AUSTRALIAN PRODUCT INFORMATION – LENVIMA® (LENVATINIB) HARD CAPSULE

1 NAME OF THE MEDICINE

Lenvatinib as lenvatinib mesilate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each LENVIMA 10 mg hard capsule contains 10 mg lenvatinib (as mesilate).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Hard capsule.

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

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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 was approved via the **provisional approval** pathway, based on objective response rate and duration of response in a single-arm trial. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials.

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

LENVIMA is indicated in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma whose disease has progressed following one prior vascular endothelial growth factor targeted therapy.

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

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Starting dose in RAI–refractory differentiated thyroid cancer (DTC)

The recommended dose of LENVIMA is 24 mg orally once daily.

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

Starting dose in advanced renal cell carcinoma

The recommended dose of LENVIMA is 18 mg orally once daily in combination with 5 mg everolimus orally once daily. Treatment should continue as long as there is clinical benefit or until unacceptable toxicity occurs.

Starting dose in hepatocellular carcinoma

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

- 8 mg orally once daily for patients with a body weight of < 60 kg or
- 12 mg orally once daily for patients with a body weight of ≥ 60 kg.

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

Starting dose in endometrial carcinoma

The recommended dose 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. Treatment should continue as long as there is clinical benefit or until unacceptable toxicity occurs. Refer to the pembrolizumab product information for recommended pembrolizumab dosing information.

Dose adjustment during therapy

Management of adverse reactions may require dose interruption, adjustment, or discontinuation of LENVIMA. For toxicities thought to be related to LENVIMA, general advice about dose management is included in Table 1, and recommendations for dose reduction increments are in Table 2.

When administering LENVIMA in combination with everolimus for the treatment of renal cell carcinoma, for toxicities thought to be related to both drugs, LENVIMA should be reduced prior to reducing everolimus. For toxicities thought to be related only to everolimus, everolimus treatment should be interrupted, reduced to alternate day dosing, or discontinued (see the everolimus PI for advice on specific adverse reactions).

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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 product information.

Medical management of nausea, vomiting and diarrhoea should be optimised to reduce the risk of dehydration and renal failure (See Section 4.4 Special warnings and precautions for use, Renal failure and impairment) prior to any LENVIMA therapy interruption or dose reduction.

Table 1 Dose modifications for adverse reactions

Adverse reaction	CTCAE Grade[a]	Action	When/whether to resume LENVIMA (at reduced dose)
Hypertension	Grade 3[b]	Interrupt	Resolves to Grade 0, 1 or 2. See detailed guidance in Table 3 in Section 4.4 Special warnings and precautions for use, Hypertension section
	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[c]	Discontinue	Do not resume
Cardiac failure	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[c]	Discontinue	Do not resume
Arterial thromboembolisms	Any Grade	Discontinue	Do not resume
Haemorrhage and Thrombocytopenia[c]	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
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[d]	Discontinue	Do not resume

a National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0
b Grade 3 despite optimal antihypertensive therapy.
c Grade 4 laboratory abnormalities judged to be non-life-threatening, may be managed as severe reactions (e.g., Grade 3)
d Grade 4 despite medical management

Table 2 Recommended LENVIMA dose reduction increments 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

Special populations

Dose adjustment in severe hepatic impairment

A reduced starting dose of LENVIMA is recommended for patients with DTC, RCC or endometrial carcinoma who have severe hepatic impairment (Child-Pugh C):

- 14 mg orally once daily for DTC
- 10 mg orally once daily for RCC
- 10 mg orally once daily for endometrial carcinoma

The available data do not allow for a dosing recommendation for patients with HCC and moderate hepatic impairment (Child-Pugh B). The available data do not allow for a dosing recommendation for patients with HCC and severe hepatic impairment (Child-Pugh C), and use in this population is not recommended.

Dose adjustment in renal impairment

A reduced starting dose of LENVIMA is recommended for patients with DTC, RCC or endometrial carcinoma who have severe renal impairment (CrCL <30 mL/min):

- 14 mg orally once daily for DTC
- 10 mg orally once daily for RCC
- 10 mg orally once daily for endometrial carcinoma

LENVIMA has not been studied in patients with end stage renal disease, and use in this population is not recommended.

The available data do not allow for a dosing recommendation for patients with HCC and severe renal impairment, and use in this population is not recommended.

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Paediatric population

LENVIMA should not be used in children younger than 2 years of age because of safety concerns identified in animal studies. The safety and efficacy of LENVIMA in children aged 2 to <18 years have not yet been established (see Section 5.1 Pharmacodynamic properties, Clinical trials). No data are available.

Method of administration

LENVIMA should be taken at about the same time each day, with or without food. The capsules should be swallowed whole with water.

Alternatively, if unable to swallow the capsule whole place the capsule, without breaking or crushing, in a glass of approximately 25 mL of water or apple juice. The capsules must be left to disintegrate in the liquid for at least 10 minutes and then gently stirred for at least 3 minutes to dissolve the capsules shells. The suspension is to be swallowed. After drinking, the same amount of water or apple juice (25 mL) must be added to the glass and swirled a few times. The additional liquid must be swallowed. Do not mix more than one medicine in the glass at the same time.

The person preparing the suspension should ensure their hands are thoroughly washed on completion of preparation and taking of the medication.

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

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (see Section 6.1 List of excipients)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Gastrointestinal toxicity: diarrhoea and dehydration

Diarrhoea has been reported frequently in patients treated with LENVIMA usually occurring early in the course of treatment (see Section 4.8 Adverse effects, Selected Adverse Reactions). Prompt medical management of diarrhoea should be instituted in order to prevent dehydration. LENVIMA should be discontinued in the event of persistent Grade 4 diarrhoea despite medical management (see Section 4.2 Dose and method of administration).

Gastrointestinal toxicity (including events of diarrhoea, nausea and vomiting) should be actively managed in order to reduce the risk of development of renal impairment or renal failure. Serious adverse events of both hypokalaemia and hyperkalaemia have occurred and renal function and electrolytes should be monitored closely. (See Section 4.4 Special warnings and precautions for use, Renal failure and impairment).

Renal failure and impairment

Patients with baseline renal function <60ml/minute experienced more adverse events, including fatal and serious adverse events and Grade 3 or 4 events, than those with normal renal function and were more likely to require a treatment interruption, dose reduction or discontinuation of treatment. The recommended starting dose is lower for patients with renal impairment (see Section 4.2 Dose and method of administration) and it is also recommended these patients be monitored closely during treatment. There is no clinical trial experience of patients with severe renal impairment.

Renal impairment (including renal failure) has been reported in patients treated with LENVIMA (see Section 4.8 Adverse effects, Selected Adverse Reactions). The primary risk factors identified were pre-existing renal impairment and dehydration and/or hypovolemia due to gastrointestinal toxicity. (See Section 4.4 Special warnings and precautions for use, Gastrointestinal toxicity: Diarrhoea and dehydration). 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 Dose and method of administration).

If patients have severe renal impairment, the initial dose of LENVIMA should be adjusted (see Section 4.2 Dose and method of administration).

Hypertension

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

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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 LENVIMA and initiate antihypertensive therapy, if not already receiving OR Continue LENVIMA 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 LENVIMA 2. When systolic BP ≤150 mmHg, diastolic BP ≤ 95 mmHg, and patient has been on a stable dose for at least 48 hours, resume LENVIMA at a reduced dose (see Section 4.2 Dose and method of administration)
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue LENVIMA and institute appropriate medical management.

Proteinuria

Proteinuria has been reported in patients treated with LENVIMA, usually occurring early in the course of the treatment (see Section 4.8 Adverse effects, Selected Adverse Reactions). Monitor urine protein regularly. If urine dipstick proteinuria ≥ 2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary (see Section 4.2 Dose and method of administration). LENVIMA should be discontinued in the event of nephrotic syndrome.

Cardiac dysfunction

Cardiac failure and decreased left ventricular ejection fraction have been reported in patients treated with LENVIMA (see Section 4.8 Adverse effects, 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 Dose and method of administration).

LENVIMA has not been studied in patients who have had cardiac failure within the previous 6 months and therefore should be used with caution in such patients.

Posterior reversible encephalopathy syndrome (PRES) / Reversible Posterior Leucoencephalopathy Syndrome (RPLS)

Posterior reversible encephalopathy syndrome (PRES, also known as RPLS) has been reported in patients treated with LENVIMA (observed in < 1% or patients; ADVERSE EFFECTS, 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 Special warnings and precautions for use, Hypertension). In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary (see Section 4.2 Dose and method of administration).

Hepatotoxicity

In DTC and RCC, liver-related adverse reactions most commonly reported in patients treated with LENVIMA included increases in alanine aminotransferase (ALT), increases in aspartate aminotransferase (AST), and increases in blood bilirubin (see Section 4.8 Adverse effects, Selected Adverse Reactions). Hepatic failure and acute hepatitis (observed in < 1% of patients) have been reported in patients with DTC and RCC treated with LENVIMA. The hepatic failure events were generally reported in patients with progressive metastatic liver disease.

Liver-related adverse reactions including hepatic encephalopathy and hepatic failure (including fatal reactions) were reported at a higher frequency in LENVIMA treated HCC patients (see Section 4.8 Adverse effects) compared to DTC and RCC patients. Patients with worse hepatic impairment and/or greater liver tumour burden at baseline had a higher risk of developing hepatic encephalopathy and hepatic failure. Hepatic encephalopathy also occurred more frequently in patients aged 75 years and older. Approximately half of the events of hepatic failure were reported in patients with disease progression.

Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. Patients with HCC should be monitored for worsening liver function including hepatic encephalopathy. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary (see Section 4.2 Dose and method of administration).

If patients have any degree of liver impairment they need to be monitored closely for liver related adverse reactions. For DTC and RCC patients with severe hepatic impairment, the initial dose of LENVIMA should be adjusted. The available data do not allow for a dosing recommendation for patients with HCC and moderate hepatic impairment (Child-Pugh B). LENVIMA has not been studied in patients with HCC and severe hepatic impairment (Child-Pugh C) and therefore the use of LENVIMA in these patients is not recommended.

Arterial thromboembolic events

Arterial thromboembolic events (cerebrovascular accident, transient ischaemic attack, and myocardial infarction) have been reported in patients treated with LENVIMA (see Section 4.8 Adverse effects, Selected Adverse Reactions). LENVIMA has not been studied in patients who have had an arterial thromboembolic event 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 LENVIMA should be

discontinued following an arterial thrombotic event (see Section 4.2 Dose and method of administration).

Haemorrhagic events and thrombocytopenia

Serious haemorrhagic events have been reported in patients treated with LENVIMA. The most frequently reported haemorrhagic event was mild epistaxis. Serious events of thrombocytopenia have also been reported in patients treated with LENVIMA and thrombocytopenia may increase risk of developing haemorrhagic events. (see Section 4.8 Adverse effects, Selected Adverse Reactions)

Serious tumour related bleeds have been reported, including fatal haemorrhagic events in LENVIMA treated patients and there have been reports of haemorrhage associated with thrombocytopenia.

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 LENVIMA therapy. In the case of haemorrhagic events/ thrombocytopenia, dose interruptions, adjustments, or discontinuation may be necessary (see Section 4.2 Dose and method of administration).

Wound Healing Complications

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

Gastrointestinal perforation and fistula formation

Gastrointestinal perforation or fistulae have been reported in patients treated with LENVIMA (see Section 4.8 Adverse effects, Selected Adverse Reactions). 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 Dose and method of administration).

