LI0050 及び LI0334）及びヒト胸腺癌由来細胞株（Ty-82）を移植したマウスにおいて,腫瘍増殖抑制作用を示した[18),19),20)]。

19. 有効成分に関する理化学的知見

一般名：レンバチニブメシル酸塩（Lenvatinib Mesilate）

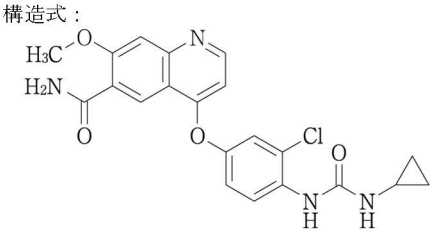
化学名：4-｛3-Chloro-4-［(cyclopropylcarbamoyl) amino］phenoxy｝-7-methoxyquinoline-6-carboxamide monomethanesulfonate

分子式：$C_{21}H_{19}ClN_4O_4 \cdot CH_4O_3S$

分子量：522.96

性　状：レンバチニブメシル酸塩は白色～うすい帯赤黄色の粉末である。
本品は水,メタノール又は N-メチルピロリドンに溶けにくく,エタノール（99.5）にほとんど溶けない。

構造式：



融点：221～224℃（分解）

分配係数：log P＝3.30（1-オクタノール／水系）

21. 承認条件

医薬品リスク管理計画を策定の上,適切に実施すること。

22. 包装

〈レンビマカプセル 4mg〉

20 カプセル［10 カプセル（PTP）×2］

〈レンビマカプセル 10mg〉

20 カプセル［10 カプセル（PTP）×2］

23. 主要文献

1) 社内資料：固形がん患者を対象とした臨床第 I 相試験（国内試験）（2015 年 3 月 26 日承認,CTD 2.7.6.6）［LEN-0001］
2) Shumaker, R. et al. : Int. J. Clin. Pharmacol. Ther., 2014 ; 52 (4) : 284-291［LEN-0002］
3) 社内資料：血漿蛋白結合率（*in vitro*）（2015 年 3 月 26 日承認,CTD 2.6.4.4.2）［LEN-0005］
4) Yamada, K. et al. : Clin. Cancer Res., 2011 ; 17 (8) : 2528-2537［LEN-0006］
5) 社内資料：代謝（*in vitro* 及び *in vivo*）（2015 年 3 月 26 日承認,CTD 2.7.2.3.2.3）［LEN-0003］
6) 社内資料：がん患者を対象としたマスバランス試験（外国試験）（2015 年 3 月 26 日承認,CTD 2.7.2.2.2.2.1,2.7.6.9）［LEN-0004］
7) 社内資料：腎機能障害患者を対象とした臨床薬理試験（外国試験）（2015 年 3 月 26 日承認,CTD 2.7.2.2.2.3.2）［LEN-0009］
8) 社内資料：肝機能障害患者を対象とした臨床薬理試験（外国試験）（2015 年 3 月 26 日承認,CTD 2.7.2.2.2.3.1）［LEN-0008］
9) 社内資料：ケトコナゾールとの薬物相互作用試験（外国試験）（2015 年 3 月 26 日承認,CTD 2.7.2.2.2.3.3.1）［LEN-0010］
10) 社内資料：リファンピシンとの薬物相互作用試験（外国試験）（2015 年 3 月 26 日承認,CTD 2.7.2.2.2.3.3.2）［LEN-0011］
11) 社内資料：トランスポーター（*in vitro*）（2015 年 3 月 26 日承認,CTD 2.6.4.8.1）［LEN-0018］
12) 社内資料：^{131}I 難治性の甲状腺分化癌患者を対象とした臨床第Ⅲ相試験（国際共同試験）（2015 年 3 月 26 日承認,CTD 2.7.6.17）［LEN-0012］
13) 社内資料：進行性甲状腺癌患者を対象とした臨床第Ⅱ相試験（国内試験）（2015 年 3 月 26 日承認,CTD 2.7.6.16）［LEN-0014］
14) 社内資料：切除不能な肝細胞癌患者を対象とした臨床第Ⅲ相試験（国際共同試験）（2018 年 3 月 23 日承認,CTD 2.7.6.1）［LEN-0168］
15) 社内資料：NCCH1508 試験（20xx 年 x 月 x 日承認,CTD 2.7.6.1）［LEN-xxxx］
16) 社内資料：*In vitro* 薬理試験（1）（2015 年 3 月 26 日承認,CTD 2.6.2.2.1）［LEN-0015］
17) 社内資料：*In vitro* 薬理試験（2）（2018 年 3 月 23 日承認,CTD 2.6.2.2.1）［LEN-0169］
18) 社内資料：*In vivo* 薬理試験（1）（2015 年 3 月 26 日承認,CTD 2.6.2.2.2）［LEN-0016］
19) 社内資料：*In vivo* 薬理試験（2）（2018 年 3 月 23 日承認,CTD 2.6.2.2.2）［LEN-0170］
20) 社内資料：効力を裏付ける試験（20xx 年 x 月 x 日承認,CTD 2.6.2.2）［LEN-xxxx］

