PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrLENVIMA®

Lenvatinib capsules

4mg and 10mg Lenvatinib (as lenvatinib mesylate)

Multiple Receptor Tyrosine Kinase Inhibitor

Antineoplastic Agent, ATC code:L01XE29

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Date of Revision:
December 19, 2018

Submission Control No: 212989

Table of Contents

[Pr]LENVIMA®

Lenvatinib capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-Medicinal Ingredients
Oral	Each capsule contains lenvatinib mesylate equivalent to 4 mg or 10 mg lenvatinib	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

LENVIMA (lenvatinib) is indicated:

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

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

- for the first-line treatment of adult patients with unresectable hepatocellular carcinoma (HCC). Efficacy and safety data for Child-Pugh Class B and Class C are not available.

Geriatrics (≥65 years of age): Of 261 patients who received LENVIMA in the Pivotal DTC Phase 3 SELECT trial, 118 (45.2%) were ≥65 years of age and 29 (11.1%) were ≥75 years of age. Subjects 75 years or older had a higher incidence of fatal AEs. Compared with subjects younger than 65, subjects who were 75 years or older were also more likely to experience (in descending order of frequency) Grade 3-4 hypertension, proteinuria, decreased appetite, and dehydration. Of the 62 patients who received LENVIMA + everolimus in the Pivotal RCC Study 205, 22 (35.5%) were ≥65 years of age and conclusions are limited due to the small sample size. Although there appeared to be no overall differences in effectiveness between these subjects and younger subjects, elderly patients may experience greater toxicity (see WARNINGS AND PRECAUTIONS; Special Populations).

Of the 476 patients who received LENVIMA in the pivotal HCC Study 304, 150 (32%) were ≥65 but < 75 years of age and 57 (12%) were ≥75 years of age. No overall differences in safety

or effectiveness were observed between patients ≥65 years but <75 years and younger subjects. Patients ≥75 years showed reduced tolerability to LENVIMA (see: WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Hepatotoxicity; Special Populations, Geriatrics (≥65 years of age).

Pediatrics (< 18 years of age): The safety and efficacy of lenvatinib in children and adolescents <18 years have not been established. LENVIMA should not be used in children younger than 2 years of age because of safety concerns identified in animal studies (see WARNINGS AND PRECAUTIONS; Special Populations and TOXICOLOGY).

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

LENVIMA (lenvatinib) should be prescribed and supervised by a qualified health care professional who is experienced in the use of antineoplastic therapy.

Serious reactions and/or life threatening events include:

- **Hypertension and its complications, including fatal aortic dissection (see WARNINGS AND PRECAUTIONS, Cardiovascular)**
- **Cardiac failure including fatal cases (see WARNINGS AND PRECAUTIONS, Cardiovascular)**
- **Arterial thromboembolism including fatal cases (see WARNINGS AND PRECAUTIONS, Arterial Thromboembolism)**
- **Gastrointestinal perforation and fistula formation (see WARNINGS and PRECAUTIONS, Gastrointestinal Perforation and Fistula Formation)**
- **Hepatotoxicity/hepatic failure, including fatal cases (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic)**
- **Renal Failure and Impairment including fatal cases (see WARNINGS AND PRECAUTIONS, Renal)**
- **Hemorrhage including fatal cases (see WARNINGS AND PRECAUTIONS, Hematologic)**
- **Posterior Reversible Encephalopathy Syndrome (PRES) (see WARNINGS AND PRECAUTIONS, Neurologic)**

General

Lower starting doses are recommended for DTC (14 mg, qd) and RCC (10 mg, qd) patients with severe renal impairment (CrCl <30 mL/min) and severe hepatic impairment (Child-Pugh C). Close monitoring of overall safety is recommended in these patients. In patients with hepatocellular carcinoma (HCC), the available very limited data in moderate hepatic impairment (Child-Pugh B) are not sufficient to allow for a dosing recommendation. LENVIMA has not been studied in patients with severe hepatic impairment (Child-Pugh C) and is not recommended for use in these patients. (see WARNINGS AND PRECAUTIONS; Special Populations, Patients with Hepatic Impairment and DOSAGE AND ADMINISTRATION).

Prior Anticancer Treatments

There are no data on the use of LENVIMA immediately following sorafenib or other systemic anticancer treatments. Therefore there may be a potential risk for additive toxicities unless there is an adequate washout period between treatments. The minimal washout period in DTC and RCC clinical trials was 3 weeks. The washout period from prior locoregional therapies for HCC was 4 weeks.

Wound Healing Complications
Wound healing complications, including fistula formation and wound dehiscence, can occur with LENVIMA. Withhold LENVIMA for at least 6 days prior to scheduled surgery.
Resume LENVIMA after surgery based on clinical judgment of adequate wound healing. Permanently discontinue LENVIMA in patients with wound healing complications (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Cardiovascular

Hypertension
In the pivotal DTC Phase 3 SELECT trial, hypertension was reported in 73% of LENVIMA-treated patients and 16% of patients in the placebo-treated group (see ADVERSE REACTIONS). The median time to onset was 16 days for LENVIMA-treated patients. The incidence of Grade 3 hypertension was 44% as compared to 4% for placebo, and the incidence of Grade 4 hypertension was less than 1% in LENVIMA-treated patients and none in the placebo group.

In the RCC Phase 1b+2 Study 205, hypertension was reported in 42% of patients in the LENVIMA + everolimus-treated group and 10% of patients in the everolimus-treated group. The median time to onset of new or worsening hypertension was 35 days for LENVIMA + everolimus-treated patients. The incidence of Grade 3 hypertension was 13% in the LENVIMA + everolimus-treated group as compared to 2% in the everolimus-treated group. Systolic blood pressure ≥ 160mmHg occurred in 29% and 21% of patients had a diastolic blood pressure ≥100 in the LENVIMA + everolimus-treated group.

In the HCC Phase 3 REFLECT Study 304, 45% (n=212) of patients in the LENVIMA-treated group reported hypertension including 24% (n=112) Grade 3. The median time to first onset of new or worsening hypertension was 26 days for LENVIMA-treated patients (see ADVERSE REACTIONS, *Additional Safety Information from HCC Clinical Trial Experience,* Cardiovascular*, Hypertension*).

Serious cases of aortic dissection, some with a fatal outcome, have been reported in patients with increases in blood pressure over baseline levels or with poorly controlled hypertension (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Blood pressure should be well controlled prior to treatment with LENVIMA. The early detection and effective management of hypertension are important to minimize the need for LENVIMA dose interruptions and reductions.

Blood pressure should be monitored after 1 week of treatment with LENVIMA, then every 2 weeks for the first 2 months and then monthly thereafter while on treatment. If a patient develops systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg active management is recommended. Withhold LENVIMA for Grade 3 hypertension that persists despite optimal antihypertensive therapy; resume at a reduced dose when hypertension is controlled at less than or equal to Grade 2. Discontinue LENVIMA for life-threatening hypertension (see WARNINGS AND PRECAUTIONS; Monitoring and Laboratory Tests and DOSAGE AND ADMINISTRATION).

Cardiac Failure
In the pivotal DTC Phase 3 SELECT trial, cardiac failure was reported in <1% of LENVIMA-treated patients and no patients in the placebo-treated group and decreased left ventricular ejection fraction was reported in 5% of LENVIMA-treated patients and <1% of patients in the placebo-treated group.

In the RCC Phase 1b+2 Study 205, decreased ejection fraction and cardiac failure were reported in 10% of patients in the LENVIMA + everolimus-treated group and 6% of patients in the everolimus-treated group. Grade 3 events occurred in 3% of LENVIMA + everolimus-treated patients and 2% of everolimus-treated patients. In the LENVIMA + everolimus-treated group there were two patients with a Grade 2 to 4 decrease in LVEF as assessed by MUGA.

In the HCC Phase 3 REFLECT Study 304, cardiac dysfunction events, defined as cardiopulmonary failure, congestive cardiac failure, cardiogenic shock and cardiac failure, were reported in 0.6% (n=3) including 0.4% (n=2) Grade 3 or greater events in patients in the LENVIMA-treated group. Worsening of left ventricular ejection fraction (LVEF) from normal baseline function was reported in 0.4% (n=1) of patients (as moderate dysfunction) in the LENVIMA-treated group as assessed by echocardiograms or multiple gated acquisition scans (MUGA) (see ADVERSE REACTIONS).

Patients should be monitored for clinical symptoms or signs of cardiac decompensation. Withhold LENVIMA for development of Grade 3 cardiac dysfunction until improved to Grade 0 or 1 or baseline. Either resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of cardiac dysfunction. Discontinue LENVIMA for Grade 4 cardiac dysfunction (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Arterial Thromboembolism
In the pivotal DTC Phase 3 SELECT trial, arterial thromboembolic events were reported in 5% of LENVIMA-treated patients and 2% of patients in the placebo-treated group. The incidence of arterial thromboembolic events of Grade 3 or greater was 3% in LENVIMA-treated patients and 1% in the placebo group. There were two fatal events in LENVIMA-treated patients (myocardial infarction and hemorrhagic stroke, in one patient each) and one in the placebo-treated patient group (myocardial infarction).

In the RCC Phase 1b+2 Study 205, 2% of patients in the LENVIMA + everolimus-treated group and 6% of patients in the everolimus-treated group had arterial thromboembolic events reported. The incidence of arterial thromboembolic events of Grade 3 or greater was 2% with LENVIMA + everolimus-treated patients and 4% in the everolimus-treated group.

In the HCC Phase 3 REFLECT Study 304, Grade 3 or greater arterial thromboembolic events were reported in 2% (n=9) of patients in the LENVIMA-treated group (see ADVERSE REACTIONS).

Use LENVIMA with caution in patients who are at risk for, or who have a history of, these events. LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months. A treatment decision should be made based upon assessment of the individual patients benefit/risk. Discontinue LENVIMA following an arterial thromboembolic event (see DOSAGE AND ADMINISTRATION).

QT Interval Prolongation

LENVIMA can cause QTc prolongation (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests; ADVERSE REACTIONS, Electrocardiography; ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology & Hemodynamics).

In the pivotal DTC Phase 3 SELECT trial, QT interval prolongation was reported in 9% of LENVIMA-treated patients and 2% in the placebo group. The incidence of QT interval prolongation of Grade 3 or greater was 2% in LENVIMA-treated patients compared to no reports in the placebo group.

In the RCC Phase 1b+2 Study 205, the proportion of subjects with QTcF values >500 ms was 4/62 (6%) in the LENVIMA 18 mg + everolimus 5 mg group and 0/50 in the everolimus 10 mg group. The proportion of subjects with QTcF increases from baseline >60 ms was 7/62 (11%) in the LENVIMA 18 mg + everolimus 5 mg group and 0/50 in the everolimus 10 mg group.

In the HCC Phase 3 REFLECT Study 304, QTc interval increases greater than 60 ms were reported in 8% (n=37) of patients in the LENVIMA-treated group. The incidence of QTc interval greater than 500 ms was 2% (n=11) of patients in the LENVIMA-treated group (see ADVERSE REACTIONS, *Additional Safety Information from HCC Clinical Trial Experience,* Cardiovascular*, Electrocardiography*).