Non-Gastrointestinal fistula

Patients may be at increased risk for the development of fistulae when treated with LENVIMA. 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 gastrointestinal perforation, fistula and pneumothorax

occurred in association with tumour regression or necrosis. Prior surgery and radiotherapy may be contributing risk factors. LENVIMA should not be started in patients with fistulae to avoid worsening and LENVIMA should be permanently discontinued in patients with oesophageal or tracheobronchial tract involvement and any Grade 4 fistula (see Section 4.2 Dose and method of administration); 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. LENVIMA 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 LENVIMA than in patients treated with placebo (see Section 4.8 Adverse effects, Selected Adverse Reactions). The median time to onset of QTc prolongation was 16.1 weeks in the DTC study, 31.1 weeks in the HCC study for patients on LENVIMA monotherapy and 30 weeks in the RCC study for combination patients. Electrocardiograms should be monitored in patients on an ongoing basis with a special attention for those with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, and those taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. LENVIMA should be withheld in the event of development of QT interval prolongation greater than 500 ms. LENVIMA should be resumed at a reduced dose when QTc prolongation is resolved to < 480 ms or baseline (see Section 4.2 Dose and method of administration).

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 LENVIMA treatment. LENVIMA 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

LENVIMA impairs exogenous thyroid suppression (see Section 4.8 Adverse effects).

Hypothyroidism has been reported as very common in patients treated with LENVIMA in the RCC trial (see Section 4.8 Adverse effects, Selected Adverse Reactions).

Thyroid function should be monitored before initiation of treatment, and periodically at least monthly throughout treatment with LENVIMA. Hypothyroidism should be treated according to standard medical practice to maintain euthyroid state.

Special Populations

Limited data are available for patients of ethnic origin other than Caucasian or Asian. LENVIMA should be used with caution in such patients, given the reduced tolerability of LENVIMA in Asian patients (see Section 4.8 Adverse effects, Other Special Populations).

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

Patients with poor ECOG performance status

Patients with an ECOG performance status of 2 or higher were excluded from the RCC, HCC and endometrial carcinoma studies (see Section 5.1 Pharmacodynamic properties, Clinical trials). Patients with an ECOG performance 3 or higher were excluded from the DTC studies (see Section 5.1 Pharmacodynamic properties, Clinical trials). Benefit-risk in these patients has not been evaluated.

Patients with hypertension

Blood pressure should be well controlled prior to treatment with LENVIMA, and should be regularly monitored during treatment (See Section 4.4 Special warnings and precautions for use and Section 4.8 Adverse effects).

Use in hepatic impairment

See 4.2 Dose and method of administration, Dosage adjustment in hepatic impairment and Section 5.2 Pharmacokinetic Properties, Special Populations, Hepatic Impairment,

Use in renal impairment

See 4.2 Dose and method of administration, Dosage adjustment in renal impairment and Section 5.2 Pharmacokinetic Properties, Special Populations, Renal Impairment,

Use in the elderly

Limited data are available in patients aged ≥75 years. LENVIMA should be used with caution in such patients, given the reduced tolerability of LENVIMA in elderly patients (see Section 4.2 Dose and method of administration and Section 4.8 Adverse effects, Other Special Populations).

Paediatric use

Clinical data are not yet available in this population.

Mortality was the dose-limiting toxicity in juvenile rats in which dosing was initiated on postnatal day (PND) 7 or PND21. Mortality occurred at lower doses in neonatal rats (dosing initiated on PND7), or after a shorter duration of treatment in juvenile rats (dosing initiated on PND21). The exposure (as AUC) to lenvatinib in juvenile rats was lower compared to adults, suggesting increased susceptibility to the toxic effects of lenvatinib in young animals. 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.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of other medicinal products on LENVIMA

CYP3A, P-gp, and BCRP inhibitors or inducers

LENVIMA may be administered regardless of co-administration with CYP3A, P-gp, and BCRP inhibitors. In healthy subjects, ketoconazole (400 mg for 18 days) increased lenvatinib (administered as a single dose on Day 5) $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ approximately 15% while C_{max} increased 19%. This is supported by a population PK analysis which found CYP3A4 inhibitors decreased Cl/F by 7.8%.

LENVIMA may be co-administered without dose adjustment with CYP3A and P-gp inducers, based on a study in which healthy subjects were administered repeated doses of rifampicin (600 mg for 21 days) and a single dose of lenvatinib (24 mg, Day 15). $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ decreased approximately 18% while C_{max} did not change. The effect of CYP3A induction alone was estimated by comparing the PK parameters for lenvatinib following single and multiple doses of rifampicin. Lenvatinib AUC and C_{max} were predicted to decrease by 30% and 15%, respectively, after strong induction in the absence of acute P-gp inhibition. This is supported by a population PK analysis which found CYP3A4 inducers increased Cl/F by 30%.

Gastric pH-altering agents

In a population pharmacokinetic analysis of patients receiving LENVIMA up to 24 mg once daily, agents which increase gastric pH (H2 receptor blockers, proton pump inhibitors, antacids) did not have a significant effect on lenvatinib exposure.

Other chemotherapeutic agents

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

Effect of LENVIMA on other medicinal products

Cytochrome P450 or UGT enzyme substrates

Lenvatinib is considered neither a strong inhibitor nor an inducer of cytochrome P450 or uridine 5'-diphosphoglucuronosyl transferase (UGT) enzymes.

P-gp and BCRP substrates

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

OAT, OCT, OATP, BSEP, MATE and aldehyde oxidase substrates

Lenvatinib showed inhibitory effects on organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, OCT2, organic anion transporting polypeptide (OATP)1B1, and bile salt export pump (BSEP), but minimal or no inhibitory effect on OATP1B3 and multidrug and toxin extrusion 2 (MATE2)-K. Lenvatinib weakly inhibits MATE1. In human liver cytosol, lenvatinib did not inhibit aldehyde oxidase activity.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

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

No specific studies with lenvatinib have been conducted in animals to evaluate the effect on fertility. However, testicular and ovarian changes 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.

Use in Pregnancy

Pregnancy Category D.

There is limited information on the use of LENVIMA in pregnant women. Lenvatinib was embryotoxic and teratogenic when administered to rats and rabbits during organogenesis at exposures below the clinical exposure (based on body surface area) at the maximum recommended human dose. Fetal anomalies included parietal oedema, cryptophthalmia, abnormal tail (rats), retroesophageal subclavian artery, fused ribs, and vertebral abnormalities (rabbits). These embryofetal findings are probably related to the pharmacologic activity of lenvatinib as an antiangiogenic agent.

LENVIMA 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.

Women of childbearing potential

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

Use In Lactation

It is not known whether lenvatinib is excreted in human milk. Lenvatinib and its metabolites are excreted in rat milk and neonatal rats were more sensitive to the toxicity of lenvatinib compared to adults (See Section 4.4 Special warnings and precautions for use, Paediatric

Use). Therefore, a risk to newborns or infants cannot be excluded and LENVIMA should not be used during breastfeeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. LENVIMA may cause side effects such as fatigue and dizziness. Patients who experience these symptoms should use caution when driving or operating machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials

Radioactive iodine refractory differentiated thyroid cancer

The safety of LENVIMA was evaluated in 392 patients from the Phase 3 SELECT trial with radioactive iodine-refractory differentiated thyroid cancer (RAI-refractory DTC) randomised to receive LENVIMA 24 mg once daily (n=261) or placebo (n=131) (see Section 5.1 Pharmacodynamic properties, Clinical trials).

In the SELECT study, the most common adverse reactions observed in LENVIMA-treated patients (greater than or equal to 30%) were, in order of decreasing frequency, hypertension, fatigue, diarrhoea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysaesthesia (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 and 5% of patients receiving placebo; 18% of patients discontinued LENVIMA and 5% discontinued placebo 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 diarrhoea (10%); the most common adverse reactions (at least 1%) resulting in discontinuation of LENVIMA were hypertension (1%) and asthenia (1%).

Table 4 presents the incidence rates of treatment-emergent adverse events observed in the double blind phase of the DTC study. All adverse events occurring with a treatment difference of at least 5% over placebo are included in the Table. Clinically significant events (CSEs) that were observed more frequently than placebo are also included based on an assessment of the known pharmacology of LENVIMA and class effects.

Table 4 Treatment-Emergent Adverse Events reported for LENVIMA in the double-blind phase of the DTC Study*

System Organ Class Preferred Term	LENVIMA 24 mg N=261		Placebo N=131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Blood & Lymphatic System Disorders				
Thrombocytopenia[a]	13.8	1.9	2.3	0
Lymphopenia[b]	10.7	2.3	4.6	0.8
Splenic infarction	0.8	0	0	0
Cardiac Disorders				
Ejection fraction decreased	5.4	1.1	0.8	0
Myocardial infarction[c,d]	1.1	1.1	0.8	0.8
Cardiac failure	0.8	0	0	0
Endocrine Disorders				
Hypothyroidism	5.4	0	0	0
Gastrointestinal Disorders				
Diarrhoea	67.4	9.2	16.8	0
Nausea	46.7	2.3	25.2	0.8
Stomatitis[e]	41.0	4.6	8.4	0
Vomiting	35.6	1.9	14.5	0
Abdominal pain[f]	31.4	2.3	10.7	0.8
Constipation	28.7	0.4	15.3	0.8
Oral pain[g]	24.9	1.1	2.3	0
Dry mouth	16.9	0.4	8.4	0
Dyspepsia	13.0	0.4	3.8	0
Flatulence	6.1	0	0.8	0
Anal fistula	1.1	0.4	0	0
General Disorders and Administration Site Conditions				
Fatigue	42.5	4.6	24.4	1.5
Asthenia	25.3	6.1	13.0	2.3
Oedema peripheral	20.7	0.4	7.6	0
Malaise	5.4	0	0	0
Hepatobiliary Disorders				
Hepatocellular damage / hepatitis[h]	1.1	0.8	0	0
Infections and Infestations				
Urinary tract infection	11.5	1.1	5.3	0
Perineal abscess	0.8	0.8	0	0
Investigations				
Weight decreased	51.3	13.4	14.5	0.8
Electrocardiogram QT prolonged	8.8	1.5	1.5	0
Alanine aminotransferase increased	7.7	1.5	0	0
Blood creatinine increased	7.3	0	1.5	0
Aspartate aminotransferase increased	6.9	1.9	1.5	0
Blood thyroid stimulating hormone increased	6.5	0	0	0
Blood alkaline phosphatase increased	6.1	0.8	2.3	0.8
Blood urea increased	3.1	0	0	0
Hepatic function abnormal	2.3	0.4	0	0
Blood bilirubin increased	1.9	0	0	0
Gamma-glutamyltransferase increased	1.5	0.8	0.8	0
Metabolism and Nutrition Disorders				
Decreased appetite	54.4	6.9	18.3	0.8
Hypokalaemia	13.8	3.4	3.8	0
Hypocalcaemia	12.6	5.0	0	0

Table 4 Treatment-Emergent Adverse Events reported for LENVIMA in the double-blind phase of the DTC Study*

