**Attachment 1: Product information for AusPAR Lenvima Eisai Australia Pty Ltd PM-2014-04321-1-4 Final 30 August 2016. This Product Information was approved at the time this AusPAR was published.**

# PRODUCT INFORMATION

## Lenvima™ lenvatinib (as lenvatinib mesilate) hard capsules

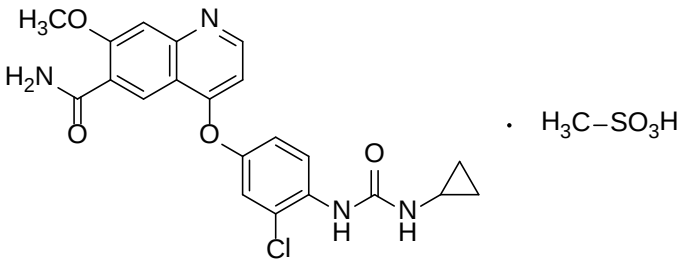
## NAME OF THE MEDICINE

Lenvatinib as lenvatinib mesilate

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: 857890-39-2

DESCRIPTION

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.

Each 4 mg hard capsule contains lenvatinib mesilate equivalent to 4 mg lenvatinib.
Each 10 mg hard capsule contains lenvatinib mesilate equivalent to 10 mg lenvatinib.
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.

## PHARMACOLOGY

### 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.

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 lenvatinib than in patients treated with placebo.

### Pharmacokinetics

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

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). Lenvatinib is a substrate for P-gp and BCRP. Lenvatinib is not a substrate for OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, 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 had a minimal effect on lenvatinib exposure (see DRUG INTERACTIONS).

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.

Elimination

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

Following administration of radiolabelled lenvatinib to 6 patients with solid tumours, approximately two-thirds and one-fourth of the radiolabel were eliminated in the faeces and urine, respectively. The 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).

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 DOSAGE AND 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 patients with severe renal impairment (See DOSAGE AND ADMINISTRATION).

*Age, sex, weight, race*
Based on a population pharmacokinetic analysis of patients receiving up to 24 mg lenvatinib once daily, weight showed a statistically significant effect, but only explained 2.8% of the inter-individual variability, on apparent clearance. Subjects weighing <60 kg had 36% higher exposure to lenvatinib than subjects weighing ≥60 kg. Simulations showed that the small effect of body weight on lenvatinib exposure does not warrant any dose adjustment. After accounting for body weight, neither age, sex, nor race (Japanese vs. other, Caucasian 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.

## 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 enrollment. 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 lenvatinib treatment at the time of confirmed disease progression.

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

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

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 lenvatinib, 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 lenvatinib treatment.

Table 1 - Efficacy Results

| | Lenvatinib N=261 | Placebo N=131 |
|---|---|---|
| **Progression-Free Survival (PFS)[a]** | | |
| Number of progressions or deaths (%) | 107 (41.0) | 113 (86.3) |
| Median PFS in months (95% CI) | 18.3 (15.1, NE) | 3.6 (2.2, 3.7) |
| Hazard Ratio (99% CI)[b,c] | 0.21 (0.14, 0.31) | |
| P-value[b] | <0.0001 | |
| **Patients who had received 0 prior VEGF/VEGFR-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 | |

CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival; RPSFT, rank preserving structural failure time model; VEGF/VEGFR, vascular endothelial growth factor /vascular endothelial growth factor receptor.
a: Independent radiologic review.
b: Stratified by region (Europe vs. North America vs. Other), age group (≤65 year vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs. 1).
c: Estimated with Cox proportional hazard model.
d: Estimated using the Kaplan-Meier method; the 95% CI was constructed with a generalised Brookmeyer and Crowley method in patients with a best overall response of complete response or partial response.
e: Not adjusted for crossover effect.