QTc prolongation may lead to an increased risk of ventricular arrhythmias including torsade de pointes. Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death. Treatment with LENVIMA is not recommended in patients with congenital long QT syndrome or who are taking medicinal products known to prolong the QTc interval (see DRUG INTERACTIONS). Hypokalemia, hypomagnesemia, and hypocalcemia should be corrected prior to LENVIMA administration.

Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender; age ≥65 years; baseline prolongation of the QT/QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years of age; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease); history of arrhythmias; electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders); bradycardia; acute neurological events (e.g., intracranial or

subarachnoid hemorrhage, stroke, intracranial trauma); diabetes mellitus; and autonomic neuropathy.

When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug. Patients should be advised to contact their healthcare provider immediately to report any new chest pain or discomfort, changes in heartbeat, palpitations, dizziness, lightheadedness, fainting, or changes in or new use of other medications. Monitor electrocardiogram and electrolytes regularly, and correct electrolyte abnormalities in all patients (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Endocrine and Metabolism

Hypocalcemia
In the pivotal DTC Phase 3 SELECT trial, 13% (n=33) of LENVIMA-treated patients experienced Grade 3 or greater hypocalcemia compared to 0% in the placebo group. In most cases hypocalcemia responded to replacement and dose interruption/dose reduction.

In the RCC Phase 1b+2 Study 205, 6% (n=3) of patients in the LENVIMA + everolimus-treated group and 2% (n=1) of patients in the everolimus-treated group experienced Grade 3 or greater hypocalcemia. No patients discontinued due to hypocalcemia (see ADVERSE REACTIONS).

In the HCC Phase 3 REFLECT Study 304, 0.4% (n=2) of patients in the LENVIMA-treated group experienced Grade 3 hypocalcemia (see ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings and *Additional Safety Information from HCC Clinical Trial Experience*).

Monitor blood calcium levels at least monthly and replace calcium as necessary during LENVIMA treatment. Interrupt and adjust LENVIMA dosing as necessary depending on severity, presence of ECG changes, and persistence of hypocalcemia (see DOSAGE AND ADMINISTRATION).

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction
LENVIMA impairs exogenous thyroid suppression. In the pivotal DTC Phase 3 SELECT trial, 88% of all patients had a baseline thyroid stimulating hormone (TSH) level less than or equal to 0.5 mU/L. In those patients with normal TSH level at baseline, elevation of TSH level above 0.5 mU/L was observed post baseline in 61% of LENVIMA-treated patients as compared with 14% of patients receiving placebo.

In the RCC Phase 1b+2 Study 205, Grade 1 or 2 hypothyroidism occurred in 24% of patients in the LENVIMA + everolimus-treated group and 2% of patients in the everolimus-treated group. In those patients with a normal or low TSH at baseline, an elevation of TSH was observed post baseline in 60% of LENVIMA + everolimus-treated patients as compared with 3% of patients

receiving everolimus monotherapy.

In the HCC Phase 3 REFLECT Study 304, Grade 1 or 2 hypothyroidism occurred in 21% (n=100) of patients in the LENVIMA-treated group. Elevation of TSH was observed post baseline in 70% (n=316) of LENVIMA-treated patients (see ADVERSE REACTIONS, *Additional Safety Information from HCC Clinical Trial Experience,* Endocrine and Metabolism*, Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction*).

TSH should be monitored before initiation of treatment with LENVIMA and monthly throughout treatment. Thyroid replacement medication should be adjusted as needed. Hypothyroidism should be treated according to standard medical practice to maintain euthyroid state. (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests)

Gastrointestinal

Diarrhea
In the RCC Phase 1b+2 Study 205, diarrhea was reported in 81% of LENVIMA + everolimus-treated patients and 34% of everolimus-treated patients. Grade 3 or 4 events occurred in 19% of LENVIMA + everolimus-treated patients and 2% of everolimus-treated patients. Diarrhea was the most frequent cause of dose interruption/reduction and recurred despite dose reduction. Diarrhea resulted in discontinuation in one patient (see ADVERSE REACTIONS*)*.

Initiate prompt medical management for the development of diarrhea. Monitor for dehydration. Withhold for Grade 3 diarrhea and resume at a reduced dose of LENVIMA when diarrhea resolves to Grade 1 or baseline. Permanently discontinue LENVIMA for Grade 4 diarrhea despite medical management.

Gastrointestinal Perforation and Fistula Formation
Serious events of gastrointestinal perforation or fistula formation and their sequelae have been commonly reported in clinical trials with LENVIMA, including reactions resulting in death. Fistulas (e.g. gastrointestinal, bronchopleural, tracheo-oesophageal, oesophageal, cutaneous, pharyngeal, female genital tract) have been reported in LENVIMA clinical trials and in post-marketing experience 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 median latency of about 3 months. 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 tumor regression or necrosis. In most cases, gastrointestinal perforation and fistula formation occurred in subjects with risk factors such as prior surgery or radiotherapy (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

In the pivotal DTC, events of gastrointestinal perforation or fistula were reported in 2% of LENVIMA-treated patients and 0.8% of patients in the placebo group.

In RCC Phase 1b+2 Study 205, Grade 3 or greater gastrointestinal perforation, abscess or fistula

was reported in 2% of patients in the LENVIMA + everolimus-treated group and no patients in the everolimus-treated group. The events resolved in all patients.

In the HCC Phase 3 REFLECT Study 304, events of gastrointestinal perforation or fistula were reported in 2% (n=9) of the LENVIMA-treated group. Grade 3 or greater gastrointestinal perforation or fistula was reported in 1% (n=5) of patients in the LENVIMA-treated group (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Discontinue LENVIMA in patients who develop gastrointestinal perforation or fistula (see DOSAGE AND ADMINISTRATION).

Hematologic

Hemorrhage
In the pivotal DTC Phase 3 SELECT trial, hemorrhagic events were reported in 35% of LENVIMA-treated patients and 18% of patients in the placebo-treated group. The most frequently reported hemorrhagic event was epistaxis (11% Grade 1 and 1% Grade 2). However, the incidence of Grade 3-5 hemorrhage was similar between arms at 2% and 3%, respectively.

In the RCC Phase 1b+2 Study 205, hemorrhagic events occurred in 34% of patients in the LENVIMA + everolimus-treated group and 26% of patients in the everolimus-treated group. The most frequently reported hemorrhagic event was epistaxis (LENVIMA + everolimus 23% and everolimus 24%). Grade 3 or greater events occurred in 8% of LENVIMA + everolimus-treated patients and in 2% of everolimus-treated patients. In the LENVIMA + everolimus-treated patients, this included one fatal cerebral hemorrhage. Discontinuation due to a hemorrhagic event occurred in 3% of patients in the LENVIMA + everolimus-treated group.

In the HCC Phase 3 REFLECT Study 304, hemorrhagic events occurred in 23% (n=110) of patients in the LENVIMA-treated group. The most frequently reported hemorrhagic events were epistaxis (7%; n=34), hematuria (5%; n=25), and gingival bleeding (4%; n=18). Grade 3 or greater events occurred in 5% (n=24) of LENVIMA-treated patients. In the LENVIMA-treated group, 1.5% (n=7) of patients had a fatal hemorrhage. Discontinuation due to a hemorrhagic event occurred in 2% (n=8) of patients in the LENVIMA-treated group (see ADVERSE REACTIONS, *Additional Safety Information from HCC Clinical Trial Experience,* Hematologic*, Hemorrhage*).

Serious tumor related bleeds have been reported, including fatal intracranial hemorrhagic events in LENVIMA-treated patients with brain metastases (in DTC and non-DTC studies). The degree of tumor invasion/infiltration of major blood vessels (e.g. carotid artery) should be considered prior to the initiation of LENVIMA because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following LENVIMA therapy.

Withhold LENVIMA for the development of Grade 3 hemorrhage until resolved to Grade 0 or 1. Either resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of hemorrhage. Discontinue LENVIMA in patients who experienced Grade 4 hemorrhage (see DOSAGE AND ADMINISTRATION).

Hepatic/Biliary/Pancreatic

Hepatotoxicity
Lenvatinib is predominately metabolized in the liver.

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

Hepatotoxicity including hepatic encephalopathy and hepatic failure (including fatal reactions) were reported at a higher frequency in LENVIMA-treated patients with HCC than with DTC and RCC. In patients with HCC, hepatic encephalopathy occurred in 8% (n=38) of LENVIMA-treated patients. Discontinuations due to hepatic encephalopathy occurred in 2% (n=7) of LENVIMA-treated patients and discontinuations due to hepatic failure occurred in 1% of LENVIMA-treated patients. Grade 3 or greater hepatic encephalopathy occurred in 5% (n=23) of the LENVIMA. Grade 3 or greater hepatic failure occurred in 3% (n=15) of patients in the LENVIMA-treated group. Patients with worse hepatic impairment and/or greater liver tumor 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.

In the pivotal DTC Phase 3 SELECT trial, 4% of LENVIMA-treated patients experienced an increase in alanine aminotransferase (ALT) and 5% experienced an increase in aspartate aminotransferase (AST) that was Grade 3 or greater. No patients in the placebo group experienced Grade 3 or greater increases in ALT or AST.

In the RCC Phase 1b+2 Study 205, 3% of LENVIMA + everolimus-treated patients experienced an increase in ALT and 3% experienced an increase in AST that was Grade 3 or greater. 2% of patients in the everolimus-treated group experienced an increase in ALT and none experienced an increase in AST that was Grade 3 or greater.

In the HCC Phase 3 REFLECT Study 304, data in HCC patients with moderate hepatic impairment (Child-Pugh B) are very limited and no data is available in HCC patients with severe hepatic impairment (Child-Pugh C). No dosing recommendations are available for HCC patients with moderate and severe hepatic impairment. In the REFLECT study, patients with a baseline Child Pugh (CP) score of 6 (about 20% of patients) had a higher incidence of decreased appetite, fatigue, proteinuria, hepatic encephalopathy and hepatic failure compared to patients with a baseline CP score of 5. Hepatotoxicity events and hemorrhage events also occurred at a higher incidence in CP score 6 patients compared to CP score 5 patients (see ADVERSE REACTIONS, *Additional Safety Information from HCC Clinical Trial Experience,* Hepatic*, Hepatotoxicity)*.

Liver function tests should be monitored before initiation of treatment with LENVIMA, and then

every 2 weeks for the first 2 months, and monthly thereafter during treatment. Patients with HCC treated with LENVIMA should be monitored for worsening liver function including hepatic encephalopathy. Withhold LENVIMA for the development of Grade 3 or greater liver impairment until resolved to Grade 0 or 1 or baseline. Either resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of hepatotoxicity. Discontinue LENVIMA for hepatic failure (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and DOSAGE AND ADMINISTRATION).

Neurologic

Posterior Reversible Encephalopathy Syndrome / Reversible Posterior Leukoencephalopathy Syndrome. (PRES / RPLS)
In clinical studies with LENVIMA monotherapy, events of posterior reversible encephalopathy syndrome (PRES) also known as reversible posterior leukoencephalopathy syndrome (RPLS) were reported in <1% LENVIMA-treated patients.

In the RCC Phase 2 Study 205, 1 patient who received LENVIMA monotherapy experienced PRES.

In the HCC Phase 3 REFLECT Study 304, 0.2% (n=1) of patients who received LENVIMA monotherapy experienced PRES.