System Organ Class Preferred Term	LENVIMA 24 mg N=261		Placebo N=131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hypoalbuminaemia	9.6	0.4	1.5	0
Dehydration	8.8	2.3	2.3	0.8
Hypomagnesaemia[i]	6.5	0.4	1.5	0
Hypercholesterolaemia[j]	5.0	0.4	0	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	26.1	0.4	6.9	0.8
Myalgia	19.2	1.5	4.6	0
Back pain	17.6	1.9	9.2	0
Musculoskeletal pain	16.1	0.4	8.4	0.8
Pain in extremity	15.3	1.1	6.9	1.5
Nervous System Disorders				
Headache	38.3	3.1	11.5	0.8
Dysgeusia	18.0	0	3.1	0
Dizziness	15.3	0.4	9.2	0
Monoparesis	1.1	0.8	0	0
Cerebrovascular accident	0.8	0.4	0	0
Transient ischaemic attack	0.8	0	0	0
Reversible posterior leucoencephalopathy syndrome	0.4	0	0	0
Psychiatric Disorders				
Insomnia	11.9	0	3.1	0
Renal and Urinary Disorders				
Proteinuria	33.7	10.7	3.1	0
Renal failure events[d,k]	5.0	2.7	0.8	0.8
Renal impairment	1.9	0.4	0	0
Respiratory, Thoracic, and Mediastinal Disorders				
Dysphonia	31.4	1.1	5.3	0
Cough	23.8	0	17.6	0
Pulmonary embolism[d]	3.1	3.1	1.5	1.5
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysaesthesia syndrome	32.2	3.4	0.8	0
Rash	18.8	0.4	1.5	0
Alopecia	12.3	0	5.3	0
Hyperkeratosis	6.9	0	1.5	0
Palmar erythema	1.1	0	0	0
Vascular Disorders				
Haemorrhage[d, l]	34.9	1.5	18.3	3.1
Hypertension[m]	72.8	44.4	16.0	3.8
Hypotension	8.8	1.5	2.3	0

a) Includes the following terms: thrombocytopenia, platelet count decreased
b) Includes the following terms: lymphopenia, lymphocyte count decreased
c) Includes the following terms: acute myocardial infarction, myocardial infarction
d) Includes fatal events and these are counted in all Grade column
e) Includes the following terms: aphthous stomatitis, stomatitis, glossitis, mouth ulceration, mucosal inflammation
f) Includes the following terms: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, gastrointestinal pain
g) Includes the following terms: oral pain, glossodynia, oropharyngeal pain
h) Includes the following terms: drug-induced liver injury, cholestatic liver injury, hepatic steatosis
i) Includes the following terms: hypomagnesaemia, blood magnesium decreased

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j) Includes the following terms: hypercholesterolaemia and blood cholesterol increased
k) Includes the following terms: acute prerenal failure, renal failure, renal failure acute, renal tubular necrosis
l) Includes the following terms: epistaxis, haematuria, contusion, gingival bleeding, haematochezia, pulmonary haemorrhage, vaginal haemorrhage, rectal haemorrhage, haematoma, haemorrhoidal haemorrhage, laryngeal haemorrhage, petechiae, intracranial tumour haemorrhage, haemorrhagic stroke, pleural haemorrhage, splenic haemorrhage, blood urine present, conjunctival haemorrhage, eye haemorrhage, gastroduodenitis haemorrhagic, haematemesis, increased tendency to bruise, proctitis haemorrhagic, purpura, renal haematoma, skin haemorrhage, splinter haemorrhages
m) Includes the following terms: hypertension, hypertensive crisis, blood pressure diastolic increased, blood pressure increased

*TEAEs reported at 4 months after the cut-off for the final PFS analysis

Renal Cell Carcinoma

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

Adverse reactions led to dose reductions or interruption in 89% of patients receiving LENVIMA + everolimus and 54% in patients receiving everolimus. The most common adverse reactions (≥ 5%) resulting in dose reductions in the LENVIMA + everolimus-treated group were diarrhoea (21%), fatigue (8%), thrombocytopaenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%).

Treatment discontinuation due to an adverse reaction occurred in 29% of patients in the LENVIMA + everolimus-treated group and 12% of patients in the everolimus-treated group.

Table 5 presents the adverse reactions in > 15% of patients in the LENVIMA + Everolimus arm.

Table 5 Grades 1-4 Adverse Reactions in > 15% of Patients in the LENVIMA + Everolimus Arm

	LENVIMA 18 mg + Everolimus 5 mg (N=62)		**Everolimus 10 mg (N=50)**	
System Organ Class Preferred Term	**Grade 1-4 (%)**	**Grade 3-4 (%)**	**Grade 1-4 (%)**	**Grade 3-4 (%)**
Endocrine Disorders				
Hypothyroidism	24	0	2	0
Gastrointestinal Disorders				
Constipation	16	0	18	0
Diarrhoea	81	19	34	2
Dyspepsia/Gastro-oesophageal reflux	21	0	12	0
Abdominal pain[a]	37	3	8	0
Nausea	45	5	16	0
Oral pain[b]	23	2	4	0
Stomatitis/Oral inflammation[c]	44	2	50	4
Vomiting	48	7	12	0

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General Disorders and Administration Site Conditions				
Fatigue[d]	73	18	40	2
Peripheral oedema	42	2	20	0
Pyrexia/Increased body temperature	21	2	10	2
Investigations				
Weight decreased	34	3	8	0
Metabolism and Nutrition Disorders				
Decreased appetite	53	5	18	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/Myalgia[e]	55	5	32	0
Musculoskeletal chest pain	18	2	4	0
Nervous System Disorders				
Headache	19	2	10	2
Psychiatric Disorders				
Insomnia	16	2	2	0
Renal and Urinary Disorders				
Proteinuria/Urine protein present	31	8	14	2
Renal failure event[f]	18	10	12	2
Respiratory, Thoracic and Mediastinal Disorders				
Cough	37	0	30	0
Dysphonia	18	0	4	0
Dyspnoea/Exertional dyspnoea	35	5	28	8
Skin and Subcutaneous Tissue Disorders				
Rash[g]	35	0	40	0
Vascular Disorders				
Haemorrhagic events[h]	32	6	26	2
Hypertension/Increased blood pressure	42	13	10	2

a) Includes abdominal discomfort, gastrointestinal pain, lower abdominal pain, and upper abdominal pain
b) Includes gingival pain, glossodynia, and oropharyngeal pain
c) Includes aphthous stomatitis, gingival inflammation, glossitis, and mouth ulceration
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 haemorrhagic diarrhoea, epistaxis, gastric haemorrhage, haemarthrosis, haematoma, haematuria, haemoptysis, lip haemorrhage, renal haematoma, and scrotal haematocele

Table 6 Grade 3-4 Laboratory Abnormalities in ≥ 3% of Patients in the LENVIMA + Everolimus Arm[a,b]

Laboratory Abnormality	**LENVIMA 18 mg + Everolimus 5 mg N=62**	**Everolimus 10 mg N=50**
	Grades 3-4 (%)	**Grades 3-4 (%)**
Chemistry		
Aspartate aminotransferase (AST) increased	3	0
Alanine aminotransferase (ALT) increased	3	2
Alkaline phosphatase increased	3	0
Hyperkalaemia	6	2
Hypokalaemia	6	2
Hyponatraemia	11	6
Hypocalcaemia	6	2
Hypophosphataemia	11	6
Hyperglycaemia	3	16
Hypertriglyceridaemia	18	18

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Laboratory Abnormality	**LENVIMA 18 mg + Everolimus 5 mg N=62**	**Everolimus 10 mg N=50**
	Grades 3-4 (%)	**Grades 3-4 (%)**
Elevated cholesterol	11	0
Creatine kinase increased	3	4
Lipase increased	13	12
Haematology		
Haemoglobin decreased	8	16
Platelet count decreased	5	0
Lymphocyte count decreased	10	20

a) With at least 1 grade increase from baseline
b) Subject with at least 1 post baseline laboratory value

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 Section 5.1, Pharmacodynamic properties, Clinical trials). 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, diarrhoea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysaesthesia syndrome, proteinuria, dysphonia, haemorrhagic 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%), diarrhoea (8%), proteinuria (7%), hypertension (6%), and palmar-plantar erythrodysaesthesia 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

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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)

	LENVIMA 8 mg/12 mg N=476		**Sorafenib 800 mg N=475**	
System Organ Class Preferred Term	**Grade 1-4 (%)**	**Grade 3-4 (%)**	**Grade 1-4 (%)**	**Grade 3-4 (%)**
Endocrine Disorders				
Hypothyroidism[a]	21	0	3	0
Gastrointestinal Disorders				
Diarrhoea	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/Oral inflammation[d]	11	0.4	14	1
General Disorders and Administration Site Conditions				
Fatigue[e]	44	7	36	6
Pyrexia[f]	15	0	14	0.2
Peripheral oedema	14	1	7	0.2
Investigations				
Weight decreased	31	8	22	3
Metabolism and Nutrition Disorders				
Decreased appetite	34	5	27	1
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/Myalgia[g]	31	1	20	2
Nervous System Disorders				
Headache	10	1	8	0
Renal and Urinary Disorders				
Proteinuria[h]	26	6	12	2
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	24	0.2	12	0
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysaesthesia syndrome	27	3	52	11
Rash[i]	14	0	24	2
Vascular Disorders				
Hypertension[j]	45	24	31	15
Haemorrhagic events[k]	23	4	15	4

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, multicentre, open-label trial in 94 patients with endometrial carcinoma whose tumours had progressed following one line of systemic therapy and were not MSI-H or dMMR (see Section 5.1, Pharmacodynamic properties, Clinical trials). The median duration of study treatment was 7 months (range: 0.03 to 37.8 months). Pembrolizumab was continued for a

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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 haemorrhage, and intracranial haemorrhage.

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%), haemorrhage (4%), fatigue (4%), nausea (4%), confusional state (4%), pleural effusion (4%), adrenal insufficiency (3%), colitis (3%), dyspnoea (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%), diarrhoea (18%), nausea (13%), palmar-plantar erythrodysaesthesia (13%), vomiting (13%), decreased appetite (12%), musculoskeletal pain (11%), stomatitis (9%), abdominal pain (7%), haemorrhages (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
Haemorrhagic events[d]	28	4
Gastrointestinal		
Diarrhoea[e]	64	4
Nausea	48	5

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 (%)**
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
Dyspnoea[k]	24	2
Cough	21	0
Skin and Subcutaneous Tissue		
Palmar-plantar erythrodysaesthesia syndrome	26	3
Rash[l]	21	3

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 haemorrhage, haematemesis, haematuria, haemorrhage intracranial, injection site haemorrhage, intraventricular haemorrhage, large intestinal haemorrhage, metrorrhagia, mouth haemorrhage, uterine haemorrhage, and vaginal haemorrhage
e Includes diarrhoea, gastroenteritis, gastrointestinal viral infection, and viral diarrhoea
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 dyspnoea and exertional dyspnoea
l Includes rash, rash generalized, rash macular, and rash maculo-papular

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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
Hyperglycaemia	53	1
Hypercholesteraemia	49	6
Hypoalbuminaemia	48	0
Hypomagnesaemia	47	2
Increased aspartate aminotransferase	43	4
Hyponatraemia	42	13
Increased lipase	42	18
Increased alanine aminotransferase	35	3
Increased alkaline phosphatase	32	1
Hypokalaemia	27	5
Increased amylase	19	6
Hypocalcaemia	14	3
Hypermagnesaemia	4	3
Haematology		
Thrombocytopaenia	48	0
Leukopaenia	38	2
Lymphopaenia	36	7
Anaemia	35	1
Increased INR	21	3
Neutropaenia	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)

Post-marketing adverse drug reactions

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 Disorders: amylase increased, lipase increased, pancreatitis
Hepatobiliary Disorders: cholecystitis
General Disorders and Administration Site Conditions: impaired healing
Renal and urinary disorders: nephrotic syndrome
Respiratory, thoracic and mediastinal disorders: pneumothorax
Vascular Disorders: aortic dissection

Selected adverse reactions in DTC, RCC and HCC

Hypertension

In the pivotal DTC Phase 3 SELECT trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), hypertension (including hypertension, hypertensive crisis, blood pressure diastolic increased, and blood pressure increased) was reported in 72.8% of LENVIMA-treated patients and 16.0% of patients in the placebo-treated group. The median time to onset in LENVIMA-treated patients was 16 days. Events of Grade 3 or higher (including 1 event of Grade 4) occurred in 44.4% of LENVIMA-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.