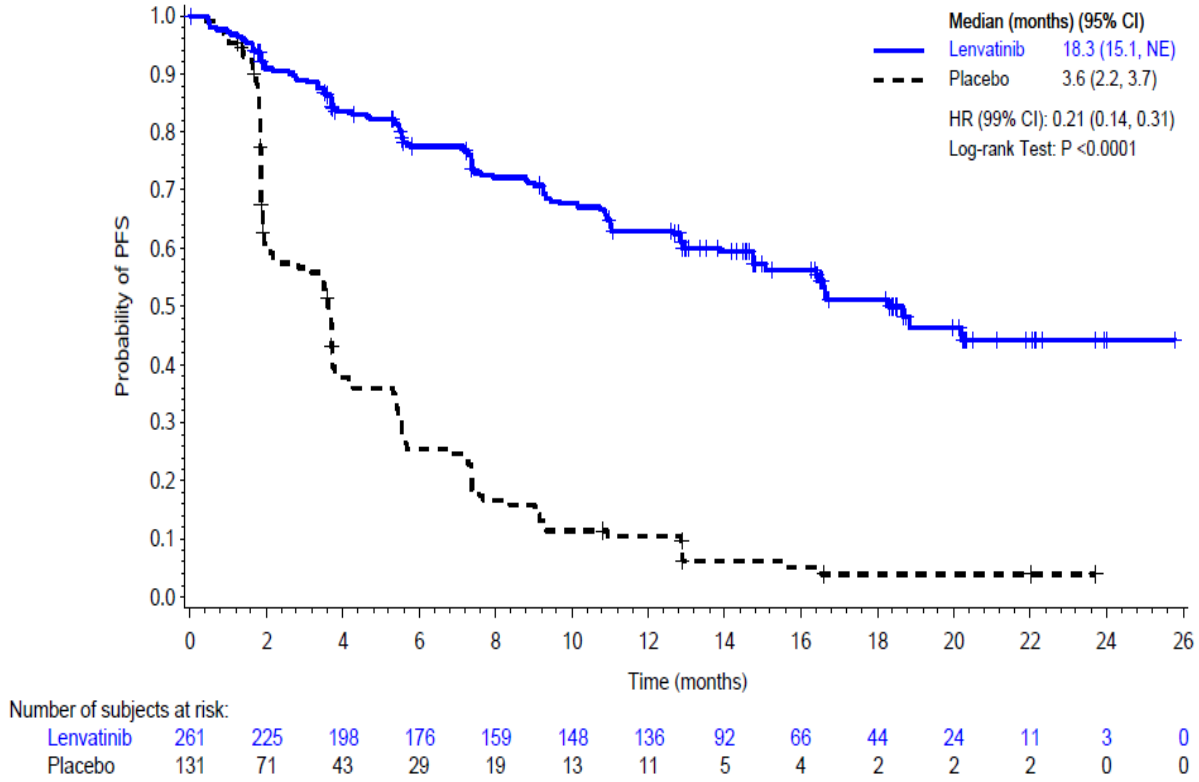



**Figure 1 Kaplan-Meier Plot of Progression-Free Survival**

## INDICATIONS

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

## CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (see DESCRIPTION)

## PRECAUTIONS

Hypertension

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

class of antihypertensive should be added. For patients with hypertension and proteinuria, treatment with an angiotensin-converting enzyme inhibitor or angiotensin-II-receptor antagonist is preferred. When necessary, manage hypertension as recommended in Table 2.

**Table 2 Recommended Management of Hypertension**

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

BP, blood pressure

Proteinuria

Proteinuria has been reported in patients treated with lenvatinib, usually occurring early in the course of the treatment (see ADVERSE EFFECTS). Monitor urine protein regularly. If urine dipstick proteinuria ≥2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary (see DOSAGE AND ADMINISTRATION). Lenvima should be discontinued in the event of nephrotic syndrome.

Renal failure and impairment

Events of renal impairment (including renal failure) have been reported in patients treated with lenvatinib (see ADVERSE EFFECTS). The primary risk factor identified was dehydration and/or hypovolemia due to gastrointestinal toxicity. Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or renal failure. Dose interruptions, adjustments, or discontinuation may be necessary (see DOSAGE AND ADMINISTRATION).

If patients have severe renal impairment, the initial dose of lenvatinib should be adjusted (See DOSAGE and ADMINISTRATION)

Cardiac failure

Cardiac failure (observed in <1% of patients) and decreased left ventricular ejection fraction have been reported in patients treated with lenvatinib (see ADVERSE EFFECTS). Patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose

interruptions, adjustments, or discontinuation may be necessary (see DOSAGE AND ADMINISTRATION).