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. Withhold LENVIMA. Appropriate measures should be taken to control blood pressure. In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary until PRES is fully resolved. Upon resolution, resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of neurologic symptoms (see WARNINGS AND PRECAUTIONS, Cardiovascular, *Hypertension* and DOSAGE AND ADMINISTRATION).

Renal

Renal Failure and Impairment
In the pivotal DTC Phase 3 SELECT trial, events of renal impairment (including renal failure) were reported in 14% of LENVIMA-treated patients and 2% of patients in the placebo-treated group. The incidence of Grade 3 or greater renal failure or impairment was 3% in LENVIMA-treated patients and 1% in the placebo group.

In the Phase 1b+2 Study 205 in RCC, renal impairment was reported in 18% of LENVIMA + everolimus-treated group and 12% in the everolimus-treated group. The incidence of Grade 3 or greater renal failure or impairment was 10% in the LENVIMA + everolimus-treated group and 2% in the everolimus-treated group.

In the HCC Phase 3 REFLECT Study 304, renal impairment was reported in 7% (n=34) of

LENVIMA-treated group including. Grade 3 or greater renal failure or impairment occurred in 2% (n=9) in the LENVIMA-treated group. HCC Patients with baseline renal impairment had a higher incidence of fatigue, hypothyroidism, dehydration, diarrhea, decreased appetite, proteinuria and hepatic encephalopathy. These patients also had a higher incidence of renal reactions and arterial thromboembolic events. (see ADVERSE REACTIONS, *Additional Safety Information from HCC Clinical Trial Experience,* Renal*, Renal Impairment and Renal Failure*).

The primary risk factor identified was dehydration/hypovolemia due to diarrhea and vomiting. Active management of diarrhea and any other gastrointestinal symptoms should be initiated for Grade 1 events in order to reduce the risk of development of renal impairment or renal failure. Withhold LENVIMA for development of Grade 3 or 4 renal failure/impairment until resolved to Grade 0 to 1 or baseline. Either resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of renal impairment (see DOSAGE AND ADMINISTRATION). Patients with end stage renal disease were not studied, thus the use of LENVIMA in these patients is not recommended.

Proteinuria

In the pivotal DTC Phase 3 SELECT trial, proteinuria was reported in 34% of LENVIMA-treated patients and 3% of patients in the placebo-treated group (see ADVERSE REACTIONS). The incidence of Grade 3 proteinuria in LENVIMA-treated patients was 11% compared to none in the placebo group.

In the RCC Phase 1b+2 Study 205, proteinuria was reported in 31% of patients in the LENVIMA + everolimus-treated group and 14% of patients in the everolimus-treated group. The incidence of Grade ≥ 3 proteinuria in LENVIMA + everolimus-treated patients was 8% compared to 2% in everolimus-treated patients.

The median time to onset of proteinuria was 6.1 weeks for any grade and 20.1 weeks for Grade ≥ 3 proteinuria and the rate of discontinuation was 5% in the LENVIMA + everolimus- treated group. In comparison the median time to onset was 11.9 weeks for any grade and 18.6 weeks for Grade ≥ 3 proteinuria and rate of discontinuation was 0% in everolimus-treated patients.

In the pivotal HCC Phase 3 REFLECT Study 304, proteinuria was reported in 26% (n=125) of patients in the LENVIMA-treated group with 6% (n=28) Grade 3 (see ADVERSE REACTIONS, *Additional Safety Information from HCC Clinical Trial Experience,* Renal*, Proteinuria*).

Monitor urine protein regularly. If urine dipstick proteinuria ≥2+ is detected, obtain a 24 hour urine protein. Withhold LENVIMA for ≥2 grams of proteinuria/24hours and resume at a reduced dose when proteinuria is <2 grams/24 hours. Discontinue LENVIMA for nephrotic syndrome (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and (see DOSAGE AND ADMINISTRATION)).

Sexual Function/Reproduction, Fertility

The effect of LENVIMA on male and female fertility in humans is not known. Based on toxicology findings LENVIMA may result in decreasing male and female fertility (see TOXICOLOGY). Prior to initiating LENVIMA therapy, physicians should advise and counsel

their patients as appropriate.

Special Populations

Females of Childbearing Potential
Females 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 lenvatinib may reduce the effectiveness of hormonal contraceptives, and therefore females using oral contraceptives should add a barrier method.

Male Subjects
Men must be advised to use an acceptable method of contraception (defined as barrier methods in conjunction with spermicides).

Pregnant Women
While there is insufficient data on the use of LENVIMA in pregnant women, based on its mechanism of action, LENVIMA administration during pregnancy is likely to cause fetal harm. In animal studies lenvatinib caused significant embryo and fetal toxicity at doses below the recommended clinical dose. Lenvatinib was teratogenic when administered to rats and rabbits (see TOXICOLOGY). 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 fetus. Pregnant women must be advised of the potential risk of fetal harm. Women should avoid becoming pregnant and use effective contraception while on treatment with LENVIMA.

Nursing Women
It is not known whether lenvatinib is excreted in human milk. Lenvatinib and its metabolites are excreted in rat milk at levels greater than those measured in maternal plasma, thus transfer of lenvatinib through breastfeeding may occur. A risk to newborn or infants cannot be excluded and therefore LENVIMA should not be used during breastfeeding (see TOXICOLOGY).

Geriatrics (≥65 years of age)
In the pivotal DTC Phase 3 SELECT trial, 118 (45%) of 261 patients treated with LENVIMA were ≥ 65 years of age. Elderly patients (≥ 65 years of age) had a trend toward a higher incidence of severe and serious adverse events or adverse events leading to treatment discontinuation (20.8% vs. 13.5%) compared with younger subjects (<65 years). In the placebo arm, the difference between age groups was less apparent.

Although no overall difference in effectiveness was observed between elderly and younger patients treated with LENVIMA + everolimus in the pivotal RCC Phase 2 study, the following common adverse events occurred at higher rates in patients 65 years of age or greater as compared to younger subjects: cough, dyspnea, lethargy, nausea, peripheral swelling and vomiting. Elderly patients should be treated with caution and monitored for signs of toxicity.

HCC patients of age ≥75 years appear to have demonstrated reduced tolerability to LENVIMA and 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 (see WARNINGS AND PRECAUTIONS, Cardiovascular, *Arterial thromboembolism* and ADVERSE REACTIONS).

Pediatrics (< 18 years of age)
The safety and efficacy of LENVIMA in children and adolescents <18 years have not been established. The results of animal studies suggest the potential for lenvatinib on bone growth in children LENVIMA should not be used in children younger than 2 years of age because of these safety concerns identified in animal studies (see TOXICOLOGY).

Patients with Hepatic Impairment
No dose adjustment is required in patients with mild hepatic impairment in DTC, RCC, and HCC; or moderate hepatic impairment in DTC and RCC. In DTC patients with severe (Child-Pugh C) hepatic impairment, the starting dose is 14 mg (one 10 mg capsule plus one 4 mg capsule) taken once daily. In RCC patients with severe (Child-Pugh C) hepatic impairment, the recommended dose is 10 mg of LENVIMA in combination with the dose of everolimus recommended for patients with severe hepatic impairment in the everolimus Product Monograph.

In patients with HCC patients, with mild hepatic impairment (Child-Pugh A), no dose adjustments were required on the basis of hepatic function. Patients with Child-Pugh score of 6 compared to score of 5 appear to have reduced tolerability to LENVIMA. Close monitoring of hepatic function is recommended in these patients. Further dose adjustments may be necessary based on the individual tolerability. (see DOSAGE AND ADMINISTRATION, Hepatic Impairment, WARNINGS AND PRECAUTIONS, General and Hepatotoxicity, and ADVERSE REACTIONS).

The available very limited data in moderate hepatic impairment (Child-Pugh B), are not sufficient to allow for a dosing recommendation. LENVIMA has not been studied in patients with HCC and severe hepatic impairment (Child-Pugh C) thus LENVIMA is not recommended for use in these patients

Patients with Renal Impairment
No dose adjustment is required in patients with mild or moderate renal impairment in DTC and RCC. In DTC patients with severe renal impairment, the starting dose is 14 mg taken once daily. Further dose adjustments may be necessary based on individual tolerability. In RCC patients with severe renal impairment, the recommended dose is 10mg of LENVIMA in combination with 5mg everolimus taken once daily. (see DOSAGE AND ADMINISTRATION, Renal Impairment). DTC and RCC patients with end stage renal disease were not studied, thus the use of LENVIMA in these patients is not recommended.

In patients with HCC, with mild and moderate renal impairment, no dose adjustment is required. However, for patients with HCC and severe renal impairment, the available data do not allow for a dosing recommendation.

Race

In the pivotal DTC Phase 3 SELECT trial, Asian patients had a higher incidence than Caucasian patients of peripheral edema, hypertension, fatigue, palmar-plantar erythrodysesthesia (PPE), proteinuria, thrombocytopenia, and blood thyroid stimulating hormone increased.

In HCC patients, 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, anxiety, asthenia, thrombocytopenia, and vomiting.

Gender
In the pivotal DTC Phase 3 SELECT trial, 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 the pivotal RCC Phase 1b+2 Study, females had a higher incidence of liver events whereas males had a higher incidence of hemorrhage, renal events, PPE and proteinuria.

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

Patients with Body Weight < 60kg
In the pivotal DTC Phase 3 SELECT trial, patients with low body weight (<60kg) had a higher incidence of PPE, proteinuria, of Grade 3-4 hypocalcaemia and hyponatremia, and a trend toward higher incidence of Grade 3-4 decreased appetite.

In patients with HCC
Lenvatinib PK was affected by body weight in subjects with HCC (HCC Phase 3 REFLECT Study 304) but not DTC (pivotal DTC Phase 3 SELECT trial) or RCC (pivotal RCC Phase 1b+2 study). Lenvatinib exposures in HCC subjects (pivotal HCC Phase 3 REFLECT Study 304) were comparable between those weighing < 60 kg with an 8 mg starting dose and ≥ 60 kg with a starting dose of 12 mg (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Monitoring and Laboratory Tests

Blood pressure should be monitored after 1 week of treatment with LENVIMA, then every 2 weeks for the first 2 months and monthly thereafter while on treatment. If a patient develops systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg active management is recommended (see WARNINGS AND PRECAUTIONS; Hypertension and DOSAGE AND ADMINISTRATION).

Patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or discontinuation may be necessary (see WARNINGS AND PRECAUTIONS; Cardiac Failure and DOSAGE AND ADMINISTRATION).

Monitor complete blood cell count (CBC).

Monitor electrolytes and electrocardiogram regularly (see WARNINGS AND PRECAUTIONS, QT Interval Prolongation).

Monitor urine protein regularly. If urine dipstick proteinuria ≥2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary (see WARNINGS AND PRECAUTIONS, Proteinuria and DOSAGE AND ADMINISTRATION).

Thyroid stimulating hormone (TSH) should be monitored before initiation of treatment with LENVIMA and monthly throughout treatment. Thyroid replacement medication should be adjusted as needed (see WARNINGS AND PRECAUTIONS, Impairment of Thyroid Stimulating Hormone Suppression).