In the RCC study (see Section 5.1 Pharmacodynamic properties, Clinical trials) Phase 1b plus Phase 2 population, hypertension was reported in 41.9% of patients in the LENVIMA 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 LENVIMA plus everolimus-treated group.

In the Phase 3 HCC trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), hypertension (including hypertension, blood pressure increased, blood pressure diastolic increased and orthostatic hypertension) was reported in 44.5% of LENVIMA-treated patients compared with 30.9% of patients in the sorafenib-treated group and Grade 3 hypertension occurred in 23.5% (14.5% in the sorafenib-treated group). The median time to onset was 26 days. The majority of cases recovered following dose interruption or reduction, which occurred in 3.6% and 3.4% of patients respectively. One subject (0.2%) discontinued LENVIMA due to hypertension.

Proteinuria

In the pivotal DTC Phase 3 SELECT trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), proteinuria was reported in 33.7% of LENVIMA treated patients and 3.1% of patients in the placebo-treated group. The median time to onset was 6.7 weeks. Grade 3 events occurred in 10.7% of LENVIMA-treated patients and no 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.

In the RCC study (see Section 5.1 Pharmacodynamic properties, Clinical trials) Phase 1b plus Phase 2 population, proteinuria was reported in 30.6% of patients in the LENVIMA plus everolimus-treated group (8.1% were Grade ≥ 3) and 14.0% of patients in the everolimus-treated group (2.0% were Grade 3 or greater). The median time to onset of proteinuria was 6.1 weeks (any grade) and 20.1 weeks (Grade ≥ 3) in the LENVIMA plus everolimus-treated group. Proteinuria led to permanent treatment discontinuation in 4.8% of patients.

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In the Phase 3 HCC trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), proteinuria was reported in 26.3% of LENVIMA-treated patients compared with 12.2% of patients in the sorafenib-treated group and Grade 3 reactions occurred in 5.9% (1.7% in the sorafenib-treated group). The median time to onset was 6.1 weeks. The majority of cases recovered following dose interruption or reduction, which occurred in 6.9% and 2.5% of patients respectively. Proteinuria led to permanent treatment discontinuation in 0.6% of patients.

Renal failure and impairment

In the pivotal DTC Phase 3 SELECT trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), 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).

In the RCC study (see Section 5.1 Pharmacodynamic properties, Clinical trials) Phase 1b plus Phase 2 population, 8.1% of patients in the LENVIMA 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 of impairment). In the everolimus monotherapy group 2.0% of patients developed renal failure (2.0% were Grade 3).

In the Phase 3 HCC trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), 7.1% of LENVIMA-treated patients developed a renal failure/impairment event compared with 4.0% in the sorafenib-treated group. Grade 3 or greater reactions occurred in 1.9% of LENVIMA-treated patients and in 1.3% of sorafenib-treated patients

Cardiac dysfunction

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

In the RCC study (see Section 5.1 Pharmacodynamic properties, Clinical trials) Phase 1b plus Phase 2 population, decreased ejection fraction/cardiac failure was reported in 4.8% of patients (3.2% were Grade ≥ 3) in the LENVIMA 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 LENVIMA plus everolimus-treated group.

In the Phase 3 HCC trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), cardiac dysfunction (including congestive cardiac failure, cardiogenic shock, and cardiopulmonary failure) was reported in 0.6% of patients in the LENVIMA-treated group compared with 0.2% of patients in the sorafenib-treated group. 0.4% in the LENVIMA-treated group experienced events of Grade ≥ 3 compared to none in the sorafenib-treated group. There were no events of decreased ejection fraction in the LENVIMA arm.

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

In the pivotal DTC Phase 3 SELECT trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), there was 1 event of PRES (Grade 2) in the LENVIMA-treated group and no reports in the placebo group.

In the RCC study (see Section 5.1 Pharmacodynamic properties, Clinical trials) Phase 1b plus Phase 2 population, there was 1 event of PRES (Grade 3) in the LENVIMA-treated group, occurring after 18.4 weeks of treatment. There were no reports in the LENVIMA plus everolimus or everolimus monotherapy groups.

In the Phase 3 HCC trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), there was 1 event of PRES (Grade 2) in the LENVIMA treated group and no events in the sorafenib-treated group.

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

Hepatotoxicity

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

In the RCC study (see Section 5.1 Pharmacodynamic properties, Clinical trials) Phase 1b plus Phase 2 population, the most commonly reported liver-related adverse reactions in the LENVIMA 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 LENVIMA plus everolimus-treated group. Grade 3 liver-related reactions occurred in 3.2% of LENVIMA 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 Phase 3 HCC trial (see Section 5.1 Pharmacodynamic properties, Clinical trials) hepatotoxicity events were reported in 47.7% of LENVIMA-treated patients compared to 41.7% of sorafenib-treated patients. The most commonly reported hepatotoxicity adverse reactions in the LENVIMA-treated patients were blood bilirubin increased (14.9%), aspartate

aminotransferase increased (13.7%), alanine aminotransferase increased (11.1%), hypoalbuminaemia (9.2%), hepatic encephalopathy (8.0%), gamma-glutamyltransferase increased (7.8%) and blood alkaline phosphatase increased (6.7%). The median time to onset of hepatotoxicity adverse reactions was 6.4 weeks.

Hepatotoxicity reactions of ≥ Grade 3 occurred in 26.1% of LENVIMA-treated patients and 23.4% of sorafenib-treated patients. In LENVIMA-treated patients Hepatic failure (HF) (including fatal events) occurred in 3.2% of patients (all were ≥ Grade 3). Hepatic encephalopathy (HE) (including fatal events) occurred in 8.0% of patients (4.8% were ≥ Grade 3). Hepatotoxicity adverse reactions led to dose interruptions and reductions in 12.2% and 7.4% of LENVIMA-treated patients respectively, and to permanent discontinuation in 5.5%. The events of HF and HE were reported at a higher frequency in LENVIMA-treated HCC patients (3.6% and 8.0% for HF and HE, respectively) in comparison to sorafenib-treated HCC patients (2.5% and 1.9% for HF and HE, respectively).

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

Arterial thromboembolisms

In the pivotal DTC Phase 3 SELECT trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), arterial thromboembolic events were reported in 5.4% of LENVIMA-treated patients and 2.3% of patients in the placebo group.

In the RCC study (see Section 5.1 Pharmacodynamic properties, Clinical trials) Phase 1b plus Phase 2 population, 1.6% of patients in the LENVIMA 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 Phase 3 HCC trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), arterial thromboembolic events were reported in 2.3% of patients treated with LENVIMA as compared to 1.7% in sorafenib-treated patients.

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

Haemorrhagic events and thrombocytopenia

In the pivotal DTC Phase 3 SELECT trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), haemorrhagic events were reported in 34.9% of LENVIMA-treated patients versus 18.3% of placebo-treated patients. Events 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

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intracranial tumour haemorrhage (0.8%). When adjusted to account for the 4-fold greater duration of exposure in the LENVIMA versus the placebo arm, the following reactions occurred less frequently on LENVIMA than placebo: haemoptysis (0.05 episodes/subject-year on LENVIMA vs. 0.21 episodes/subject-year on placebo) and pulmonary haemorrhage (0.02 episodes/subject year on LENVIMA vs. 0.09 episodes/subject-year on placebo).

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

Thrombocytopenia or platelet count decreased was reported in 15.3% of LENVIMA-treated patients (1.9% were Grade ≥ 3) versus 2.3% in the placebo arm (none were Grade ≥ 3). There were no Grade 4 TEAEs. The incidence of serious thrombocytopenia was 0.8%. Most reactions resolved following supportive treatment, although 5.0% of patients had events of thrombocytopenia that required dose interruption, and 1.9% required dose reduction. No patients discontinued treatment as a result of thrombocytopenia.

In the RCC study (see Section 5.1 Pharmacodynamic properties, Clinical trials) Phase 1b plus Phase 2 population, haemorrhage was reported in 38.7% (8.1% were Grade 3 or greater) of patients in the LENVIMA 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 was 10.2 weeks (any grade) and 7.6 weeks (Grade ≥ 3) in the LENVIMA 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 LENVIMA plus everolimus-treated group. There was one case of fatal cerebral haemorrhage in the LENVIMA plus everolimus-treated group and one case of fatal intracranial haemorrhage in the LENVIMA-treated group.

Thrombocytopenia or platelet count decreased was reported in 14.5% of patients in the LENVIMA plus everolimus-treated group (4.8% were Grade ≥ 3) and 10.0% of patients in the everolimus-treated group (none were Grade ≥ 3). There was one Grade 4 TEAE. The incidence of serious thrombocytopenia was 4.8%. Dose reduction or interruption due to thrombocytopenia occurred in 9.7% of patients and 3.2% of patients discontinued treatment due to thrombocytopenia.

In the Phase 3 HCC trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), haemorrhage was reported in 24.6% of LENVIMA-treated patients as compared to 16.0% of sorafenib-treated patients. 5.0% of LENVIMA-treated patients experienced Grade ≥ 3 events as compared to 4.6% of sorafenib-treated patients. Grade 3 reactions occurred in 3.4%, Grade 4 reactions in 0.2% and 7 patients (1.5%) had a grade 5 reaction including cerebral haemorrhage, upper gastrointestinal haemorrhage, intestinal haemorrhage and tumour haemorrhage. The median time to first onset was 11.9 weeks. A haemorrhage event led to

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dose interruption or reduction in 3.2% and 0.8% patients respectively and to treatment discontinuation in 1.7% of patients.

Thrombocytopenia or platelet count decreased was reported in 25.0% of LENVIMA-treated patients as compared to 18.1% of sorafenib-treated patients. Of the LENVIMA-treated patients, 7.4% experienced Grade ≥ 3 reactions compared to 4.6% of sorafenib-treated patients. There was one Grade 4 TEAE and no serious events. Dose reduction or interruption due to thrombocytopenia or platelet count decreased occurred in 1.3% and 4.6% of patients respectively and there were no discontinuations.

Amongst 1,823 patients treated with LENVIMA monotherapy in clinical trials, 30% of patients experienced haemorrhagic events (3.9% were Grade ≥ 3), 4 patients (0.2 %) had a Grade 4 haemorrhage and 15 patients (0. 8%) had a Grade 5 reaction including arterial haemorrhage, cerebral haemorrhage, haemorrhagic stroke, intracranial haemorrhage, intracranial tumour haemorrhage, intestinal haemorrhage, haematemesis, melaena, haemoptysis, upper gastrointestinal haemorrhage, and tumour haemorrhage.

Hypocalcaemia

In the pivotal DTC Phase 3 SELECT trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), hypocalcaemia was reported in 12.6% of LENVIMA treated patients vs. no events in the placebo arm. The median time to first onset in LENVIMA-treated patients was 11.1 weeks. Events of Grade 3 or 4 severity occurred in 5.0% of LENVIMA-treated vs 0 placebo-treated patients. Most events 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.

In the RCC study (see Section 5.1 Pharmacodynamic properties, Clinical trials) Phase 1b plus Phase 2 population, hypocalcaemia was reported in 8.1% of patients in the LENVIMA 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 LENVIMA 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 Phase 3 HCC trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), was reported in 1.1% of patients compared with 1.7% of sorafenib-treated patients.0.4% of patients treated with LENVIMA experienced Grade ≥ 3 reactions and this figure was 0.2% in sorafenib-treated patients. LENVIMA dose interruption due to hypocalcaemia occurred in one subject (0.2%) and there were no dose reductions or discontinuations.

Gastrointestinal perforation and fistula formation

In the pivotal DTC Phase 3 SELECT trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), events of gastrointestinal perforation or fistula were reported in 1.9% of LENVIMA treated patients and 0.8% of patients in the placebo group.