24. 文献請求先及び問い合わせ先

エーザイ株式会社　hhc ホットライン
〒112-8088　東京都文京区小石川 4-6-10
フリーダイヤル　0120-419-497

26. 製造販売業者等

26.1 製造販売元

エーザイ株式会社
東京都文京区小石川4-6-10

26.2 販売提携

MSD株式会社
東京都千代田区九段北1-13-12

1.8.2 効能・効果，用法・用量及びその設定根拠

1.8.2.1 効能・効果及びその設定根拠

【効能・効果】

切除不能な胸腺癌

【効能・効果の設定根拠】

NCCH1508 試験は，1 レジメン以上の化学療法歴を有する切除不能又は再発胸腺癌患者を対象とし，主要評価項目を中央判定の ORR とした本薬の有効性及び安全性を評価する試験である。本薬の用法・用量は，固形がんの推奨用量であり，105 試験で日本人における忍容性が確認された 1 日 1 回 24 mg 連続投与を用いて実施された。

本試験において，主要評価項目である中央判定による ORR は 38.1%（95%CI：23.6% – 54.4%）であった。事前に設定した閾値奏効率 10%を ORR の 90%信頼区間の下限が上回り，臨床的に意義のある抗腫瘍効果が確認された。そのため効能・効果を切除不能な胸腺癌と設定した。

1.8.2.2 効能・効果に関連する使用上の注意及びその設定根拠

【効能・効果に関連する使用上の注意】

（1）本剤の術前補助療法としての有効性及び安全性は確立していない。

（2）「17.臨床成績」の項の内容を熟知し，本剤の有効性及び安全性を十分に理解した上で，適応患者の選択を行うこと。［17.1.4 参照］

【効能・効果に関連する使用上の注意の設定根拠】

（1）レンバチニブを術前補助療法として推奨できる根拠はないため，設定した。

（2）切除不能な胸腺癌のうち，化学療法歴のない胸腺癌患者における本薬の使用経験がないこと，対照群を設定しない試験における少数例のデータであることから，本薬の適応となる患者の選択に際して注意喚起及び情報提供する必要があると考え，設定した。

1.8.2.3 用法・用量及びその設定根拠

【用法・用量】

通常，成人にはレンバチニブとして 1 日 1 回 24mg を経口投与する。なお，患者の状態により適宜減量する。

【用法・用量の設定根拠】

本薬の用法・用量は，既承認である根治切除不能な甲状腺癌と同一の用法・用量を用いて実施した NCCH1508 試験で有効性及び安全性が確認されたため，設定した。

1.8.2.4 用法及び用量に関連する注意

【用法及び用量に関連する注意】（下線部を変更）

〈効能共通〉
本剤と他の抗悪性腫瘍剤との併用について，有効性及び安全性は確立していない。

〈根治切除不能な甲状腺癌，切除不能な胸腺癌〉
副作用があらわれた場合は，症状，重症度等に応じて以下の基準を考慮して，本剤を減量，休薬又は中止すること。減量して投与を継続する場合には，1 日 1 回 20mg，14mg，10mg，8mg 又は 4mg に減量すること。