Liver function tests should be monitored before initiation of treatment with LENVIMA, then every 2 weeks for the first 2 months, and monthly thereafter during treatment. Withhold LENVIMA for the development of Grade 3 or greater liver impairment until resolved to Grade 0 or 1 or baseline. Either resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of hepatotoxicity. Discontinue LENVIMA for hepatic failure (see WARNINGS AND PRECAUTIONS, Hepatotoxicity and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety data for DTC described below are derived from the pivotal DTC Phase 3 SELECT trial which randomized (2:1) patients with radioactive iodine-refractory differentiated thyroid cancer to LENVIMA (n=261) or placebo (n=131).

The safety data for RCC described below are derived from the RCC Phase 1b +2 Study 205, which randomized (1:1:1) patients with unresectable advanced or metastatic renal cell carcinoma (RCC) to LENVIMA 18 mg + everolimus 5 mg (n=62), LENVIMA 24 mg (n=52), or everolimus 10 mg (n=50) once daily.

The safety data for HCC described below are derived from the HCC Phase 3 REFLECT Study 304 in which patients with unresectable hepatocellular carcinoma (HCC) were randomized (1:1) to receive LENVIMA (n=476) or sorafenib (n=475).

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Clinical Trial Adverse Reactions in DTC

In the pivotal DTC Phase 3 SELECT trial, the LENVIMA and placebo treatment arms were well balanced with respect to demographic and baseline characteristics. All subjects (100%) underwent prior anti-thyroid cancer surgery. 100% of patients in the placebo arm and 98.6% of subjects in the LENVIMA arm had metastatic disease (4 subjects in the LENVIMA arm had locally advanced disease that met the inclusion criteria). The type and frequency of metastatic disease were similar between the 2 treatment arms. All subjects were documented to be ^{131}I refractory/resistant. The median treatment duration was 16.1 months for LENVIMA and 3.9 months for placebo. Among 261 patients who received LENVIMA in the pivotal DTC Phase 3 SELECT trial, median age was 64 years, 52% were female, 80% were Caucasian, 18% were Asian, and 2% were Black; 4% identified themselves as having Hispanic or Latino ethnicity.

In the pivotal DTC Phase 3 SELECT trial, the most common adverse reactions observed in LENVIMA-treated patients (≥30%) were, in order of decreasing frequency, hypertension, diarrhea, decreased appetite, decreased weight, nausea, fatigue, stomatitis, vomiting, proteinuria, palmar-plantar erythrodysesthesia (PPE) syndrome, abdominal pain, and dysphonia. The most common serious adverse reactions (at least 2%) were pneumonia (4%), hypertension (3%), renal failure and impairment (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 diarrhea (10%); the most common adverse reactions (at least 1%) resulting in discontinuation of LENVIMA were hypertension (1%) and asthenia (1%) (see WARNINGS AND PRECAUTIONS). Clinically significant serious adverse reactions were hypertension (3.4%), renal failure and impairment (3.4%), pulmonary embolism (1.9%), cardiac failure (0.7%), intracranial tumor haemorrhage (0.7%), PRES / RPLS (0.4%), hepatic failure (0.4%), arterial thromboembolisms [cerebrovascular accident (0.8%), transient ischaemic attack (0.4%), and myocardial infarction (1.1%)], and gastrointestinal perforation (0.8%) and fistula (0.4%). Fatal adverse events included myocardial infarction, cardiorespiratory arrest, intracranial tumor, hemorrhage, hemorrhagic stroke, pulmonary embolism, hepatic failure, and renal failure (see WARNINGS AND PRECAUTIONS; Serious Warnings and Precautions).

Clinical Trial Adverse Reactions for DTC

Table 1 Per-Patient Incidence of Adverse Reactions Occurring in ≥5% of Patients with a Between-Group Difference of ≥5% (All CTCAE Grades) or ≥2% (CTCAE Grades 3 and 4) - Pivotal DTC Phase 3 SELECT trial

	LENVIMA 24 mg N = 261		Placebo N = 131	
System Organ Class Preferred Term	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Blood and Lymphatic System Disorders				
Lymphopenia	7.3	1.1	1.5	0

Table 1 Per-Patient Incidence of Adverse Reactions Occurring in ≥5% of Patients with a Between-Group Difference of ≥5% (All CTCAE Grades) or ≥2% (CTCAE Grades 3 and 4) - Pivotal DTC Phase 3 SELECT trial

	LENVIMA 24 mg N = 261		Placebo N = 131	
System Organ Class Preferred Term	**All Grades (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Thrombocytopenia	13.8	1.9	2.3	0
Endocrine Disorder				
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[a]	41.0	4.6	8.4	0
Vomiting	35.6	1.9	14.5	0
Abdominal pain[b]	31.4	2.3	10.7	0.8
Constipation	28.7	0.4	15.3	0.8
Oral pain[c]	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
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
General physical health deterioration	4.2[d]	2.7	0.8	0
Infections and Infestations				
Urinary tract infection	11.5	1.1	5.3	0
Investigations				
Weight decreased	51.3	13.4	14.5	0.8
Electrocardiogram QT prolonged	8.8	1.5	1.5	0
Metabolism and Nutrition Disorders				
Decreased appetite	54.4	6.9	18.3	0.8
Dehydration	8.8	2.3	2.3	0.8
Hypoalbuminemia	9.6	0.4	1.5	0
Hypocalcemia	12.6	5.0	0	0
Hypokalemia	13.8	3.4	3.8	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
Psychiatric Disorders				
Insomnia	11.9	0	3.1	0
Renal and Urinary Disorders				
Proteinuria	33.7	10.7	3.1	0

Table 1 Per-Patient Incidence of Adverse Reactions Occurring in ≥5% of Patients with a Between-Group Difference of ≥5% (All CTCAE Grades) or ≥2% (CTCAE Grades 3 and 4) - Pivotal DTC Phase 3 SELECT trial

System Organ Class Preferred Term	LENVIMA 24 mg N = 261		Placebo N = 131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	31.4	1.1	5.3	0
Cough	23.8	0	17.6	0
Epistaxis	11.9	0	0.8	0
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia	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
Vascular Disorders				
Hypertension[e]	72.8	44.4	16.0	3.8
Hemorrhage [d,f]	34.9	1.5	18.3	3.1
Hypotension	8.8	1.5	2.3	0

[a] Includes the following terms: aphthous stomatitis, stomatitis, glossitis, mouth ulceration, mucosal inflammation

[b] Includes the following terms: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, gastrointestinal pain

[c] Includes the following terms: oral pain, glossodynia, oropharyngeal pain

[d] Includes reports of fatal events

[e] Includes the following terms: hypertension, hypertensive crisis, blood pressure diastolic increased, blood pressure increased

[f] 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

A clinically important serious adverse reaction occurring more frequently in LENVIMA-treated patients than placebo-treated patients, but with an incidence of <5% was pulmonary embolism (3.1%, including fatal reports vs. 1.5%, respectively).

Table 2 Per-Patient Incidence of Serious Adverse Reactions Occurring in ≥1% of LENVIMA-Treated Patients - Pivotal DTC Phase 3 SELECT trial

System Organ Class Preferred Term	LENVIMA 24 mg N = 261	Placebo N = 131
Gastrointestinal Disorders		
Dehydration	2.7	0
Dysphagia	1.1	2.3
Vomiting	1.5	0
General Disorders and Administration Site Conditions		

Table 2 Per-Patient Incidence of Serious Adverse Reactions Occurring in ≥1% of LENVIMA-Treated Patients - Pivotal DTC Phase 3 SELECT trial

System Organ Class Preferred Term	LENVIMA 24 mg N = 261	Placebo N = 131
General physical health deterioration	2.7	0
Infection		
Pneumonia	3.8	2.3
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	1.1	3.8
Malignant pleural effusion	1.1	0.8
Vascular Disorders		
Hypertension	3.4	0
Hypotension	1.5	0
Pulmonary embolism	1.9	1.5

Electrocardiography: In the Phase 3 clinical trial of DTC, the proportion of subjects with QTcF values >480 ms was 30/225 (11.5%) during treatment with LENVIMA and 3/123 (2.3%) during treatment with placebo.

The proportion of subjects with PR values >220 ms was 27/251 (10.3%) during treatment with LENVIMA and 5/125 (3.8%) during treatment with placebo.

The proportion of subjects with heart rate values <50 bpm was 28/252 (10.7%) during treatment with LENVIMA and 2/128 (1.5%) during treatment with placebo (see WARNINGS AND PRECAUTIONS, Cardiovascular & Monitoring and Laboratory Tests; DRUG INTERACTIONS; ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology and Hemodynamics).

Blood Pressure: On day 1 of Cycle 2 in the placebo-controlled trial in DTC, LENVIMA was associated with statistically significant ($p<0.0001$) placebo-adjusted mean increases from baseline in systolic and diastolic blood pressure of 12.4 mmHg and 9.0 mmHg, respectively (see WARNINGS AND PRECAUTIONS, Cardiovascular & Monitoring and Laboratory Tests; ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology & Hemodynamics).

Less Common Clinical Trial Serious Adverse Reactions (<1%)

The following serious adverse events were reported with LENVIMA-treated patients in the pivotal DTC Phase 3 SELECT trial during randomized treatment with a frequency of <1%:

Blood and lymphatic system disorders: Anemia, neutropenia, thrombocytopenia
Cardiac disorders: Acute myocardial infarction, atrial fibrillation, atrial flutter, bundle branch block right, cardio-respiratory arrest, coronary artery stenosis, myocardial infarction, pericardial effusion, right ventricular hypertrophy
Eye disorders: Retinal vein thrombosis
Gastrointestinal disorders: Abdominal pain upper, anal fistula, colitis, constipation, diarrhea, functional gastrointestinal disorder, gastrointestinal reflux disease, intestinal obstruction,

pancreatitis, pneumatosis intestinalis, stomatitis
General disorders and administration site conditions: Asthenia, death, impaired healing, multi-organ failure, non-cardiac chest pain, sudden death
Hepatobiliary disorders: Cholecystitis, gallbladder mucocele, gallbladder perforation, hepatic failure, hepatic function abnormal, liver injury
Immune system disorders: Anaphylactic reaction
Infections and infestations: Abscess limb, abscess soft tissue, appendicitis, bacteremia, bronchitis, chest wall abscess, chronic sinusitis, diverticulitis, eryspilelas, gastroenteritis, intervertebral discitis, lung infection, pneumonia necrotising, pyelonephritis, testicular abscess, urosepsis, wound infection
Injury, poisoning and procedural complications: Femur fracture, hip fracture, renal hematoma, vascular pseudoaneurysm, wound dehiscence, wound secretion
Investigations: Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood uric acid increased, lipase increased, platelet count decreased, weight decreased
Metabolism and nutrition disorders: Decreased appetite, hypercalcemia, hypokalemia, hypomagnesaemia, hyponatremia
Musculoskeletal and connective tissue disorders: Arthalgia, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, osteoarthritis, pain in extremity, pathological fracture, rhabdomyolysis
Neoplasms benign, malignant and unspecified (including cysts and polyps): Adenocarcinoma, intracranial tumor hemorrhage, malignant neoplasm progression, metastatic pain, plasmacytoma
Nervous system disorders: Cerebral ischemia, cerebrovascular accident, dizziness, epilepsy, hemorrhagic stroke, ischemic stroke, loss of consciousness, metabolic encephalopathy, monoparesis, paresis, Parkinson's disease, posterior reversible encephalopathy syndrome, postictal paralysis, spinal cord compression, syncope, vocal cord paralysis
Psychiatric disorders: Anxiety, confusional state
Renal and urinary disorders: Acute prerenal failure, dysuria, nephrotic syndrome, renal failure, renal impairment, renal tubular necrosis, urinary retention
Reproductive system breast disorders: Cystocele, rectocele, uterine prolapse
Respiratory, thoracic and mediastinal disorders: Acute respiratory failure, aspiration, bronchospasm, chronic obstructive pulmonary disease, dyspnea exertional, epistaxis, hypoxia, laryngeal hemorrhage, laryngeal edema, pleural effusion, pleural hemorrhage, pneumonia aspiration, pneumonitis, productive cough, pulmonary hemorrhage, respiratory distress
Skin and subcutaneous tissue disorders: Erythema, rash, skin ulcer
Vascular disorders: Deep vein thrombosis

Abnormal Hematologic and Clinical Chemistry Findings

Table 3 presents the percentage of DTC patients experiencing laboratory abnormalities in ≥5% and at a higher rate in LENVIMA-treated patients than placebo-treated patients in the double-blind phase of the pivotal Phase 3 SELECT trial.