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In the RCC study (see Section 5.1 Pharmacodynamic properties, Clinical trials) Phase 1b plus Phase 2 population, 1.6% of cases of perforated appendicitis (of Grade 3) occurred in the LENVIMA plus everolimus-treated group; there were no reports in the LENVIMA or everolimus groups.

In the Phase 3 HCC trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), events of gastrointestinal perforation or fistula were reported in 1.9% of LENVIMA-treated patients and in 1.1% of sorafenib-treated patients.

Non-Gastrointestinal fistulae (See Section 4.4 Special warnings and precautions for use)

LENVIMA 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 LENVIMA, with a median latency of about 3 months.

QT interval prolongation

In the pivotal DTC Phase 3 SELECT trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), QT/QTc interval prolongation was reported in 8.8% of LENVIMA 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 LENVIMA-treated patients compared to no reports in the placebo group.

In the RCC study (see Section 5.1 Pharmacodynamic properties, Clinical trials) Phase 1b plus Phase 2 population, QTc interval increases greater than 60 ms were reported in 11% of patients in the LENVIMA plus everolimus-treated group. The incidence of QTc interval greater than 500 ms was 6% in the LENVIMA 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 Phase 3 HCC trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), QT/QTc interval prolongation was reported in 6.9% of LENVIMA-treated patients and 5.1% of sorafenib-treated patients. The incidence of QTcF interval prolongation of greater than 500ms was 2.4%.

Blood thyroid stimulating hormone increased (See Section 4.4 Special warnings and precautions for use, Impairment of thyroid stimulating hormone suppression / Thyroid dysfunction)

In the pivotal DTC Phase 3 SELECT trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), 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 LENVIMA-treated patients as compared with 14% of placebo-treated patients.

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In the RCC study (see Section 5.1 Pharmacodynamic properties, Clinical trials) Phase 1b plus Phase 2 population, hypothyroidism occurred in 24% of patients in the LENVIMA plus everolimus-treated group and 2% of patients in the everolimus-treated group. All events of hypothyroidism in the LENVIMA 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 LENVIMA plus everolimus-treated patients as compared with none in patients receiving everolimus alone.

In the Phase 3 HCC trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), 10.4% of patients had a baseline TSH level over the upper limit of normal. Elevation of TSH above the upper limit of normal was observed post baseline in 69.6% of LENVIMA-treated patients. On the sorafenib arm, 9.9% of patients had a baseline TSH level over the upper limit of normal and post baseline, was observed to be above the upper limit of normal in 32.2% of patients.

Dyslipidaemia

In the pivotal DTC Phase 3 SELECT trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), hypercholesterolaemia or blood cholesterol increased were reported in 5.0% of LENVIMA treated patients (0.4% were Grade ≥ 3) vs. no events in the placebo arm. Hypertriglyceridaemia or blood triglycerides increased were reported in 2.7% of LENVIMA treated patients (0.8% were Grade ≥ 3) vs. no events in the placebo arm. Most events resolved following supportive treatment, without dose interruption or reduction, which occurred in 0.4% and 0.4% of patients, respectively. No patients discontinued treatment as a result of dyslipidaemia.

In the RCC study (see Section 5.1 Pharmacodynamic properties, Clinical trials) Phase 1b plus Phase 2 population, dyslipidaemia was reported in 50.0% of patients in the LENVIMA plus everolimus-treated group (17.7% were Grade ≥ 3) and 34.0% of patients in the everolimus-treated group (8.0% were Grade ≥ 3). Reactions that occurred at an incidence of ≥ 30.0% were: hypertriglyceridaemia (40.3%), and hypercholesterolaemia (30.6%). The median time to onset of dyslipidaemia was 4.1 weeks (any grade) and 6.1 weeks (Grade ≥ 3) in the LENVIMA plus everolimus-treated group. The incidence of serious dyslipidaemia was 1.6%. Most reactions resolved following supportive treatment, although 8.1% of patients had events of dyslipidaemia that required dose interruption, and 3.2% required dose reduction. No patients discontinued treatment as a result of dyslipidaemia.

In the HCC Phase 3 study (see Section 5.1 Pharmacodynamic properties, Clinical trials), there were no events of hypercholesterolaemia on the LENVIMA arm vs. a frequency of 1.3% reported in sorafenib-treated patients. Events of blood cholesterol increased were reported in 1.5% of LENVIMA treated patients (there were no Grade ≥ 3 events) and in 0.2% of sorafenib-treated patients. Hyperlipidaemia was reported in 0.6 % of LENVIMA treated patients (no Grade ≥ 3 event) and none were reported in sorafenib-treated patients. Hypertriglyceridaemia was reported in one patient (0.2%, Grade 3 event) on the LENVIMA

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arm with no events in the sorafenib arm. No dose interruptions /reductions or discontinuations occurred as a result of these events

Diarrhoea

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

In the RCC study (see Section 5.1 Pharmacodynamic properties, Clinical trials) Phase 1b plus Phase 2 population, diarrhoea was reported in 80.6% of patients in the LENVIMA 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 LENVIMA 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 Phase 3 HCC trial (see Section 5.1 Pharmacodynamic properties, Clinical trials), diarrhoea was reported in 38.7% of patients treated with LENVIMA compared with 46.3% of patients treated with sorafenib. There was an equal frequency (4.2%) of Grade ≥ 3 events in both treatment arms.

Other special populations

Elderly

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

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

In HCC, patients of age ≥75 years were more likely to experience hypertension, proteinuria, decreased appetite, asthenia, dehydration, dizziness and hepatic encephalopathy. Arterial thromboembolic events also occurred at an increased incidence in this age group.

Sex

In 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.

In HCC, females had a higher incidence of hypertension, fatigue and ECG QT prolongation. Hepatic failure events were observed in male patients only.

Race

In DTC, Asian patients had a higher incidence than Caucasian patients of oedema peripheral, hypertension, fatigue, PPE, proteinuria, thrombocytopenia, and blood thyroid stimulating hormone increased. Japanese patients had a higher incidence of Grade 3 or 4 hypertension,

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decreased appetite, fatigue, and thrombocytopenia compared with non-Japanese subjects. There are limited data on Asian patients with RCC.

In HCC, Asian patients had a higher incidence than Caucasian patients of proteinuria and PPE syndrome, while Caucasian patients had a higher incidence of fatigue, hepatic encephalopathy and acute kidney injury.

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 events of dehydration, hypotension, pulmonary embolism, malignant pleural effusion, atrial fibrillation, and GI symptoms (abdominal pain, diarrhoea, vomiting).

Hepatic impairment

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. There are limited data on patients with hepatic impairment in RCC and endometrial carcinoma.

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

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 and pneumonia compared with subjects with normal renal function. These patients also had a higher incidence of renal events and a trend towards a higher incidence of liver events.

See also Section 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use.

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

Patients with body weight < 60 kg

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

There have been reports of overdose with LENVIMA including a single administration of 144 mg, 6 times the recommended daily dose. These cases were associated with adverse reactions consistent with the known safety profile of LENVIMA, or were without adverse reactions. Death due to multiorgan dysfunction occurred in a patient who received a single dose of LENVIMA 120 mg orally. There is no specific antidote for overdose with LENVIMA, due to the high plasma protein binding, lenvatinib is not expected to be dialyzable. In case of suspected overdose, LENVIMA should be withheld and appropriate supportive care given as required.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Lenvatinib is a multiple receptor tyrosine kinase (RTK) inhibitor that 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.

In addition, lenvatinib inhibited the proliferation of human hepatocellular carcinoma (HCC) cell lines dependent on FGFR signaling *in vitro* and caused a concurrent inhibition of FGF-receptor substrate 2α (FRS2α) phosphorylation.

In syngeneic mouse tumour models, lenvatinib decreased tumour-associated macrophages, increased activated cytotoxic T cells, and demonstrated greater antitumour 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 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.

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Pharmacodynamic effects

Cardiac electrophysiology

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

Clinical trials

Radioactive iodine refractory differentiated thyroid cancer

The SELECT study was a multicentre, randomised, double-blind, placebo-controlled trial that was conducted in 392 patients with radioactive iodine refractory differentiated thyroid cancer with independent, centrally reviewed, radiographic evidence of disease progression within 12 months (+1 month window) prior to enrolment. Radioiodine-refractory status was defined as one or more measurable lesions either with a lack of iodine uptake or with progression in spite of radioactive-iodine (RAI) therapy, or having a cumulative activity of RAI of >600 mCi or 22 GBq with the last dose at least 6 months prior to study entry.

Randomisation was stratified by geographic region (Europe, North America, and Other), prior VEGF/VEGFR-targeted therapy (patients may have received 0 or 1 prior VEGF/VEGFR-targeted therapy), and age (≤65 years or >65 years). The main efficacy outcome measure was progression-free survival (PFS) as determined by blinded independent radiologic review using Response Evaluation Criteria in Solid Tumours (RECIST) 1.1.

Secondary efficacy outcome measures included overall response rate and overall survival (OS). Patients in the placebo arm could opt to receive LENVIMA treatment at the time of confirmed disease progression.

Eligible patients with measurable disease according to RECIST 1.1 were randomised 2:1 to receive LENVIMA 24 mg once daily (n=261) or placebo (n=131). Baseline demographics and disease characteristics were well balanced for both treatment groups. Of the 392 patients randomised, 76.3% were naïve to prior VEGF/VEGFR-targeted therapies, 49.0% were female, 49.7% were European, and the median age was 63 years. Histologically, 66.1% had a confirmed diagnosis of papillary thyroid cancer and 33.9% had follicular thyroid cancer which included Hürthle cell 14.8% and clear cell 3.8%. Metastases were present in 99% of the patients: lungs in 89.3%, lymph nodes in 51.5%, bone in 38.8%, liver in 18.1%, pleura in 16.3%, and brain in 4.1%. The majority of patients (54%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0; 42.1% had a status of 1; 3.9% had a status above 1. The median cumulative RAI activity administered prior to study entry was 350 mCi (12.95 GBq).

A statistically significant prolongation in PFS was demonstrated in LENVIMA-treated patients compared with those receiving placebo ($p < 0.0001$). The positive effect on PFS was similar in the subgroups that received 0 or 1 prior VEGF/VEGFR-targeted therapy (see Table 11). In addition, the positive effect on PFS was seen across the subgroups of age, sex,

Attachment 1: Product information for AusPAR - LENVIMA - lenvatinib (as mesilate) - Eisai Australia Pty Limited - PM-2019-02448-1-4 FINAL 5 May 2020. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>

race, histological subtype, and geographic region. Following independent review confirmation of disease progression, 109 (83.2%) patients randomised to placebo crossed over to receive open-label LENVIMA.

There was no statistically significant difference in overall survival in the treatment arm compared to the placebo group at the primary analysis (HR (95% CI): 0.73 (0.59, 1.07)). However, the SELECT study was not powered to demonstrate an improvement in OS, and the high rate of crossover of patients in the placebo arm to the treatment arm after confirmed disease progression made demonstration of a statistically significant difference in OS difficult.

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

The study did not measure quality of life (QoL). The effect of treatment on QoL can therefore not be assessed and QoL may not be improved with LENVIMA treatment.