減量，休薬及び中止基準

副作用	程度*	処置
高血圧［8.1，9.1.1，11.1.1 参照］	収縮期血圧 140mmHg 以上又は拡張期血圧 90mmHg 以上のとき	本剤の投与を継続し，降圧剤の投与を行う。
	降圧治療にも係らず，収縮期血圧 160mmHg 以上又は拡張期血圧 100mmHg 以上のとき	収縮期血圧 150mmHg 以下及び拡張期血圧 95mmHg 以下になるまで本剤を休薬し，降圧剤による治療を行う。 本剤の投与を再開する場合，1 段階減量する。
	Grade 4 の副作用が発現した場合	本剤の投与を中止する。
上記以外の副作用	忍容性がない Grade 2 又は Grade 3 の副作用が発現した場合	本剤の投与開始前の状態又は Grade 1 以下に回復するまで休薬する（悪心・嘔吐・下痢に対しては休薬の前に適切な処置を行い，コントロールできない場合に本剤を休薬すること）。 本剤の投与を再開する場合，1 段階減量する。
	Grade4 の副作用が発現した場合 （生命を脅かさない臨床検査値異常の場合は，Grade 3 の副作用と同じ処置とする）	本剤の投与を中止する。

*：Grade は CTCAE（Common Terminology Criteria for Adverse Events）version 4.0 に準じる。

【用法・用量に関する注意の設定根拠】

切除不能な胸腺癌を対象とした臨床試験で用いた休薬・減量基準は，甲状腺癌を対象とした臨床試験で用いた基準と同様であったため，根治切除不能な甲状腺癌の減量，休薬及び中止基準の項目に切除不能な胸腺癌を追記した。

1.8.3 使用上の注意（案）及びその設定根拠

使用上の注意案及びその設定根拠を以下に示す。なお，改訂前（現行）はレンビマカプセル 4mg，レンビマカプセル 10mg 添付文書（2019 年 12 月改訂，第 1 版）の「使用上の注意」を示し，改訂後の変更箇所には下線を付した。