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

Events of posterior reversible encephalopathy syndrome (PRES, also known as RPLS) have been reported in patients treated with lenvatinib (observed in <1% or patients; ADVERSE EFFECTS). 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 Table 2 Recommended Management of Hypertension). In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary (see DOSAGE AND ADMINISTRATION).

Hepatotoxicity

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

If patients have severe hepatic impairment, the initial dose of lenvatinib should be adjusted (see DOSAGE and ADMINISTRATION)

Haemorrhagic events

Serious haemorrhagic events have been reported in patients treated with lenvatinib (see section ADVERSE EFFECTS, Selected Adverse Effects).Cases of fatal intracranial haemorrhage have been reported in some patients with brain metastases. . In the case of bleeding, dose interruptions, adjustments, or discontinuation may be necessary (see DOSAGE AND ADMINISTRATION).

Arterial thromboembolic events

Arterial thromboembolic events (cerebrovascular accident, transient ischaemic attack, and myocardial infarction) have been reported in patients treated with lenvatinib (see ADVERSE EFFECTS). Lenvatinib 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.

Gastrointestinal perforation and fistula formation

Events of gastrointestinal perforation or fistula have been reported in patients treated with lenvatinib (see ADVERSE EFFECTS). 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 DOSAGE AND ADMINISTRATION).

QT interval prolongation

The effect of a single 32-mg dose of lenvatinib on the QT/QTc interval was evaluated in a thorough QT study in healthy subjects. In this study lenvatinib did not prolong the QT/QTc interval. QT/QTc interval prolongation has been reported at a higher incidence in patients treated with lenvatinib than in patients treated with placebo (see ADVERSE EFFECTS). Electrocardiograms should be monitored in patients 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. 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.

Hypocalcaemia

Hypocalcaemia was observed in patients taking LENVIMA during clinical studies (see ADVERSE EFFECTS). Close monitoring of blood calcium level is recommended.

Impairment of thyroid stimulating hormone suppression

Lenvatinib impairs exogenous thyroid suppression (see ADVERSE EFFECTS). Thyroid stimulating hormone (TSH) levels should be monitored on a regular basis and thyroid hormone administration should be adjusted to reach appropriate TSH levels, according to the patient's therapeutic target.

**Special Populations**

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

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

**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** (Category D)

There is insufficient information on the use of lenvatinib 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.

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

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

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

**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.

### Carcinogenicity

Carcinogenicity studies have not been conducted with lenvatinib.

### 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 lenvatinib.

### Effects on ability to drive and use machines

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

## INTERACTIONS WITH OTHER MEDICINES

### Drug Interaction Studies

Effect of other medicinal products on lenvatinib

*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 lenvatinib 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 drugs.

Effect of lenvatinib 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, 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. In human liver cytosol, lenvatinib did not inhibit aldehyde oxidase activity.

## ADVERSE EFFECTS

### Clinical Trials

Summary of safety profile

The safety profile of lenvatinib is based on a pooled analysis of safety data from clinical trials in which 1108 patients were treated with lenvatinib including 452 patients with radioactive iodine refractory differentiated thyroid cancer (RAI - Refractory DTC), who received the recommended dose in the pivotal Phase 3 SELECT trial and two Phase 2 clinical trials, and 656 patients with other cancer types.

The most frequently reported adverse reactions in 452 patients with RAI - Refractory DTC (occurring in ≥30% of patients) were hypertension, diarrhoea, decreased appetite, weight decreased, fatigue, nausea, proteinuria, stomatitis, vomiting, dysphonia, headache, and palmar-plantar erythrodysaesthesia syndrome (PPE). Hypertension and proteinuria tend to occur early during lenvatinib treatment (see Selected Adverse Reactions). The majority of Grade 3 or 4 adverse reactions occurred during the first 6 months of treatment except for diarrhoea, which occurred throughout treatment, and weight loss, which tended to be cumulative over time.
Adverse events led to dose reductions in 63.1% and discontinuations in 19.5% of 452 patients with RAI - Refractory DTC.