Table 11 Efficacy Results in radioactive iodine refractory differentiated thyroid cancer

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

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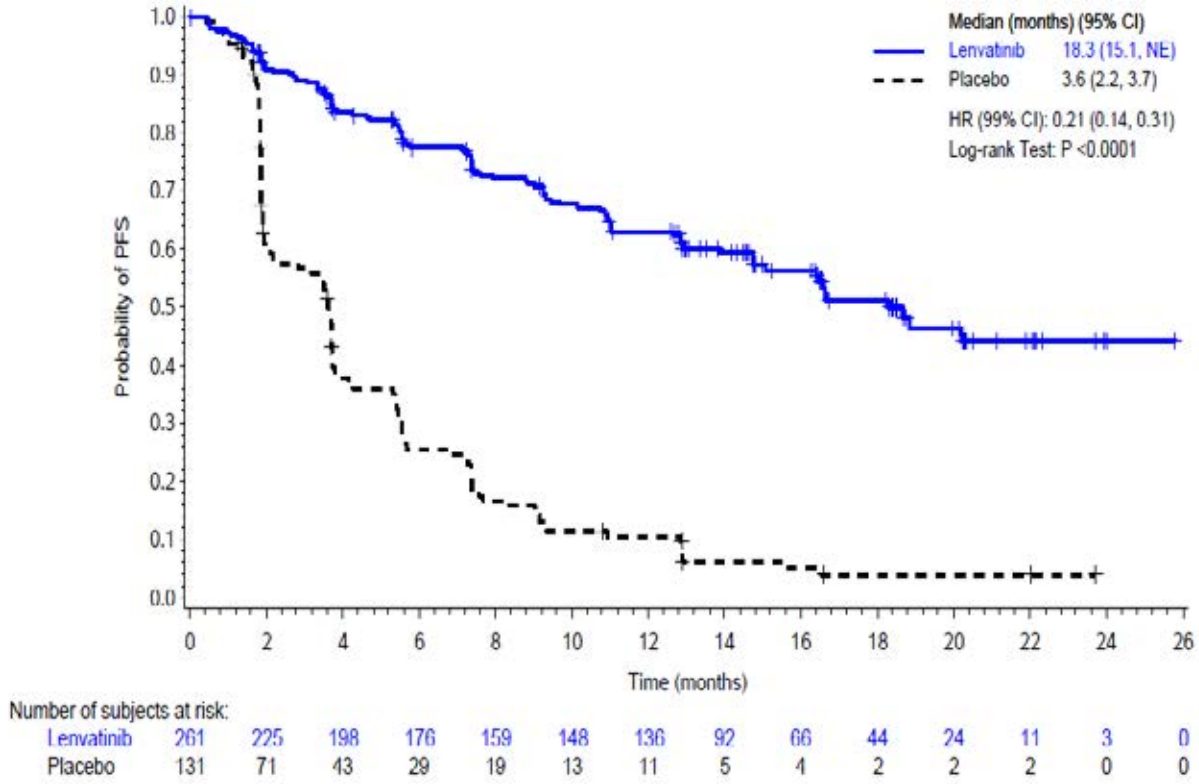
CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival; RPSFT, rank preserving structural failure time model; VEGF/VEGFR, vascular endothelial growth factor /vascular endothelial growth factor receptor.

a) Independent radiologic review.
b) Stratified by region (Europe vs. North America vs. Other), age group (≤65 year vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs. 1).
c) Estimated with Cox proportional hazard model.
d) Estimated using the Kaplan-Meier method; the 95% CI was constructed with a generalised Brookmeyer and Crowley method in patients with a best overall response of complete response or partial response.
e) Not adjusted for crossover effect.

Figure 1 Kaplan-Meier Curveof Progression-Free Survival - DTC



Renal Cell Carcinoma

A multicentre, randomised, open-label, trial was conducted to determine the safety and efficacy of LENVIMA administered alone or in combination with everolimus in subjects with unresectable advanced or metastatic Renal Cell Carcinoma (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 LENVIMA plus 5 mg of everolimus. The Phase 2 portion enrolled a total of 153 patients with unresectable advanced or metastatic RCC, who had previously received 1 prior VEGF-targeted treatment, 1:1:1 to LENVIMA 18 mg plus everolimus 5 mg, LENVIMA 24 mg monotherapy, or everolimus 10 mg monotherapy. All medications were administered orally once daily. Patients were required to have histological confirmation of predominant clear cell RCC, and ECOG Performance Status of 0 or 1. Patients were stratified by haemoglobin level (≤ 13 g/dL vs. > 13 g/dL for males and

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≤ 11.5 g/dL vs > 11.5 g/dL for females) and corrected serum calcium (≥ 10 mg/dL vs. < 10 mg/dL).

Of the 101 patients randomly allocated to the LENVIMA plus everolimus arm and everolimus monotherapy, 72% were male, the median age was 60 years, 31% were 65 years or older, and 96% were Caucasian. All patients were classified as having Stage IV RCC. All patients had a baseline ECOG PS of either 0 (54%) or 1 (46%) with similar distribution across the 2 treatment arms. Memorial Sloan Kettering Cancer Center (MSKCC) favourable, intermediate, and poor risk categories were observed respectively, in 24%, 37%, and 39% of patients in the LENVIMA plus everolimus arm, and 24%, 38%, and 38% of patients in the everolimus arm.

The primary efficacy outcome measure was investigator assessed PFS evaluated according to RECIST 1.1. Efficacy results are summarised in Table 12 and Figure 2 and Figure 3. The treatment effect of the combination on PFS was supported by a retrospective independent blinded 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 (investigator assessment)

	LENVIMA 18 mg + Everolimus 5 mg (N=51)	**Everolimus 10 mg (N=50)**
Progression-Free Survival (PFS)[ab]		
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)[c] LENVIMA + Everolimus vs Everolimus	0.37 (0.22, 0.62)	-
Overall Survival[d]		
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)[c] LENVIMA + Everolimus vs Everolimus	0.59 (0.36, 0.97)	-
Objective Response Rate (Confirmed)[b]		
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)

Tumour assessments were based on RECIST v1.1 criteria for progression but only confirmed responses are included for ORR.
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 Data cutoff date = 13 Jun 2014
c Hazard ratio is based on a stratified Cox regression model including treatment as a covariate factor and haemoglobin and corrected serum calcium as strata.
d Data cutoff date = 31 Jul 2015

Figure 2 Kaplan-Meier Curve of Progression-Free Survival (Investigator Assessment - RCC)

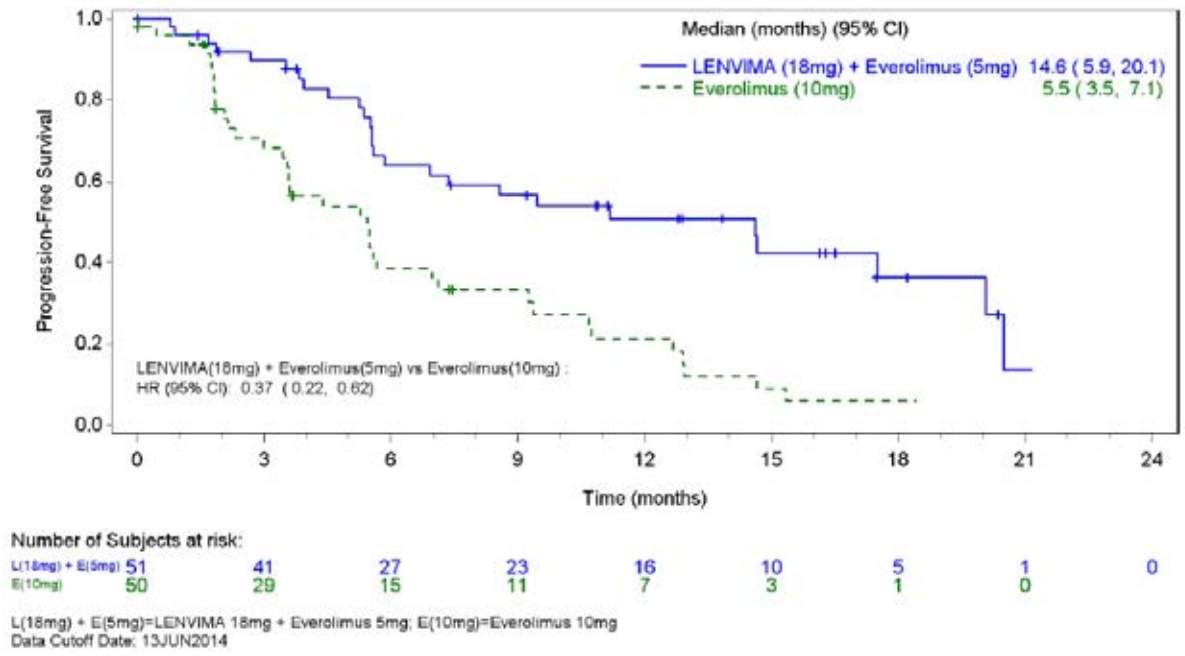
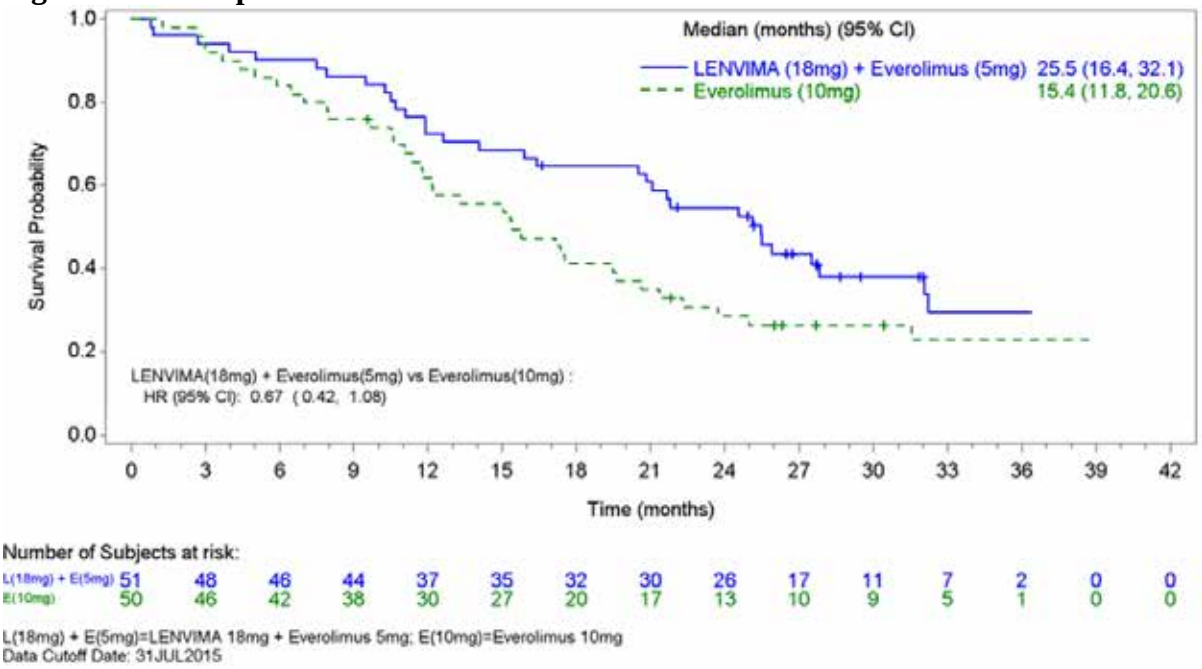


Figure 3 Kaplan-Meier Curve of Overall Survival - RCC



Hepatocellular Carcinoma

A multicenter, open-label study was conducted in 954 patients with unresectable hepatocellular carcinoma who were randomized to LENVIMA or sorafenib. The starting dose of LENVIMA, given once daily, was based on baseline body weight: 12 mg for patients with a body weight ≥60 kg and 8 mg for patients with a body weight <60 kg. The dose of sorafenib was 400 mg given orally twice daily.