改訂前（現行）	改訂後（下線部：変更箇所）	設定根拠
1. 警告 本剤は，緊急時に十分対応できる医療施設において，がん化学療法に十分な知識・経験を持つ医師のもとで，本剤の使用が適切と判断される症例についてのみ投与すること。また，治療開始に先立ち，患者又はその家族に本剤の有効性及び危険性を十分説明し，同意を得てから投与すること。	1. 警告 本剤は，緊急時に十分対応できる医療施設において，がん化学療法に十分な知識・経験を持つ医師のもとで，本剤の使用が適切と判断される症例についてのみ投与すること。また，治療開始に先立ち，患者又はその家族に本剤の有効性及び危険性を十分説明し，同意を得てから投与すること。	変更なし
2. 禁忌（次の患者には投与しないこと） 2.1 本剤の成分に対し過敏症の既往歴のある患者 2.2 妊婦又は妊娠している可能性のある女性［9.5 参照］	2. 禁忌（次の患者には投与しないこと） 2.1 本剤の成分に対し過敏症の既往歴のある患者 2.2 妊婦又は妊娠している可能性のある女性［9.5 参照］	変更なし
8. 重要な基本的注意 〈効能共通〉 8.1 血圧の上昇が認められることがあるので，本剤の投与開始前及び投与期間中は定期的に血圧測定を行うこと。［7.2，7.4，9.1.1，11.1.1 参照］ 8.2 蛋白尿があらわれることがあるので，本剤の投与開始前及び投与期間中は定期的に尿蛋白を観察すること。［7.4，11.1.7 参照］ 8.3 骨髄抑制があらわれることがあるので，定期的に血液学的検査を行うなど，患者の状態を十分に観察すること。［7.4，11.1.13 参照］ 8.4 肝障害があらわれることがあるので，本剤の投与期間中は定期的に肝機能検査，血中アンモニア値の測定を行うなど，患者の状態を十分に観察すること。［11.1.5 参照］ 8.5 心機能不全があらわれることがあるので，本剤の投与開始前及び投与期間中は定期的に心エコー，十二誘導心電図検査等の心機能検査を行うなど，患者の状態を十分に観察すること。［11.1.10 参照］	8. 重要な基本的注意 〈効能共通〉 8.1 血圧の上昇が認められることがあるので，本剤の投与開始前及び投与期間中は定期的に血圧測定を行うこと。［7.2，7.4，9.1.1，11.1.1 参照］ 8.2 蛋白尿があらわれることがあるので，本剤の投与開始前及び投与期間中は定期的に尿蛋白を観察すること。［7.4，11.1.7 参照］ 8.3 骨髄抑制があらわれることがあるので，定期的に血液学的検査を行うなど，患者の状態を十分に観察すること。［7.4，11.1.13 参照］ 8.4 肝障害があらわれることがあるので，本剤の投与期間中は定期的に肝機能検査，血中アンモニア値の測定を行うなど，患者の状態を十分に観察すること。［11.1.5 参照］ 8.5 心機能不全があらわれることがあるので，本剤の投与開始前及び投与期間中は定期的に心エコー，十二誘導心電図検査等の心機能検査を行うなど，患者の状態を十分に観察すること。［11.1.10 参照］	8.9 甲状腺癌承認時，肝細胞癌効能追加及び胸腺癌効能追加時の臨床試験結果の安全性評価結果に基づき甲状腺機能低下に関する防止策等の注意を記載した。

改訂前（現行）	改訂後（下線部：変更箇所）	設定根拠
8.6 創傷治癒を遅らせる可能性があるので，外科的処置が予定されている場合には，外科的処置の前に本剤の投与を中断すること。外科的処置後の投与再開は，患者の状態に応じて判断すること。[9.1.4，11.1.15 参照] 8.7 疲労，無力症，めまい，筋痙縮等があらわれることがあるので，自動車の運転等，危険を伴う機械の操作に従事する際には注意するよう患者に十分に説明すること。 8.8 定期的に血清カルシウム濃度を測定すること。[11.1.14 参照] 8.9 定期的に甲状腺刺激ホルモン濃度を測定すること。 〈根治切除不能な甲状腺癌〉 8.10 本剤投与前には頸動脈・静脈等への腫瘍浸潤を十分確認するとともに，本剤の投与期間中は患者の状態の観察や瘻孔形成の有無の確認を十分に行うこと。[9.1.5，11.1.2 参照]	8.6 創傷治癒を遅らせる可能性があるので，外科的処置が予定されている場合には，外科的処置の前に本剤の投与を中断すること。外科的処置後の投与再開は，患者の状態に応じて判断すること。[9.1.4，11.1.15 参照] 8.7 疲労，無力症，めまい，筋痙縮等があらわれることがあるので，自動車の運転等，危険を伴う機械の操作に従事する際には注意するよう患者に十分に説明すること。 8.8 定期的に血清カルシウム濃度を測定すること。[11.1.14 参照] 8.9 甲状腺機能低下があらわれることがあるので，本剤の投与開始前及び投与期間中は定期的に甲状腺機能検査を行うなど，患者の状態を十分に観察すること。[11.1.17 参照] 〈根治切除不能な甲状腺癌〉 8.10 本剤投与前には頸動脈・静脈等への腫瘍浸潤を十分確認するとともに，本剤の投与期間中は患者の状態の観察や瘻孔形成の有無の確認を十分に行うこと。[9.1.5，11.1.2 参照]	