Adverse reactions that most commonly led to dose reductions (in ≥5% of patients) were hypertension, proteinuria, diarrhoea, fatigue, PPE, weight decreased, and decreased appetite. Adverse reactions that most commonly led to discontinuation of lenvatinib were proteinuria, asthenia, hypertension, cerebrovascular accident, diarrhoea, and pulmonary embolism.

Table 3 shows the incidence rates of adverse reactions observed in 452 patients with RAI - Refractory DTC who received the recommended dose in the pivotal Phase 3 SELECT trial and two Phase 2 clinical trials.

Frequencies are defined as:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)

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

**Table 3 Adverse reactions reported in patients in clinical trials**

| **System Organ Class** (MedDRA terminology*) | **Very Common** | **Common** | **Uncommon** |
|---|---|---|---|
| Infections and infestation | Urinary tract infection | | Perineal abscess |
| Blood and lymphatic disorders | Thrombocytopenia[a] | Lymphopenia[a] | Splenic infarction |
| Endocrine disorders | | Blood thyroid stimulating hormone increased<br>Hypothyroidism | |
| Metabolism and nutrition disorders | Decreased appetite<br>Weight decreased<br>Hypocalcaemia‡<br>Hypokalaemia | Dehydration<br>Hypomagnesaemia[b]<br>Hypercholesterolaemia[b] | |
| Psychiatric disorders | Insomnia | | |
| Nervous system disorders | Headache<br>Dizziness<br>Dysgeusia | Cerebrovascular accident | Monoparesis<br>Transient ischaemic attack<br>Posterior reversible encephalopathy syndrome |
| Cardiac disorders | | Electrocardiogram QT prolonged<br>Ejection fraction decreased<br>Cardiac failure<br>Myocardial infarction[c,†] | |
| Vascular disorders | Hypertension[d,‡]<br>Hypotension<br>Haemorrhage[e, †,‡] | | |
| Respiratory, thoracic and mediastinal disorders | Dysphonia<br>Cough | Pulmonary embolism[†] | |

| **System Organ Class** (MedDRA terminology*) | **Very Common** | **Common** | **Uncommon** |
|---|---|---|---|
| Gastrointestinal disorders | Diarrhoea<br>Oral inflammation[f]<br>Gastrointestinal and abdominal pains[g]<br>Vomiting<br>Nausea<br>Oral pain[h]<br>Constipation<br>Dyspepsia<br>Dry mouth | Anal fistula<br>Flatulence | |
| Hepatobiliary disorders | | Aspartate aminotransferase increased‡<br>Hypoalbuminaemia‡<br>Alanine aminotransferase increased‡<br>Blood alkaline phosphatase increased<br>Hepatic function abnormal<br>Gamma-glutamyltransferase increased<br>Blood bilirubin increased‡ | Hepatocellular damage/hepatitis[i] |
| Skin and subcutaneous tissue disorders | Palmar-plantar erythrodysaesthesia syndrome<br>Rash<br>Alopecia | Hyperkeratosis | |
| Musculoskeletal and connective tissue disorders | Back pain<br>Arthralgia<br>Myalgia<br>Pain in extremity<br>Musculoskeletal pain | | |
| Renal and urinary disorders | Proteinuria‡ | Renal failure events[j, †]<br>Renal impairment<br>Blood creatinine increased<br>Blood urea increased | |
| General disorders and | Fatigue<br>Asthenia | Malaise | |

| **System Organ Class** (MedDRA terminology*) | **Very Common** | **Common** | **Uncommon** |
|---|---|---|---|
| administration site conditions | Oedema peripheral | | |