Patients were required to have a histologically or cytologically confirmed diagnosis of unresectable HCC, or a clinically confirmed diagnosis of HCC according to the American Association for the Study of Liver Diseases criteria, including cirrhosis of any etiology, or with chronic hepatitis B or C infection. Patients could have BCLC stage B or C disease, and could only have Child Pugh category A liver dysfunction (i.e., a score of 5-6). Patients had at least 1 measureable target hepatic or nonhepatic lesion according to mRECIST, and adequate liver, bone marrow, blood coagulation, renal, and pancreatic function. Patients were stratified by region, presence or absence of macroscopic portal vein invasion (MPVI) or extrahepatic spread (EHS) or both, Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1, and BW (<60 kg or ≥60 kg). The majority of patients in both treatment arms had an ECOG PS of 0 at Baseline (63%), Child-Pugh score of 5 (76%), and weighed ≥60 kg (69%). The median age was 62 years, 84% were male, 16% were female, 69% were Asian, 1% were black, and 29% were white. Approximately 80% of patients in Study 304 had BCLC stage C disease at study entry. This percentage was similar between the treatment arms (LENVIMA 374/478, 78.2%; sorafenib 384/476, 80.7%).

LENVIMA was non-inferior for Overall Survival (OS) to sorafenib. Median OS was 13.6 months compared to 12.3 months for sorafenib with HR = 0.92 [95% CI of (0.79, 1.06)].

Based on investigator assessment evaluated according to mRECIST, LENVIMA treatment resulted in statistically significant (P<0.00001) and clinically meaningful improvement over sorafenib in the secondary endpoints of PFS and ORR. LENVIMA treatment significantly prolonged TTP compared to sorafenib, with a median TTP that was more than twice as long as that of sorafenib. Retrospective independent review of imaging corroborated the secondary endpoints of PFS, TTP and ORR. These efficacy results are summarized in Table 13 and Figure 4, Figure 5 and Figure 6.

Table 13 Efficacy Results in Hepatocellular Carcinoma

	LENVIMA (N= 478)	**Sorafenib (N=476)**
Overall Survival		
Number of deaths, n (%)	351 (73.4)	350 (73.5)
Median OS in months (95% CI) [a]	13.6 (12.1, 14.9)	12.3 (10.4, 13.9)
Hazard Ratio (95% CI)[b, c]	0.92 (0.79,1.06)	
Progression-Free Survival (PFS) per Investigator Assessment (mRECIST)		
Number of events, n (%)	349 (73.0)	367 (77.1)
Progressive disease, n (%)	308 (64.4)	343 (72.1)
Death, n (%)	41 (8.6)	24 (5.0)
Median PFS in months (95% CI)[a]	7.4 (6.9, 8.8)	3.7 (3.6, 4.6)
Hazard Ratio (95% CI) [b, c]	0.66 (0.57, 0.77)	
P-value [c,d]	<0.00001	
Time to Progression per Investigator Assessment (mRECIST)		
Subjects with Disease Progression, n (%) [e]	308 (64.4)	343 (72.1)
Censored Subjects, n (%)	170 (35.6)	133 (27.9)
Median (95% CI) [a]	8.9 (7.4, 9.2)	3.7 (3.6, 5.4)
Hazard Ratio (95% CI) [b, c]	0.63 (0.53, 0.73)	
P-value [c,d]	<0.00001	
Objective Response Rate per Investigator Assessment (mRECIST)		
Objective response rate, n (%)	115 (24.1)	44 (9.2)

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Table 13 Efficacy Results in Hepatocellular Carcinoma

	LENVIMA (N= 478)	Sorafenib (N=476)
(95% CI) [f]	(20.2, 27.9)	(6.6, 11.8)
Complete responses, n (%)	6 (1.3)	2 (0.4)
Partial responses, n (%)	109 (22.8)	42 (8.8)
Odds ratio (95% CI) [g]	3.13 (2.15, 4.56)	
P-value [g]	<0.00001	
Objective Response Rate per Independent Review (mRECIST)		
Objective response rate, n (%)	194 (40.6)	59 (12.4)
(95% CI) [f]	(36.2, 45.0)	(9.4, 15.4)
Odds ratio (95% CI) [g]	5.01 (3.59, 7.01)	
P-value [g]	<0.00001	
Objective Response Rate per Independent Review (RECIST 1.1)		
Objective response rate, n (%)	90 (18.8)	31 (6.5)
(95% CI) [f]	(15.3, 22.3)	(4.3, 8.7)
Odds ratio (95% CI) [g]	3.34 (2.17, 5.14)	
P-value [g]	<0.00001	

Data cutoff date: 13 Nov 2016.

The noninferiority margin for the HR of LENVIMA versus sorafenib is 1.08. Percentages are based on the total number of subjects within the relevant treatment group in the Full Analysis Set.

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

a Quartiles are estimated by the Kaplan-Meier method, and the 95% CIs are estimated with a generalized Brookmeyer and Crowley method.

b Hazard ratio is for LENVIMA vs. sorafenib, based on a Cox model including treatment group as a factor.

c Stratified by region (Region 1: Asia-Pacific; Region 2: Western regions), macroscopic portal vein invasion or extrahepatic spread or both (yes, no), ECOG PS (0, 1) and body weight (<60 kg, ≥60 kg).

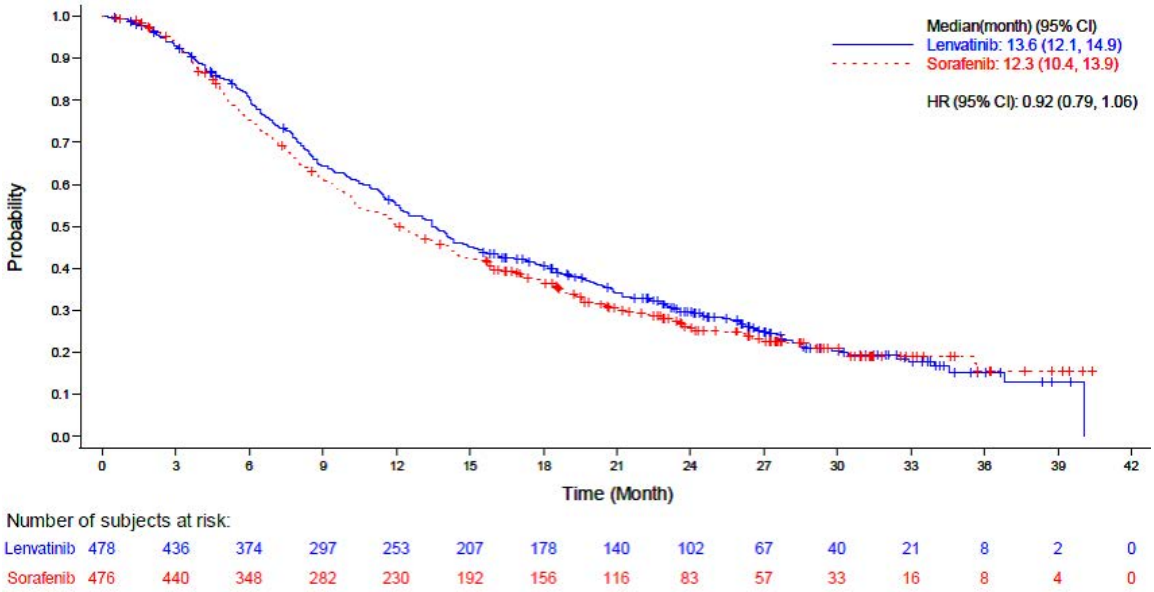
d P-value is for the superiority test of LENVIMA versus sorafenib.

e Deaths were not counted as progression events in this analysis.

f 95% CI was calculated using asymptotic normal approximation.

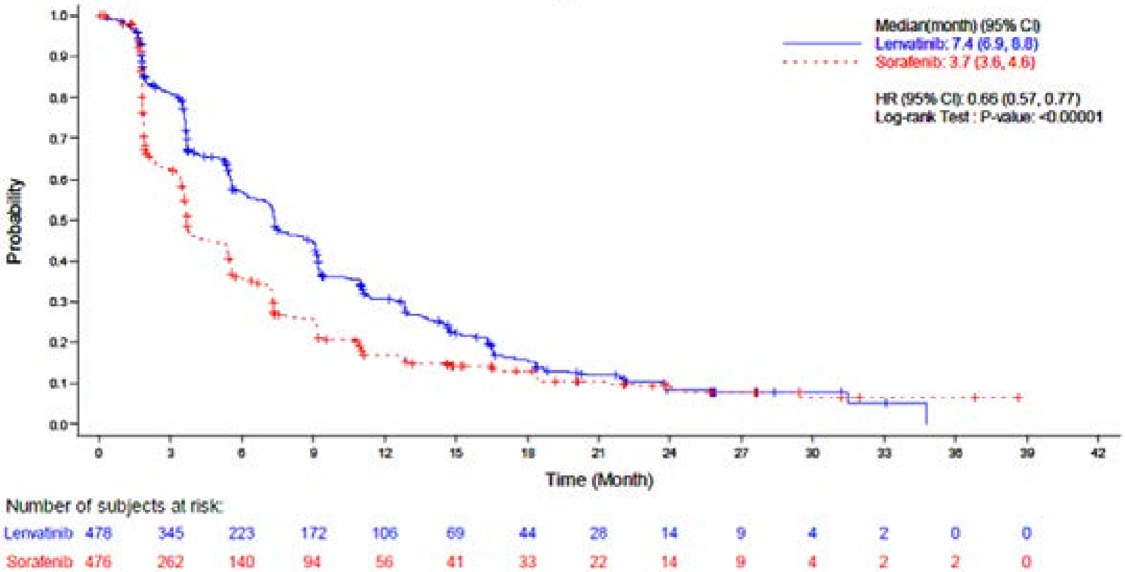
g Odds ratio and P-value (for superiority test) were calculated using the Cochran-Mantel-Haenszel method, stratified by IxRS stratification factors.

Figure 4 Kaplan-Meier Curve of Overall Survival – HCC



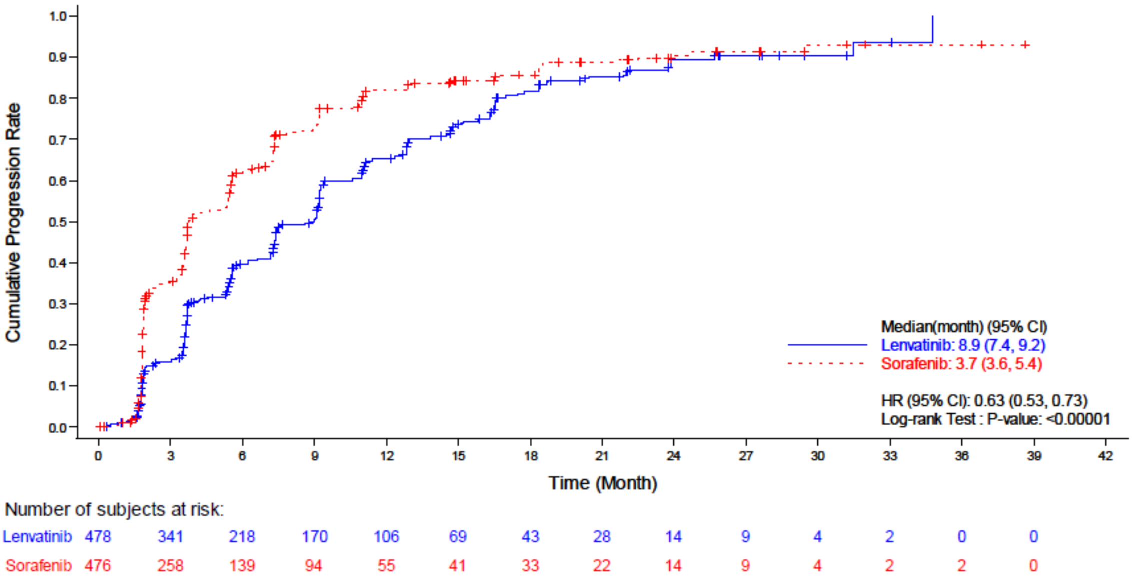
Data cutoff date = 13 Nov 2016.
Noninferiority margin for hazard ratio (HR: LENVIMA vs sorafenib = 1.08).
Median was estimated with the Kaplan-Meier method and the 95% confidence interval was constructed with a generalized Brookmeyer and Crowley method.
HR was estimated from the Cox proportional hazard model with treatment as independent variable and stratified by IxRS stratification factors. The Efron method was used for ties.
+ = censored observations
CI = confidence interval; HR = hazard ratio; IxRS = interactive response system.