改訂前（現行）	改訂後（下線部：変更箇所）	設定根拠
9. 特定の背景を有する患者に関する注意 **9.1 合併症・既往歴等のある患者** 9.1.1 高血圧症の患者 高血圧が悪化するおそれがある。［7.2，7.4，8.1，11.1.1 参照］ **9.1.2 脳転移のある患者** 転移部位からの出血があらわれるおそれがある。［11.1.2 参照］ **9.1.3 血栓塞栓症又はその既往歴のある患者** 血栓塞栓症が悪化又は再発するおそれがある。［11.1.3，11.1.4 参照］ **9.1.4 外科的処置後，創傷が治癒していない患者** 創傷治癒遅延があらわれることがある。［8.6，11.1.15 参照］ **9.1.5 頸動脈・静脈等への腫瘍浸潤のある患者** 腫瘍縮小・壊死に伴う頸動脈露出，頸動脈出血，腫瘍出血があらわれることがある。なお，甲状腺未分化癌患者では，頸動脈・静脈への腫瘍浸潤例が多いので，特に注意すること。［8.10，11.1.2 参照］ **9.1.6 肺転移を有する患者** 気胸が発現するおそれがある。［11.1.8 参照］ **9.3 肝機能障害患者** **9.3.1 重度の肝機能障害のある患者** 減量を考慮するとともに，患者の状態をより慎重に観察し，有害事象の発現に十分注意すること。本剤の血中濃度が上昇するとの報告がある。なお，重度の肝機能障害を有する肝細胞癌患者に対する臨床試験は実施していない。［16.6.2 参照］ **9.3.2 中等度の肝機能障害のある肝細胞癌患者** 減量を考慮するとともに，患者の状態を慎重に観察し，有害事象の発現に十分注意すること。なお，中等度（Child-Pugh スコア 9）の肝機能障害を有する肝細胞癌患者に対する臨床試験は実施していない。［7.3 参照］	**9. 特定の背景を有する患者に関する注意** **9.1 合併症・既往歴等のある患者** **9.1.1 高血圧症の患者** 高血圧が悪化するおそれがある。［7.2，7.4，8.1，11.1.1 参照］ **9.1.2 脳転移のある患者** 転移部位からの出血があらわれるおそれがある。［11.1.2 参照］ **9.1.3 血栓塞栓症又はその既往歴のある患者** 血栓塞栓症が悪化又は再発するおそれがある。［11.1.3，11.1.4 参照］ **9.1.4 外科的処置後，創傷が治癒していない患者** 創傷治癒遅延があらわれることがある。［8.6，11.1.15 参照］ **9.1.5 頸動脈・静脈等への腫瘍浸潤のある患者** 腫瘍縮小・壊死に伴う頸動脈露出，頸動脈出血，腫瘍出血があらわれることがある。なお，甲状腺未分化癌患者では，頸動脈・静脈への腫瘍浸潤例が多いので，特に注意すること。［8.10，11.1.2 参照］ **9.1.6 肺転移を有する患者** 気胸が発現するおそれがある。［11.1.8 参照］ **9.3 肝機能障害患者** **9.3.1 重度の肝機能障害のある患者** 減量を考慮するとともに，患者の状態をより慎重に観察し，有害事象の発現に十分注意すること。本剤の血中濃度が上昇するとの報告がある。なお，重度の肝機能障害を有する肝細胞癌患者に対する臨床試験は実施していない。［16.6.2 参照］ **9.3.2 中等度の肝機能障害のある肝細胞癌患者** 減量を考慮するとともに，患者の状態を慎重に観察し，有害事象の発現に十分注意すること。なお，中等度（Child-Pugh スコア 9）の肝機能障害を有する肝細胞癌患者に対する臨床試験は実施していない。［7.3 参照］	変更なし