*: Medical Dictionary for Regulatory Activities (MedDRA) version 16.1. Preferred terms have been reassigned to the SOC most relevant to the target organ.
†: Includes events with a fatal outcome.
‡: See see Selected Adverse Reactions for further characterisation.
The following terms have been combined:
a: Thrombocytopenia includes thrombocytopenia and platelet count decreased. Lymphopenia includes lymphopenia and lymphocyte count decreased.
b: Hypomagnesaemia includes hypomagnesaemia and blood magnesium decreased. Hypercholesterolaemia includes hypercholesterolaemia and blood cholesterol increased.
c: Myocardial infarction includes myocardial infarction and acute myocardial infarction.
d: Hypertension includes: hypertension, hypertensive crisis, blood pressure diastolic increased, and blood pressure increased.
e: Haemorrhage includes: epistaxis, haemoptysis, haematuria, contusion, haematochezia, gingival bleeding, petechiae, pulmonary haemorrhage, rectal haemorrhage, blood urine present, haematoma, vaginal haemorrhage, conjunctival haemorrhage, haemorrhoidal haemorrhage, intracranial tumour haemorrhage, laryngeal haemorrhage, ecchymosis, increased tendency to bruise, post procedural haemorrhage, purpura, skin haemorrhage, aneurysm ruptured, arterial haemorrhage, eye haemorrhage, gastric haemorrhage, gastroduodenitis haemorrhagic, gastrointestinal haemorrhage, haematemesis, haemorrhage, haemorrhagic stroke, melaena, metrorrhagia, nail bed bleeding, pleural haemorrhage, postmenopausal haemorrhage, proctitis haemorrhagic, renal haematoma, splenic haemorrhage, splinter haemorrhages, subarachnoid haemorrhage, tracheal haemorrhage, tumour haemorrhage.
f: Oral inflammation includes: aphthous stomatitis, stomatitis, glossitis, mouth ulceration, and mucosal inflammation.
g: Gastrointestinal and abdominal pain includes: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, and gastrointestinal pain.
h: Oral pain includes: oral pain, glossodynia, and oropharyngeal pain.
i: Hepatocellular damage and hepatitis includes: drug-induced liver injury, hepatic steatosis, and cholestatic liver injury.
j: Renal failure events includes: acute prerenal failure, renal failure, renal failure acute, and renal tubular necrosis.

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 lenvatinib and class effects

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

| System Organ Class<br>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[1] | 13.8 | 1.9 | 2.3 | 0 |
| Lymphopenia[2] | 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[3,4] | 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** | | | | |
| Diarrhea | 67.4 | 9.2 | 16.8 | 0 |
| Nausea | 46.7 | 2.3 | 25.2 | 0.8 |
| Stomatitis[5] | 41.0 | 4.6 | 8.4 | 0 |
| Vomiting | 35.6 | 1.9 | 14.5 | 0 |
| Abdominal pain[6] | 31.4 | 2.3 | 10.7 | 0.8 |
| Constipation | 28.7 | 0.4 | 15.3 | 0.8 |
| Oral pain[7] | 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 |
| Edema peripheral | 20.7 | 0.4 | 7.6 | 0 |
| Malaise | 5.4 | 0 | 0 | 0 |
| **Hepatobiliary Disorders** | | | | |
| Hepatocellular damage / hepatitis[8] | 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 |

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

| System Organ Class<br>Preferred Term | LENVIMA 24 mg N=261 | | Placebo N=131 | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3-4 (%) | All Grades (%) | Grades 3-4 (%) |
| **Metabolism and Nutrition Disorders** | | | | |
| Decreased appetite | 54.4 | 6.9 | 18.3 | 0.8 |
| Hypokalemia | 13.8 | 3.4 | 3.8 | 0 |
| Hypocalcemia | 12.6 | 5.0 | 0 | 0 |
| Hypoalbuminemia | 9.6 | 0.4 | 1.5 | 0 |
| Dehydration | 8.8 | 2.3 | 2.3 | 0.8 |
| Hypomagnesaemia[9] | 6.5 | 0.4 | 1.5 | 0 |
| Hypercholesterolaemia[10] | 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 ischemic attack | 0.8 | 0 | 0 | 0 |
| Reversible posterior leukoencephalopathy 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[4,11] | 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[4] | 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** | | | | |
| Hemorrhage[4, 12] | 34.9 | 1.5 | 18.3 | 3.1 |
| Hypertension[13] | 72.8 | 44.4 | 16.0 | 3.8 |
| Hypotension | 8.8 | 1.5 | 2.3 | 0 |

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

| System Organ Class<br>Preferred Term | LENVIMA 24 mg N=261 | | Placebo N=131 | |
|---|---|---|---|---|
| | All Grades (%) | Grades 3-4 (%) | All Grades (%) | Grades 3-4 (%) |