Figure 5 Kaplan-Meier Curve of Progression-free Survival – HCC



Data cutoff date = 13 Nov 2016.
Median was estimated with the Kaplan-Meier method and the 95% CI was constructed with a generalized Brookmeyer and Crowley method.
Hazard ratio is expressed as LENVIMA: sorafenib and was estimated from the Cox proportional hazard model with treatment as an independent variable and stratified by IxRS stratification factors. The Efron method was used for ties.
P-value was for superiority test (LENVIMA vs. Sorafenib) and was calculated using log-rank test stratified by IxRS stratification factors.
+ = censored observations.
CI = confidence interval; HR = hazard ratio; IxRS = interactive response system.

Figure 6 Kaplan-Meier Curve of Time to Progression – HCC



Data cutoff date: 13 Nov 2016.

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The median was estimated using the Kaplan-Meier method and the 95% CI was constructed with a generalized Brookmeyer and Crowley method.
Hazard ratio is expressed as LENVIMA: sorafenib and was estimated from the Cox proportional hazard model with treatment as an independent variable, and stratified by IxRS stratification factors. Efron method was used for ties.
P-value is for the superiority test of LENVIMA vs sorafenib and was calculated using the log-rank test stratified by IxRS stratification factors.
CI = confidence interval; HR = hazard ratio; IxRS = interactive voice/web response system.

Assessment on Quality of Life (QoL) in Patients with HCC

Three QoL questionnaires were administered EORTC QLQ-C30, EORTC QLQ-HCC18 and the EQ-5D-3L.

Compared to patients treated with LENVIMA, those treated with sorafenib experienced greater risks of more rapid time to clinically meaningful worsening of symptoms and function for the domain of Diarrhoea (nominal $p < 0.0001$) from the EORTC QLQ-C30.

Endometrial Carcinoma (EC)

The efficacy of LENVIMA in combination with pembrolizumab was investigated in Study 111 (NCT02501096), a single-arm, multicentre, 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 tumour 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 tumours that were not MSI-H or dMMR, 10% (n=11) had tumours that were MSI-H or dMMR, and in 3% (n=3) the status was not known. Tumour MSI status was determined using a polymerase chain reaction (PCR) test. Tumour MMR status was determined using an immunohistochemistry (IHC) test. The baseline characteristics of the 94 patients with tumours 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 summarised in Table 14.

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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%)

Tumour 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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Lenvatinib is rapidly absorbed after oral administration with T_{max} typically observed from 1 to 4 hours post-dose. Food does not affect the extent of absorption, but slows the rate of absorption. When administered with food to healthy subjects, peak plasma concentrations are delayed by 2 hours.

A high degree of inter-individual variability in average exposure at steady state was observed, with a 6-fold range when used as monotherapy at the 24 mg dose, and 7-fold range when LENVIMA 18 mg dose is administered in combination with 5mg everolimus. In HCC subjects, the inter-individual variability in average exposure at steady state was 6-fold and 5-fold range when used as monotherapy at 8 mg and 12 mg doses, respectively.

Distribution

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

In vitro, the lenvatinib blood-to-plasma concentration ratio ranged from 0.589 to 0.608 (0.1 - 10 μg/mL, mesilate). *In vitro* studies indicate that lenvatinib is a substrate for P-gp and BCRP. Lenvatinib is not a substrate for OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE2-K or the BSEP.

Metabolism

In vitro, cytochrome P450 3A4 was the predominant (>80%) cytochrome isoform involved in the P450- mediated metabolism of lenvatinib. *In vivo,* inducers and inhibitors of CYP 3A4

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had a minimal effect on lenvatinib exposure (see Section 4.5 Interactions with other medicines). Patients should avoid strong inducers of CYP 3A4 and exercise caution with mild or moderate inhibitors or inducers when using everolimus (see Everolimus Product Information) in combination with LENVIMA.

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

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

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

Excretion

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 M2 metabolite was the predominant analyte in excreta (~5% of the dose) with lenvatinib the second most prominent (~2.5%).

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 (QD).

Lenvatinib displays minimal accumulation at steady state. Over this range, the median accumulation index (Rac) ranged from 0.96 (20 mg) to 1.54 (6.4 mg). In patients with HCC, the mean accumulation ratio was 1.49 in those with higher Child-Pugh scores (7-8) receiving 8 mg lenvatinib.

Special populations

Hepatic impairment

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

Lenvatinib exposure, based on dose-adjusted $AUC_{0\text{-}t,unbound}$ and $AUC_{0\text{-}inf,unbound}$, was approximately 65%, 122%, and 273% of normal for subjects with mild, moderate, and severe hepatic impairment, respectively. Based on the analogous $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ data, lenvatinib exposure was 119%, 107%, and 180% of normal for subjects with mild, moderate, and severe hepatic impairment, respectively (see Section 4.2 Dose and method of administration).

Renal impairment

The pharmacokinetics of lenvatinib following a single 24 mg dose were evaluated in 6 subjects each with mild, moderate, or severe renal impairment, and compared with 8 healthy, demographically matched subjects. Subjects with end-stage renal disease were not studied. The percentage of unbound lenvatinib was similar between subjects with normal renal function (8% ± 3%, mean ± SD) and those with severely impaired renal function (9% ± 2%). $AUC_{0\text{-}inf,unbound}$ estimates for subjects with mild, moderate, or severe renal impairment were 54%, 129%,and 184%, respectively, compared with normal subjects. Additionally, a linear equation was fit to the creatinine clearance vs. $AUC_{0\text{-}inf,unbound}$ data and exposure was predicted. Subjects with severe renal impairment were predicted to have a 2.4-fold increase in exposure. Therefore dosage needs to be reduced in DTC, RCC, and endometrial carcinoma patients with severe renal impairment (see Section 4.2 Dose and method of administration). No dosage recommendations are available for HCC patients with severe renal impairment (See DOSAGE AND ADMINISTRATION). Use in HCC patients with severe renal impairment is not recommended.

Age, sex, weight, race

Based on a population pharmacokinetic analysis of patients receiving up to 24 mg LENVIMA once daily, including HCC patients weighing < 60 kg and ≥ 60 kg receiving 8 mg and 12 mg, respectively, weight showed a statistically significant effect. The final PK model for lenvatinib included body-weight effect as an allometric constant on both clearance (CL/F) and volume parameters, whereby parameters increased with increasing body weight. The decrease in CL/F in subjects with low body weight resulted in an increase in lenvatinib exposure (AUC) whereby subjects weighing < 60 kg had approximately 35% higher exposure

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to lenvatinib than subjects weighing ≥ 60 kg when receiving the same dose. Based on the individual lenvatinib AUC at steady state for subjects with HCC, the median value and range of AUC are comparable between the group of starting dose of 8 mg for body weight < 60 kg and 12 mg for body weight ≥ 60 kg, which supports the starting doses of 8 mg and 12 mg for body weight < 60 kg and ≥ 60 kg, respectively, in HCC patients.

After accounting for body weight, neither age, sex, or race (Japanese vs. other, Chinese vs other, white vs. other) influenced lenvatinib PK.

Paediatric Population

Paediatric patients have not been studied.

Genomic assessment of lenvatinib pharmacokinetic parameters

Because of lenvatinib's extensive metabolism, the effect of selected drug-metabolising enzyme phenotypes on lenvatinib clearance was investigated using data derived from the Affymetrix drug-metabolising enzyme and transporter (DMET Plus) microarray genotyping platform. None of the phenotypes for CYP3A5, CYP1A2, CYP2A6, or CYP2C19 had a significant impact on lenvatinib clearance.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Lenvatinib was not mutagenic in the in vitro Ames and mouse lymphoma tests and not clastogenic in an in vivo micronucleus assay in rats. These studies indicate a low genotoxic potential for LENVIMA.

Carcinogenicity

Carcinogenicity studies have not been conducted with LENVIMA.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The capsules contain the excipients Calcium carbonate, Mannitol, Microcrystalline cellulose, Hydroxypropylcellulose, and Purified talc. The capsule shell contains the excipients Hypromellose, Titanium dioxide, Iron oxide yellow and Iron oxide red. The printing ink on the capsules contains the excipients Shellac, Iron oxide black, Potassium hydroxide and Propylene glycol.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

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6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

LENVIMA 4 mg hard capsules are available in polyamide/aluminium/PVC/aluminium blisters of 30 capsules.

LENVIMA 10 mg hard capsules are available in polyamide/aluminium/PVC/aluminium blisters of 30 capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

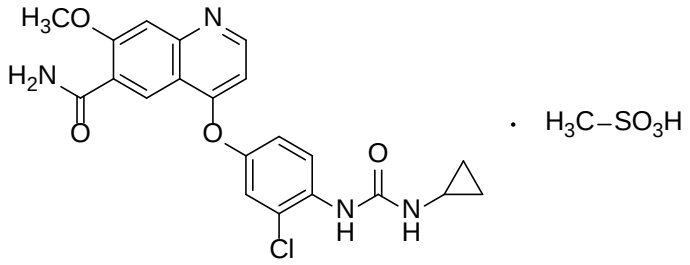
Lenvatinib mesilate is a white powder and is sparingly soluble in acetic acid and slightly soluble in water, *N*,*N*-dimethylformamide, methanol, *N*-methylpyrrolidone, and pyridine. It is very slightly soluble in 1,3-dimethyl-2-imidazolidinone and practically insoluble in acetonitrile, dehydrated ethanol, 1-propanol, 2-propanol, 1-octanol and isopropyl acetate. In aqueous solutions, lenvatinib mesilate is very slightly soluble in 0.1 mol/L HCl and practically insoluble in Britton-Robinson buffer, pH 3-11.

Chemical structure

Lenvatinib is a multiple receptor tyrosine kinase (RTK) inhibitor.

Chemical Name: 4-[3-chloro-4-(*N*'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate.

The empirical formula of lenvatinib is $C_{21}H_{19}ClN_4O_4 \cdot CH_4O_3S$



CAS Number:

CAS: 857890-39-2

7 MEDICINE SCHEDULE (POISON STANDARD)

Schedule 4 – Prescription only medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

28 January 2016

10 DATE OF REVISION

17 September 2019

Summary Table of changes

Version Number	Section changed	Summary of new information
2.1	All	Product Information reformatted in accordance with the new TGA template.
2.1	4.4	Addition of precaution regarding wound healing complications
2.1	4.4	Addition of information to hypertension precaution regarding complications associated with poorly controlled hypertension.
2.1	4.8	Addition of adverse events identified in post-marketing monitoring
3	4.1, 4.2, 4.4, 4.8, 5.1, 5.2	Addition of text to support extension of indication for the treatment of patients with hepatocellular carcinoma.
3.1	4.4	Addition of pneumothorax information to Non-Gastrointestinal fistula precaution.
3.1	4.8	Addition of adverse events identified in post-marketing monitoring.
4	4.1, 4.2, 4.8, 5.1, 5.2	Addition of text to support extension of indication for the treatment of patients with endometrial carcinoma.
4	4.2	Amendment of Dose and method of administration section to improve presentation and simplify information provided.