Table 3 Per-Patient Incidence of Laboratory Abnormalities Occurring in ≥5% and at a Higher Incidence in LENVIMA-Treated Patients[a] - Pivotal DTC Phase 3 SELECT trial

Laboratory Abnormality	LENVIMA 24 mg N = 261		Placebo N = 131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Clinical chemistry				
Creatinine increased	87.0	2.7	80.2	0
Hyperglycemia	52.9	0.8	35.9	3.8
Alanine aminotransferase (ALT) increased	51.7	4.2	9.9	0
Hypoalbuminemia	49.4	1.9	17.6	0.8
Aspartate aminotransferase (AST) increased	49.0	4.6	11.5	0
Hypocalcemia	39.5	8.8	13.0	1.5
Alkaline phosphatase increased	27.6	1.9	10.7	0.8
Hypernatremia	24.9	0	13.0	0
Hypokalemia	23.8	6.1	5.3	0.8
Hyponatremia	21.5	5.0	10.7	3.8
Hypomagnesemia	20.3	1.5	2.3	0
Hypoglycemia	19.2	0	6.1	0
Creatinine phosphokinase (CPK) increased	18.0	1.1	17.6	0
Hypertriglyceridemia	14.9	0	7.6	0
Lipase increased	11.5	3.8	5.3	0.8
Hypophosphatemia	11.1	1.1	7.6	0.8
Blood bilirubin increased	11.1	1.1	4.6	0
Hypercalcemia	11.1	0.8	5.3	0.8
Cholesterol high	10.0	0.4	3.1	0
Serum amylase increased	9.6	3.1	5.3	1.5
Hyperkalemia	8.0	1.1	1.5	0.8
Hematology				
Lymphocyte count decreased	36.8	8.0	33.6	7.6
Platelet count decreased	33.0	2.3	5.3	0
White blood cell decreased	29.9	1.5	20.6	0
Neutrophil count decreased	17.2	1.5	13.0	0
Hemoglobin increased	14.9	0	1.5	0

[a] With at least one grade increase from baseline

Clinical Trial Adverse Reactions in RCC

The data described below are derived from the RCC Phase 2 Study 205 which randomized (1:1:1) patients with unresectable advanced or metastatic renal cell carcinoma (RCC) to LENVIMA 18 mg + everolimus 5 mg (n=51), LENVIMA 24 mg (n=52), or everolimus 10 mg (n=50) once daily. This data also includes patients on the dose escalation portion (1b) of the study who received LENVIMA 18 mg + everolimus 5 mg (n=11). The median treatment duration was 8.1 months for LENVIMA + everolimus and 4.1 months for everolimus. Among

62 patients who received LENVIMA + everolimus in Study 1b+2, the median age was 61 years, 71% were men, and 98% were White.

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

Within the RCC study, adverse reactions reported in more than 15% of subjects and at ≥ 10% higher incidence in the LENVIMA + everolimus group compared to the everolimus monotherapy group were: hypothyroidism (24% vs. 2%), diarrhea (81% vs. 34%), abdominal pain (37% vs. 8%), nausea (45% vs. 16%), oral pain (23% vs. 4%), vomiting (48% vs. 12%), fatigue (73% vs. 40%), peripheral edema (42% vs. 20%), pyrexia (21% vs. 10%), weight decreased (34% vs. 8%), decreased appetite (53% vs. 18%), arthralgia/myalgia (55% vs. 32%), musculoskeletal chest pain (18% vs. 4%), insomnia (16% vs. 2%), proteinuria (31% vs. 14%), dysphonia (18% vs. 4%), and hypertension (42% vs. 10%).

Grade 3 or 4 adverse reactions reported at ≥ 4% higher incidence in the LENVIMA + everolimus group compared to the everolimus monotherapy group were: diarrhea (19% vs. 2%), nausea (5% vs. 0%), vomiting (7% vs. 0%), fatigue (18% vs. 2%), decreased appetite (5% vs. 0%), arthralgia/myalgia (5% vs. 0%), proteinuria (8% vs. 2%), and hypertension (13% vs. 2%)

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 diarrhea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%).

Treatment discontinuation due to an adverse reaction occurred in 29% of patients in the LENVIMA + everolimus-treated group and 12% of patients in the everolimus-treated group. The most common adverse reactions leading to treatment discontinuation in the LENVIMA + everolimus-treated group were that of proteinuria (4.8%) and thrombocytopenia (3.2%).

Clinical Trial Adverse Reactions for RCC

Table 4: Adverse Reactions in > 15% of Patients in the LENVIMA + Everolimus Arm – RCC Phase 1b+2 Study 205				
	LENVIMA 18 mg + Everolimus 5 mg (N=62)		**Everolimus 10 mg (N=50)**	
System Organ Class Preferred Term	**All Grades (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Endocrine Disorders				
Hypothyroidism	24	0	2	0
Gastrointestinal Disorders				
Constipation	16	0	18	0
Diarrhea	81	19	34	2
Dyspepsia/Gastro-esophageal 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
General Disorders and Administration Site Conditions				
Fatigue[d]	73	18	40	2
Peripheral edema	42	2	20	0
Pyrexia/Increased body temperature	21	2	10	2
Metabolism and Nutrition Disorders				
Decreased appetite	53	5	18	0
Weight decreased	34	3	8	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
Dyspnea/Exertional dyspnea	35	5	28	8
Skin and Subcutaneous Tissue Disorders				
Rash[g]	35	0	40	0

Vascular Disorders				
Hemorrhagic 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 hemorrhagic diarrhea, epistaxis, gastric hemorrhage, hemarthrosis, hematoma, hematuria, hemoptysis, lip hemorrhage, renal hematoma, and scrotal hematocele

Table 5 Per-Patient Incidence of Serious Adverse Reactions Occurring in ≥4% - RCC Phase 1b+2 Study 205

System Organ Class Preferred Term	LENVIMA 18 mg + Everolimus 5 mg (N= 62)	Everolimus 10 mg (N=50)
Blood and Lymphatic System Disorders		
Anemia	6.5	8
Gastrointestinal Disorders		
Diarrhea	4.8	0
Vomiting	4.8	0
Metabolism and Nutrition Disorders		
Dehydration	9.7	0
Renal and Urinary Disorders		
Renal Failure Acute	8.1	0
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	4.8	4.0

Less Common Clinical Trial Serious Adverse Events (<4%) for RCC

The following serious adverse events were reported with LENVIMA-treated patients in the pivotal Phase 1b+2 RCC trial during randomized treatment with a frequency of <4%:

Blood and lymphatic system disorders: Sideroblastic anemia, thrombocytopenia
Cardiac disorders: Cardiac failure, cardiomyopathy, myocardial infarction, tachycardia
Gastrointestinal disorders: Dysphagia, gastric hemorrhage, gastritis, hemorrhoids, ileus
General disorders and administration site conditions: Asthenia, chest discomfort, fatigue, general physical health deterioration, pain, pyrexia
Hepatobiliary disorders: Cholangitis, cholecystitis
Immune system disorders: Drug hypersensitivity
Infections and infestations: Appendicitis, appendicitis perforated, bronchopneumonia, cellulitis, infection, lung infection, sepsis
Injury, poisoning and procedural complications: Joint dislocation

Investigations: Blood bilirubin increased, body temperature increased, ejection fraction decreased, fibrin D-dimer increased, transaminases increased, white blood cell count decreased
Metabolism and nutrition disorders: Decreased appetite, hypercholesterolemia, hyperkalemia, hypokalemia, hypomagnesaemia
Musculoskeletal and connective tissue disorders: Arthalgia, back pain, hemoarthrosis, musculoskeletal chest pain.
Neoplasms benign, malignant and unspecified (including cysts and polyps): Malignant pleural effusion
Nervous system disorders: Cerebral hemorrhage, convulsion, somnolence
Psychiatric disorders: Anxiety, confusional state
Renal and urinary disorders: Proteinuria, renal impairment
Respiratory, thoracic and mediastinal disorders: pleural effusion, pneumonitis, pulmonary embolism
Vascular disorders: Hot flush, venous thrombosis

Electrocardiography: In the Phase 1b+2 clinical trial of RCC, the proportion of subjects with high ECG interval outlier thresholds was as follows:

- QTc values >480 ms: 1/50 (2.0%) in the everolimus 10 mg group and 4/62 (6.5%) in the LENVIMA 18 mg + everolimus 5 mg group
- QTc values >500 ms: 0/50 in the everolimus 10 mg group and 4/62 (6.5%) in the LENVIMA 18 mg + everolimus 5 mg group
- QRS values >110 ms: 7/50 (14.0%) in the everolimus 10 mg group and 19/62 (30.6%) in the LENVIMA 18 mg + everolimus 5 mg group
- PR values >200 ms: 8/50 (16.0%) in the everolimus 10 mg group and 15/62 (24.2%) in the LENVIMA 18 mg + everolimus 5 mg group

Abnormal Hematologic and Clinical Chemistry Findings

Table 6 Per-Patient Incidence of Laboratory Abnormalities[a,b] – Phase 1b+2 RCC trial

Laboratory Abnormality	LENVIMA 18 mg + Everolimus 5 mg N=62		Everolimus 10 mg N=50	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Clinical chemistry				
Alanine aminotransferase increased	32 (51.6)	2 (3.2)	26 (52.0)	1 (2.0)
Alkaline phosphatase increased	29 (46.8)	2 (3.2)	13 (26.0)	0 (0.0)
Aspartate aminotransferase increased	35 (56.5)	2 (3.2)	22 (44.0)	0 (0.0)
Blood bilirubin increased	3 (4.8)	1 (1.6)	0 (0.0)	0 (0.0)
CK increased	32 (51.6)	2 (3.2)	22 (44.0)	2 (4.0)
Cholesterol high	48 (77.4)	7 (11.3)	39 (78.0)	0 (0.0)
Creatinine increased	56 (90.3)	1 (1.6)	40 (80.0)	1 (2.0)
Hypercalcemia	4 (6.5)	0 (0.0)	3 (6.0)	0 (0.0)
Hyperglycemia	42 (67.7)	2 (3.2)	34 (68.0)	8 (16.0)