1. Includes the following terms: thrombocytopenia, platelet count decreased
2. Includes the following terms: lymphopenia, lymphocyte count decreased
3. Includes the following terms: acute myocardial infarction, myocardial infarction
4. includes fatal events and these are counted in all Grade column
5. Includes the following terms: aphthous stomatitis, stomatitis, glossitis, mouth ulceration, mucosal inflammation
6. Includes the following terms: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, gastrointestinal pain
7. Includes the following terms: oral pain, glossodynia, oropharyngeal pain
8. Includes the following terms: drug-induced liver injury, cholestatic liver injury, hepatic steatosis
9. Includes the following terms: hypomagnesaemia, blood magnesium decreased
10. Includes the following terms: hypercholesterolaemia and blood cholesterol increased
11. Includes the following terms: acute prerenal failure, renal failure, renal failure acute, renal tubular necrosis
12. Includes the following terms: epistaxis, hematuria, contusion, gingival bleeding, hematochezia, pulmonary hemorrhage, vaginal hemorrhage, rectal hemorrhage, hematoma, hemorrhoidal hemorrhage, laryngeal hemorrhage, petechiae, intracranial tumor hemorrhage, hemorrhagic stroke, pleural hemorrhage, splenic hemorrhage, blood urine present, conjunctival hemorrhage, eye hemorrhage, gastroduodenitis hemorrhagic, hematemesis, increased tendency to bruise, proctitis hemorrhagic, purpura, renal hematoma, skin hemorrhage, splinter hemorrhages
13. 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

Selected Adverse Reactions

*Hypertension*

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

*Proteinuria*

In the pivotal Phase 3 SELECT trial (see CLINICAL TRIALS), proteinuria was reported in 33.7% of lenvatinib treated patients and 3.1% of patients in the placebo-treated group. The median time to onset was 6.7 weeks. Grade 3 events occurred in 10.7% of lenvatinib-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.

*Hepatotoxicity*
In the pivotal Phase 3 SELECT trial (see CLINICAL TRIALS), the most commonly reported liver-related adverse reactions were hypoalbuminaemia (9.6% lenvatinib vs. 1.5% placebo) and elevations of liver enzyme levels, including increases in alanine aminotransferase (7.7% lenvatinib vs. 0 placebo), aspartate aminotransferase (6.9% lenvatinib vs. 1.5% placebo), and blood bilirubin (1.9% lenvatinib vs. 0 placebo). The median time to onset of liver events in lenvatinib-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 lenvatinib-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%. Across the entire pooled analysis of safety data from clinical trials with lenvatinib (including 452 patients with RR-DTC and 656 patients with other tumour types), there were 3 cases (0.3%) of hepatic failure, all with a fatal outcome. One occurred in a patient with no liver metastases. There was also a case of acute hepatitis in a patient without liver metastases.

*Haemorrhagic events*
In the pivotal Phase 3 SELECT trial (see CLINICAL TRIALS), haemorrhagic events were reported in 34.9% of lenvatinib-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 intracranial tumour haemorrhage (0.8%). The median time to first onset in lenvatinib-treated patients was 10.1 weeks. No differences between lenvatinib and placebo-treated patients were observed in the incidences of serious 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). Across the entire pooled analysis of safety data from clinical trials with lenvatinib (including 452 patients with RAI - Refractory DTC and 656 patients with other tumour types), 3 patients (0.3%) had a Grade 4 haemorrhage and 5 patients (0.5%) had a Grade 5 event including 3 RAI - Refractory DTC patients with arterial haemorrhage, haemorrhagic stroke, and intracranial tumour haemorrhage, and 2 patients with other forms of cancer who experienced haemoptysis and tumour haemorrhage.

*Hypocalcaemia*
In the pivotal Phase 3 SELECT trial (see CLINICAL TRIALS), hypocalcaemia was reported in 12.6% of lenvatinib treated patients vs. no events in the placebo arm. The median time to first onset in lenvatinib-treated patients was 11.1 weeks. Events of Grade 3 or 4 severity occurred in 5.0% of lenvatinib-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.

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

*Sex*
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.