Table 6 Per-Patient Incidence of Laboratory Abnormalities[a,b] – Phase 1b+2 RCC trial

Laboratory Abnormality	LENVIMA 18 mg + Everolimus 5 mg N=62		Everolimus 10 mg N=50	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hyperkalemia	20 (32.3)	4 (6.5)	10 (20.0)	1 (2.0)
Hypermagnesemia	17 (27.4)	0 (0.0)	7 (14.0)	0 (0.0)
Hypernatremia	14 (22.6)	0 (0.0)	6 (12.0)	0 (0.0)
Hypertriglyceridemia	54 (87.1)	11 (17.7)	38 (76.0)	9 (18.0)
Hypoalbuminemia	25 (40.3)	0 (0.0)	13 (26.0)	0 (0.0)
Hypocalcemia	27 (43.5)	4 (6.5)	12 (24.0)	1 (2.0)
Hypoglycemia	1 (1.6)	0 (0.0)	1 (2.0)	0 (0.0)
Hypokalemia	21 (33.9)	4 (6.5)	6 (12.0)	1 (2.0)
Hypomagnesemia	12 (19.4)	1 (1.6)	0 (0.0)	0 (0.0)
Hyponatremia	15 (24.2)	7 (11.3)	15 (30.0)	3 (6.0)
Hypophosphatemia	33 (53.2)	7 (11.3)	18 (36.0)	3 (6.0)
Lipase increased	23 (37.1)	8 (12.9)	15 (30.0)	6 (12.0)
Thyroid stimulating hormone (TSH) increased	39 (62.9)	NA	9 (18.0)	NA[c]
Hematology				
Anemia	30 (48.4)	5 (8.1)	33 (66.0)	8 (16.0)
Hemoglobin increased	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocyte count decreased	26 (41.9)	6 (9.7)	19 (38.0)	10 (20.0)
Lymphocyte count increased	3 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Neutrophil count decreased	8 (12.9)	1 (1.6)	3 (6.0)	0 (0.0)
Platelet count decreased	25 (40.3)	3 (4.8)	20 (40.0)	0 (0.0)
White blood cell decreased	13 (21.0)	1 (1.6)	13 (26.0)	0 (0.0)

[a] With at least one grade increase from baseline

[b] Subjects with at least one post baseline laboratory value

[c] Not applicable as no CTCAE grading exists for TSH increased

Clinical Trial Adverse Reactions in HCC

The safety data described below are derived from the HCC Phase 3 REFLECT Study 304 to support the use of LENVIMA in treatment of patients (n=476) with unresectable hepatocellular carcinoma (HCC) and compared it with the patients treated with sorafenib (n=475). The starting dose of LENVIMA, given once daily, was based on baseline body weight: i.e. 12 mg (for patients with a body weight of ≥60 kg) and 8 mg (for patients with a body weight of < 60 kg). The dose of sorafenib was 400 mg, given twice daily. The median treatment duration was 6 months for LENVIMA and 4 months for sorafenib. Among 476 patients who received LENVIMA in Study 304, median age was 63 years, 85% were men, 28% were Caucasian and 70% were Asian.

The most common adverse reactions observed, in order of decreasing frequency, in the LENVIMA-treated group (>20%) were hypertension (45%) , fatigue (44%), diarrhea (39%), decreased appetite (34%), arthralgia/myalgia (31%), weight decreased, (31%), abdominal pain (30%), palmar-plantar erythrodysesthesia syndrome (27%), proteinuria (26%), dysphonia (24%),

hemorrhagic events (23%), hypothyroidism (21%), and nausea (20%).

The most common serious adverse reactions (≥2%) were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), decreased appetite (2%), and malignant neoplasm progression (2%).

Adverse reactions led to dose reduction or interruption in 62% of patients receiving LENVIMA and 56% of patients receiving sorafenib. The most common adverse reactions (≥5%) resulting in dose reduction or interruption in the LENVIMA treatment arm were fatigue (9%), decreased appetite (8%), diarrhea (8%), proteinuria (7%), hypertension (6%), and palmar-plantar erythrodysesthesia syndrome (5%).

Treatment discontinuation due to an adverse reactions occurred in 20% of patients in the LENVIMA-treated group and 15% of patients in the sorafenib-treated group. The most common adverse reactions (≥1%) resulting in discontinuation in the LENVIMA treatment arm were hepatic encephalopathy (2%), fatigue (1%), hyperbilirubinemia (1%), and hepatic failure (1%).

Clinical Trial Adverse Reactions in HCC

Table 7: Adverse Ractions in ≥ 10% of Patients in the LENVIMA Arm in the pivotal HCC Phase 3 REFLECT Study 304

	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				
Diarrhea	39	4	46	4
Abdominal pain[b]	30	3	28	4
Nausea	20	1	14	1
Vomiting	16	1	8	1
Constipation	16	1	11	0
Ascites[c]	15	4	11	3
Stomatitis[d]	11	0	14	1
General Disorders and Administration Site Conditions				
Fatigue[e]	44	7	36	6
Pyrexia[f]	15	0	14	0
Peripheral edema	14	1	7	0
Metabolism and Nutrition Disorders				
Decreased appetite	34	5	27	1
Weight decreased	31	8	22	3
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/Myalgia[g]	31	1	20	2
Nervous System Disorders				

Table 7: Adverse Ractions in ≥ 10% of Patients in the LENVIMA Arm in the pivotal HCC Phase 3 REFLECT Study 304				
	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 (%)
Headache	10	1	8	0
Renal and Urinary Disorders				
Proteinuria[h]	26	6	12	2
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	24	0	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
Hemorrhagic events[k]	23	4	15	4

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

Table 8 Per-Patient Incidence of Serious Adverse Reactions Occurring in ≥1% - pivotal HCC Phase 3 REFLECT Study 304

System Organ Class Preferred Term	LENVIMA 8 or 12 mg (N= 476) (%)	Sorafenib 800 mg (N=475) (%)
Gastrointestinal Disorders		
Ascites	2.5	2.3
Diarrhea	1.7	0.4
Eesophageal varices hemorrhage	1.5	1.1
Abdominal pain	1.3	2.1
Vomiting	1.3	0
Upper gastrointestinal hemorrhage	1.1	0.4

Table 8 Per-Patient Incidence of Serious Adverse Reactions Occurring in ≥1% - pivotal HCC Phase 3 REFLECT Study 304

System Organ Class Preferred Term	LENVIMA 8 or 12 mg (N= 476) (%)	Sorafenib 800 mg (N=475) (%)
General Disorders and Administration Site Conditions		
Asthenia	1.5	0.2
Pyrexia	1.3	1.1
Hepatobiliary Disorders		
Hepatic failure	2.9	1.7
Jaundice cholestatic	1.5	0.6
Infections and Infestations		
Sepsis	1.5	0.6
Pneumonia	1.1	0.8
Investigations		
Blood biribulin increased	1.5	0.2
Metabolism and Nutrition Disorders		
Decreased appetite	2.3	0.4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Malignant neoplasm progression	2.1	2.9
Nervous System Disorders		
Hepatic encephalopathy	4.4	0.6
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	1.1	0.4

Less Common Clinical Trial Serious Adverse Reactions (<1%) for HCC

The following serious adverse events were reported with LENVIMA-treated patients in the pivotal HCC Phase 3 REFLECT Study 304 during randomized treatment with a frequency of <1%:

Blood and lymphatic system disorders: Anemia, bone marrow failure, disseminated intravascular coagulation
Cardiac disorders: Myocardial infarction, atrial fibrillation, cardiopulmonary failure
Gastrointestinal disorders: Duodenal ulcer hemorrhage, nausea, duodenal ulcer, gastric ulcer, umbilical hernia, abdominal distension, dyspepsia, gastric hemorrhage, intestinal hemorrhage, pancreatitis acute
General disorders and administration site conditions: Edema peripheral, multiple organ dysfunction syndrome, death, generalized edema, organ failure, peripheral swelling, sudden death
Hepatobiliary disorders: Portal vein thrombosis, cholangitis, hepatic cirrhosis, bile duct obstruction, bile duct stone, cholecystitis, acute hepatic failure, biliary dilatation, cholecystitis acute, chronic hepatic failure, hemobilia, hepatic function abnormal, hepatic pain, hepatorenal syndrome, hydrocholecystitis, hyperbilirubinemia, jaundice, liver injury
Infections and infestations: Cellulitis, gastroenteritis,-liver abcess, lung infection, peritonitis, urinary tract infection, appendiceal abscess, bacteremia, biliary tract infection, dengue fever, diverticulitis, Escherichia sepsis, gastrointestinal viral infection, groin abscess, infection, infectious pleural effusion, lung abscess, peri hepatic abscess, periodontitis, pleural infection ,

postoperative abscess, pulmonary tuberculosis, salmonellosis, scrotal infection, septic shock, tuberculosis, urosepsis
Injury, poisoning and procedural complications: Accidental overdose, fall, intentional overdose, spinal compression fracture, thoracic vertebral fracture
Investigations: Aspartate aminotransferase increased, alanine aminotransferase increased, blood pressure decreased, clostridium test positive, hepatic enzyme increased, neutrophil count decreased, weight decreased
Metabolism and nutrition disorders: Hyponatremia, dehydration, hyperkalemia, cachexia, Diabetes mellitus, hypercalcemia, hypoalbuminemia, hypoglycemia, hypomagnesemia
Musculoskeletal and connective tissue disorders: Muscular weakness, pathological fracture, bone pain, flank pain, intervertebral disc protrusion, neck pain, osteoarthritis, pain in extremity rhabdomyolysis, spinal column stenosis
Neoplasms benign, malignant and unspecified (including cysts and polyps): Cancer pain, tumour hemorrhage, liver carcinoma ruptured, metastases to central nervous system, metastases to spine, infected neoplasm, intracranial tumour hemorrhage, meningioma, metastases to bone, renal cell carcinoma, tumour necrosis, tumour pain, tumour rupture
Nervous system disorders: Cerebral hemorrhage, coma hepatic, cerebral infarction, cerebrovascular accident, headache, seizure, spinal cord compression, diplegia, disturbance in attention, dizziness, facial paralysis, paralysis recurrent laryngeal nerve, posterior reversible encephalopathy syndrome, syncope, transient ischemic attack
Psychiatric disorders: Confusional state, major depression, suicide attempt
Renal and urinary disorders: Acute kidney injury, proteinuria, renal failure, renal impairment, hematuria, IgA nephropathy, renal tubular necrosis
Reproductive: Pelvic pain, amenorrhoea
Respiratory, thoracic and mediastinal disorders: Pulmonary embolism, pneumonia aspiration, respiratory failure, hepatopulmonary syndrome, acute respiratory failure, hiccups, necrotizing bronchitis, non-cardiogenic pulmonary edema, oropharyngeal pain, pneumothorax, pulmonary infarction
Skin: Intertrigo, seborrhoeic dermatitis
Vascular disorders: Aortic dissection, circulatory collapse, deep vein thrombosis

Additional Safety Information from HCC Clinical Trial Experience

Cardiovascular

Hypertension

In the HCC Phase 3 REFELCT Study 304, the median time to first onset of new or worsening hypertension was 26 days for LENVIMA-treated patients and 15 days for the sorafenib-treated patients. The incidence of Grade 3 hypertension was 24% in the LENVIMA-treated group as compared to 15% for the sorafenib-treated group.

Electrocardiography

In the HCC Phase 3 Study 304, QTc interval increases greater than 60 ms were reported in 8% of patients in the LENVIMA-treated group as compared with the sorafenib-treated group (4%). The incidence of QTc interval greater than 500 ms was 2% of patients in both the LENVIMA-treated group and the sorafenib-treated group.

Endocrine and Metabolism

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction

In the HCC Phase 3 REFLECT Study 304, Grade 1 or 2 hypothyroidism occurred with higher frequency in patients treated with LENVIMA (21%) than with the sorafenib-treated group (3%). Elevation of TSH was observed post baseline in 70% of LENVIMA-treated patients and in 32% of patients receiving sorafenib.

Hepatic/Biliary/Pancreatic

Hepatotoxicity

Hepatotoxicity including hepatic encephalopathy and hepatic failure (including fatal reactions) were reported at a higher frequency in LENVIMA-treated patients with HCC than with DTC and RCC. In patients with HCC, higher incidences of hepatic encephalopathy occurred in LENVIMA-treated patients (8%) than in the sorafenib group (3%). The median time to onset of hepatotoxocity adverse reactions was 6.4 weeks in the LENVIMA-treated arm and 4.4 weeks in the sorafenib-treated arm. Grade 3 or greater hepatic failure [including fatal events in 3% of patients (n=12)] occurred in 3% of patients in both the LENVIMA-treated group and in the sorafenib-treated group. Higher frequency of Grade 3 or greater hepatic encephalopathy [including fatal events in 1% of patients (n=4)] occurred in the LENVIMA (5%) than in 2% the sorafenib treated groups (2%). There were 4% of deaths due to hepatotoxicity events in the LENVIMA arm and 1% of deaths in the sorafenib arm. Discontinuations due to hepatic encephalopathy occurred in 1% of LENVIMA-treated patients. Hepatotoxicity adverse reactions led to dose interruptions and reductions in 12% and 7% of LENVIMA-treated patients respectively, and to permanent discontinuation in 6%.

Hematologic

Hemorrhage

In the HCC Phase 3 REFLECT Study 304, the frequency of hemorrhagic events was higher in patients in the LENVIMA-treated group (23%) than of patients in the sorafenib-treated group (15%). The most frequently reported hemorrhagic events were epistaxis (LENVIMA-7%) vs. sorafenib 3%), hematuria (5% vs 2%), and gingival bleeding (4% vs 2%). Grade 3 or greater events occurred with similar frequency at 5% in both LENVIMA-treated patients as well as in sorafenib-treated patients. The median time to first onset was 11.9 weeks In the LENVIMA-treated group, 1.5% of patients had a fatal hemorrhage including cerebral haemorrhage, upper gastrointestinal haemorrhage, intestinal haemorrhage and tumour haemorrhage, compared with 1.1% of patients in the sorafenib-treated group. A hemorrhage event leading to dose interruption or reduction was reported in 3.2% and 0.8% patients respectively in the LENVIMA-treated group and 2.9% and 0.8% in the sorafenib-treated group. Discontinuation due to a hemorrhagic event occurred in 2% of patients in the LENVIMA-treated group and 1% in the sorafenib-treated group

Renal

Renal Failure and Impairment

In the HCC Phase 3 REFLECT Study 304, renal impairment was reported in 7% of LENVIMA-treated group and 4% in the sorafenib-treated group. Incidences of Grade 3 or greater renal failure or impairment were higher in the LENVIMA-treated group (2%) than in the sorafenib-treated group (1%).

Proteinuria
In the HCC Phase 3 REFLECT Study 304, a higher instance of proteinuria was reported in the LENVIMA-treated group (26%) than in patients in the sorafenib-treated group (12%). The incidence of Grade 3 proteinuria in LENVIMA-treated patients was 6% compared to 2% in sorafenib-treated patients.

Abnormal Hematologic and Clinical Chemistry Findings – HCC

Incidence of abnormal hematologic and clinical chemistry findings reported in at least 10% of patients is summarized in Table 9.

Table 9 Laboratory Abnormalities[a,b] – Pivotal HCC Phase 3 REFLECT Study 304

Laboratory Abnormality	LENVIMA (N=476) (%)		Sorafenib (N=475) (%)	
	All Grades in ≥10% of patients (%)	Grades 3-4 (%)	All Grades in ≥10% of patients (%)	Grades 3-4 (%)
Clinical chemistry				
Alanine aminotransferase increased	43	8	50	9
Alkaline phosphatase increased	41	7	47	5
Aspartate aminotransferase increased	50	12	60	18
Blood bilirubin increased	52	13	50	10
Blood cholesterol increased	36	0	24	1
Creatinine increased	75	2	57	2
GGT increased	38	16	44	20
Hyperkalemia	23	3	15	2
Hypoalbuminemia	52	3	39	1
Hypokalemia	16	3	20	4
Hyponatremia	32	15	26	9
Lipase increased	14	4	25	9
Hematology				
Hemoglobin decreased	31	4	37	5
Hemoglobin increased	16	0	6	0
Lymphocyte count decreased	41	8	40	9
Neutrophil count decreased	30	7	19	3
Platelet count decreased	56	10	48	8
White blood cell decreased	39	6	30	3

Subject is counted only once for each lab abnormality

[a] With at least one grade increase from baseline

[b] Included Subject with baseline and at least one post-baseline labe values

Hypocalcemia
In the Phase 3 REFLECT trial, hypocalcaemia was reported in 6.5% of patients, with grade 3 reactions occurring in 0.4%. LENVIMA dose interruption due to hypocalcaemia occurred in one subject (0.2%) and there were no dose reductions or discontinuations (see Table 9 and

ADVERSE REACTIONS, Endocrine and Metabolism, *Hypocalcemia*).

Post-Market Adverse Drug Reactions

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

Gastrointestinal: pancreatitis, increased amylase
General: impaired wound healing
Hepatobiliary: cholecystitis
Musculoskeletal and Connective Tissue: fistula
Renal and urinary disorders: nephrotic syndrome
Respiratory, thoracic and mediastinal disorders: pneumothorax
Vascular Disorders: aortic dissection

DRUG INTERACTIONS

Overview

Lenvatinib is extensively metabolized and elimination is mediated predominantly by cytochrome P450 (CYP) 3A, aldehyde oxidase (AO) and nonenzymatic processes in humans.

Drug-Drug Interactions

Effect of Other Drugs on LENVIMA

CYP3A4 inhibitors and inducers: LENVIMA (lenvatinib) may be co-administered without dose adjustment with CYP3A inhibitors and CYP3A inducers.

P-gp inhibitors and inducers: LENVIMA (lenvatinib) may be co-administered without dose adjustment with P-glycoprotein (P-gp) inhibitors and P-gp inducers.

BCRP inhibitors: LENVIMA (lenvatinib) may be co-administered without dose adjustment with breast cancer resistance protein (BCRP) inhibitors.

Agents that increase gastric pH: In a population PK analysis of patients receiving LENVIMA up to 24 mg once daily, agents that increase gastric pH (H_2 receptor blockers, proton pump inhibitors, antacids) did not have a significant effect on lenvatinib exposure (see ACTION AND CLINICAL PHARMACOLOGY).

Effect of LENVIMA on Other Drugs

Lenvatinib is considered neither a strong inducer nor inhibitor of cytochrome P450 or UGT enzymes.

Cytochrome P450 enzymes: Lenvatinib slightly increased CYP3A enzyme activity, but had no effect on CYP1A1, CYP1A2, CYP2B6, and CYP2C9. Lenvatinib exhibited an inhibitory effect

on CYP2C8, weak inhibitory effects on CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A, and virtually no inhibitory effects on CYP2A6 and CYP2E1.

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

UGT inhibitors and inducers: Lenvatinib directly inhibited UGT1A1 and UGT1A4, but showed little or no evidence of inhibition on UGT1A6, UGT1A9, and UGT2B7. Lenvatinib did not induce UGT1A1, UGT1A4, UGT1A6, UGT1A9, or UGT2B7.

OAT, OCT, BSEP transporters: Lenvatinib showed inhibitory effects on OAT1, OAT3, OCT1, OCT2, OATP1B1, and 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 (AO) activity (IC_{50}>100 μmol/L).

Drug-Food Interactions
LENVIMA may be taken with or without a meal. A high fat, high-calorie meal increased exposure (AUC) by approximately 5% while Cmax decreased 5%. Tmax was delayed 2 hrs resulting in a mean Tmax of 4 hrs. Tlag was increased 1 hr resulting in a mean Tlag of 1 hr.

Drug-Herb Interactions
Drug-herbal products interactions have not been established. Depending upon the transporter(s) or drug metabolizing enzyme(s) the herb affects, the cautions noted above for the affected transporter or drug metabolizing enzyme should be followed.

Drug-Lifestyle Interactions
Drug-lifestyle interactions have not been established.

Drugs that Decrease Heart Rate and/or Prolong the PR Interval
LENVIMA results in a decrease in heart rate and an increase in the PR interval (See WARNINGS AND PRECAUTIONS, Cardiovascular & Monitoring and Laboratory Tests; ADVERSE REACTIONS**,** Electrocardiography; ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology and Hemodynamics). The concomitant use of LENVIMA with other drugs that lower heart rate and/or prolong the PR interval, including, but not limited to, antiarrhythmics, beta blockers, non-dihydropyridine calcium channel blockers, digitalis glycosides, cholinesterase inhibitors, alpha 2-adrenoceptor agonists, sphingosine-1 phosphate receptor modulators, and HIV protease inhibitors should be avoided to the extent possible.

QT/QTc Interval-Prolonging Drugs

The concomitant use of LENVIMA with QT/QTc interval-prolonging drugs should be avoided to the extent possible (See WARNINGS AND PRECAUTIONS, Cardiovascular & Monitoring and Laboratory Tests; ADVERSE REACTIONS, Electrocardiography, ACTIONS AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology and Hemodynamics). Drugs that have been associated with QT/QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc interval prolongation and/or torsade de pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide)
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone)
- Class 1C antiarrhythmics (e.g., flecainide, propafenone)
- antipsychotics (e.g., olanzapine, chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone)
- antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants [e.g., amitriptyline, imipramine, maprotiline])
- opioids (e.g., methadone)
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, azithromycin, tacrolimus)
- quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin)
- pentamidine
- antimalarials (e.g., quinine, chloroquine)
- azole antifungals (e.g., ketoconazole, fluconazole, voriconazole)
- domperidone
- 5-hydroxytryptamine (5-HT)3 receptor antagonists (e.g., ondansetron)
- tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, lapatinib, vandetanib)
- arsenic trioxide
- histone deacetylase inhibitors (e.g., vorinostat)
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol)

Drugs that Affect Electrolytes

The use of LENVIMA with drugs that can disrupt electrolyte levels should be avoided to the extent possible. Drugs that can disrupt electrolyte levels include, but are not limited to, the following:

- loop, thiazide, and related diuretics
- laxatives and enemas
- amphotericin B
- high-dose corticosteroids

The above list of potentially interacting drugs is not comprehensive. Current information sources should be consulted for newly approved drugs that decrease heart rate, prolong the QT/QTc or PR interval, or decrease electrolytes, as well as for older drugs for which these effects have recently been established.