*Race*
Asian patients had a higher incidence than Caucasian patients of oedema peripheral, fatigue, PPE, proteinuria, thrombocytopenia, and blood thyroid stimulating hormone increased. Japanese patients had a higher incidence of Grade 3 or 4 hypertension, decreased appetite, fatigue, and thrombocytopenia compared with non-Japanese subjects.

*Baseline hypertension*
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, and GI symptoms (abdominal pain, diarrhoea, vomiting).

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

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

## DOSAGE AND ADMINISTRATION

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

Posology
*Adults*
The recommended dose of LENVIMA is 24 mg taken once daily. The daily dose is to be modified as needed according to the dose/toxicity management plan (see dose adjustment section below). If a patient misses a dose, and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration. Treatment should continue as long as there is clinical benefit.

*Dose adjustment*
Management of some adverse reactions may require dose interruption, adjustment, or discontinuation of LENVIMA. Mild to moderate adverse reactions (eg, Grade 1 or 2) generally do not warrant interruption of LENVIMA, unless intolerable to the patient despite optimal management. Severe (eg, Grade 3) or intolerable adverse reactions require interruption of LENVIMA until resolution or improvement of the event, after which treatment should be resumed at a reduced dose as suggested in Table 5. Life-threatening

reactions (eg, Grade 4) may be managed as per severe events provided resolution or improvement of the event occurs; if not, permanent discontinuation is recommended.

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

Optimal medical management for nausea, vomiting, and diarrhoea should be initiated prior to any interruption or dose reduction of LENVIMA. Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or failure (see PRECAUTIONS, Renal failure and impairment).

**Table 5 Dose Modifications from Recommended Daily Dose**

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

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

*Special populations*
Certain subpopulations of patients appear to have reduced tolerability to lenvatinib (see ADVERSE REACTIONS, Special Populations). Following treatment initiation at the recommended dose, the dose should be adjusted on the basis of individual tolerability.

*Patients with hypertension*
Blood pressure should be well controlled prior to treatment with lenvatinib, and should be regularly monitored during treatment (see PRECAUTIONS).

*Patients with hepatic impairment*
No adjustment of starting dose is required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. In patients with severe (Child-Pugh C) hepatic impairment, the recommended dose is 14 mg taken once daily. Further dose adjustments may be necessary on the basis of individual tolerability.

*Patients with renal impairment*
No adjustment of the starting dose is required on the basis of renal function in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended dose is 14 mg taken once daily. Further dose adjustments may be necessary based on the individual tolerability. Patients with end-stage renal disease were not studied, therefore the use of lenvatinib in these patients is not recommended.

*Elderly population*
No adjustment of the starting dose is required on the basis of age. Limited data are available on the use in patients aged ≥ 75 years.

*Paediatric population*
Lenvatinib must not be used in children younger than 2 years of age because of safety concerns identified in animal studies. The safety and efficacy of lenvatinib in children aged 2 to <18 years have not yet been established (see CLINICAL TRIALS). No data are available.

*Race*
No adjustment of starting dose is required on the basis of race. Limited data are available on use in patients from ethnic origins other than Caucasian or Asian.

*Method of administration*
Lenvatinib should be taken at about the same time each day, with or without food. The capsules should be swallowed whole with water.

## OVERDOSAGE

Contact the Poisons Information Centre on telephone 13 11 26 for advice on management of overdose.

There have been reports of overdose with lenvatinib 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 lenvatinib, or were without adverse reactions. There is no specific antidote for overdose with lenvatinib, due to the high plasma protein binding, lenvatinib is not expected to be dialyzable. In case of suspected overdose, lenvatinib should be withheld and appropriate supportive care given as required.

## PRESENTATION AND STORAGE

### Presentation
Lenvima 4 mg 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 4 mg hard capsules are available in polyamide/aluminium/PVC/aluminium blisters of 30 capsules.

Lenvima 10 mg 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.

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

Storage

Store below 30 °C.

## NAME AND ADDRESS OF THE SPONSOR

Eisai (Australia) Pty Ltd
Level 2, 437 St Kilda Road
Melbourne, VIC, 3004

## POISON SCHEDULE OF THE MEDICINE

S4

## DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

28 January 2016