DOSAGE AND ADMINISTRATION

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

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

Optimal medical management (i.e. treatment or therapy) for nausea, vomiting, and diarrhoea should be initiated prior to any LENVIMA therapy interruption or dose reduction; gastrointestinal toxicity should be actively treated in order to reduce the risk of development of renal impairment or failure (see section Warnings and Precautions, Renal failure and impairment). Electrolytes, liver enzymes, urinary protein, thyroid function and hypertension should be tested prior to LENVIMA treatment and monitored periodically during LENVIMA therapy (see WARNINGS AND PRECAUTIONS, Cardiovascular, *QT Interval Prolongation*, Hepatic, *Hepatoxicity*, Renal, *Proteinuria*, Endocrine and Metabolism, *Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction* and Cardiovascular, *Hypertension*).

LENVIMA should be taken at about the same time each day, with or without food. The capsules should be swallowed whole with water. Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.

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

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.

Recommended Dose for DTC
The recommended daily dose of LENVIMA (lenvatinib) is 24 mg (two 10 mg capsules and one 4 mg capsule) orally taken once daily. The daily dose is to be modified as needed according to the dose/toxicity management plan. Treatment should continue as long as there is clinical benefit.

Recommended Dose for RCC
The recommended daily dose of LENVIMA is 18 mg (one 10 mg capsule and two 4 mg capsules) in combination with 5 mg everolimus orally taken once daily. The daily dose is to be modified as needed according to the dose/toxicity management plan. Treatment should continue as long as there is clinical benefit.

Recommended Dose for HCC
The recommended daily dose of LENVIMA is 8 mg (two 4 mg capsules) once daily for patients with a body weight of < 60 kg and 12 mg (three 4 mg capsules) once daily for patients with a body weight of ≥ 60 kg. Dose adjustments are based only on toxicities observed and not on body weight changes during treatment, unless the weight change occurs as an adverse event.

The daily dose is to be modified, as needed, according to the dose/toxicity management plan.

Dosage Adjustment, Dose Discontinuation for DTC, RCC and HCC

Management of adverse reactions may require interruption of LENVIMA therapy (see Table 10 and WARNINGS AND PRECAUTIONS). Upon resolution/improvement of an adverse reaction, treatment should be resumed at a reduced dose as suggested in Table 11 for DTC, Table 12 for RCC or Table 13 for HCC.

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

Table 10: Adverse Reactions Requiring Dose Modification of LENVIMA in DTC, RCC or HCC

Adverse Reaction	CTCAE Grade	Action	Dose Reduce and Resume LENVIMA
Hypertension	Grade 3[1]	Hold	Resolves to Grade 0, 1, or 2
	Grade 4	Discontinue	Do Not Resume
Cardiac Dysfunction	Grade 3	Hold	Resolves to Grade 0, 1, or baseline
	Grade 4	Discontinue	Do Not Resume
Arterial Thrombotic Event	Any Grade	Discontinue	Do Not Resume
Hepatotoxicity	Grade 3	Hold	Consider resuming at reduced dose if resolves to Grade 0-1 or baseline
	Grade 4[3]	Discontinue	Do not resume
Hepatic Failure	Grade 3 or 4	Discontinue	Do Not Resume
Proteinuria	Greater than or equal to 2 g/24 hours	Hold	Resolves to less than 2 g/24 hours
Nephrotic Syndrome	-------	Discontinue	Do Not Resume
Nausea, Vomiting, and Diarrhea[2]	Grade 3	Hold	Resolves to Grade 0, 1, or baseline
	Grade 4	Discontinue	Do Not Resume
Renal Failure or Impairment	Grade 3	Hold	Consider resuming at reduced dose if resolves to Grade 0-1 or baseline
	Grade 4	Discontinue	Do not resume
GI Perforation	Any Grade	Discontinue	Do Not Resume
Fistula	Grade 3 or 4	Discontinue	Do Not Resume
QTc Prolongation	Greater than 500 ms	Hold	Resolves to less than 480 ms or baseline
RPLS	Any Grade	Hold OR Discontinue	Consider resuming at reduced dose if resolves to Grade 0 to 1
Hemorrhage	Grade 3	Hold	Resolves to Grade 0 to 1
	Grade 4	Discontinue	Do Not Resume

1. Grade 3 despite optimal anti-hypertensive therapy
2. Initiate prompt medical management for nausea, vomiting or diarrhea. Permanently discontinue for Grade 4 vomiting and diarrhea despite medical management
3. Grade 4 laboratory abnormalities judged to be non-life-threatening, may be managed as severe reactions (e.g., Grade 3)

In Patients with DTC

Manage other adverse reactions according to the instructions in Table 11 for DTC patients. Based on the absence of clinical experience, there are no recommendations on resumption of dosing in patients with Grade 4 clinical adverse reactions that resolve.

Table 11 Recommended Dose Modifications for LENVIMA for Persistent and Intolerable Grade 2 or Grade 3 Adverse Reactions or Grade 4 Laboratory Abnormalities in DTC[a]

Adverse Reaction	Interruption	Adjusted Dose[b]
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	20 mg (two 10 mg capsules) orally once daily
Second occurrence[c]	Interrupt until resolved to Grade 0-1 or baseline	14 mg (one 10 mg capsule plus one 4 mg capsule) orally once daily
Third occurrence[c]	Interrupt until resolved to Grade 0-1 or baseline	10 mg (one 10 mg capsule) orally once daily[e]

[a] Initiate medical management for nausea, vomiting, or diarrhea prior to interruption or dose reduction of LENVIMA

[b] Reduce dose in succession based on the previous dose level (24, 20, or 14 mg/day). Dose increases should not occur after dose reductions have been made.

[c] Refers to the same or a different adverse reaction that requires dose modification

In Patients with RCC

Manage other adverse reactions according to the instructions in Table 12 for HCC patients. Based on the absence of clinical experience, there are no recommendations on resumption of dosing in patients with Grade 4 clinical adverse reactions that resolve.

Table 12: Recommended Dose Modifications for LENVIMA for Persistent and Intolerable Grade 2 or Grade 3 Adverse Reactions or Grade 4 Laboratory Abnormalities in RCC[a]

Adverse Reaction	Modification	Adjusted Dose[b]
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	14 mg (one 10 mg capsules plus one 4 mg capsule) orally once daily
Second occurrence[c]	Interrupt until resolved to Grade 0-1 or baseline	10 mg (one 10 mg capsule) orally once daily
Third occurrence[c]	Interrupt until resolved to Grade 0-1 or baseline	8 mg (two 4 mg capsules) orally once daily

[a] Initiate medical management for nausea, vomiting, or diarrhea prior to interruption or dose reduction of LENVIMA

[b] Reduce dose in succession based on the previous dose level (18 mg, 14 mg, 10 mg, or 8 mg per day). Dose increases should not occur after dose reductions have been made.

[c] Refers to the same or a different adverse reaction that requires dose modification

In Patients with HCC

Manage other adverse reactions according to the instructions in Table 13 for HCC patients. Based on the absence of clinical experience, there are no recommendations on resumption of dosing in patients with Grade 4 clinical adverse reactions that resolve.

Table 13 Dose Modifications from Recommended Daily Dose (HCC)

Starting Dose		≥60 kg BW 12 mg (three 4 mg capsules orally once daily)	<60 kg BW 8mg (two 4 mg capsules orally once daily)
Persistent and Intolerable Grade 2 or Grade 3 Toxicities [a]			
Adverse Reaction	**Modification**	**Adjusted Dose[b] (≥60 kg BW)**	**Adjusted Dose[b] (<60 kg BW)**
First occurrence [c]	Interrupt until resolved to Grade 0-1 or baseline [d]	8 mg (two 4 mg capsules) orally once daily	4 mg (one 4 mg capsule) orally once daily
Second occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline [d]	4 mg (one 4 mg capsule) orally once daily	4 mg (one 4 mg capsule) orally every other day
Third occurrence (same reaction or new reaction)	Interrupt until resolved to Grade 0-1 or baseline [d]	4 mg (one 4 mg capsule) orally every other day	Discontinue
Life-threatening toxicities (Grade 4): Discontinue[e]			

a Initiate medical management for nausea, vomiting, or diarrhea prior to interruption or dose reduction
b Reduce dose in succession based on the previous dose level (from 12 mg, 8 mg, 4 mg or from 8 mg to 4 mg, 4mg every other day)
c Hematologic toxicity or proteinuria-no dose adjustment required for first occurrence
d For hematologic toxicity or proteinuria can restart when resolved to Grade 2
e Excluding laboratory abnormalities judged to be non life-threatening, which should be managed as Grade 3.

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

Special Populations

Hepatic Impairment

In patients with DTC and RCC
No dose adjustments are 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 of LENVIMA is 14 mg (one 10 mg capsule plus one 4 mg capsule) in the treatment of DTC and 10 mg in the treatment of RCC, either taken orally once daily. Further dose adjustments may be necessary based on tolerability (see ACTION AND CLINICAL PHARMACOLOGY).

In patients with HCC
No dose adjustments are required on the basis of hepatic function in those patients who had mild hepatic impairment (Child-Pugh A). Patients with a baseline Child Pugh (CP) score of 6 (about 20% patients in the REFLECT study) had a higher incidence of decreased appetite, fatigue,

proteinuria, hepatic encephalopathy and hepatic failure compared to patients with a baseline CP score of 5. Hepatotoxicity events and haemorrhage events also occurred at a higher incidence in CP score 6 patients compared to CP score 5 patients.

Patients with mild hepatic impairment may require additional monitoring for adverse reactions requiring dose adjustments. Close monitoring of overall safety is recommended in these patients. Further dose adjustments may be necessary based on the individual tolerability (see DOSAGE AND ADMINISTRATION, Hepatic Impairment). LENVIMA has not been studied in patients with severe hepatic impairment (Child-Pugh C). (see WARNINGS AND PRECAUTIONS, General and Hepatotoxicity, and Special Populations).

Renal Impairment

In patients with DTC and RCC
No dose adjustments are required on the basis of renal function in patients with mild (CrCl 50 to 80 mL/min) or moderate renal impairment (CrCl 30 to 49 mL/min). In patients with severe renal impairment (CrCl <30 mL/min), the recommended dose of LENVIMA is 14 mg (one 10 mg capsule plus one 4 mg capsule) in the treatment of DTC and 10 mg in the treatment of RCC. Further dose adjustments may be necessary based on tolerability. Subjects with DTC or RCC and end stage renal disease were not studied, therefore the use of LENVIMA in these patients is not recommended.

In patients with HCC
No dose adjustments are required on the basis of renal function in patients with mild or moderate renal impairment. The available data in HCC patients do not allow for a dosing recommendation for patients with HCC and severe renal impairment (see ACTION AND CLINICAL PHARMACOLOGY).

Elderly population

No adjustment of starting dose is required on the basis of age. Limited data are available on use in patients aged ≥75 years. Patients of age ≥75 years had reduced tolerability.

Pediatric population

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

Weight

In patients with DTC and RCC
No adjustment of starting dose is required on the basis of body weight in patients with DTC or RCC. DTC and RCC patients with body weight below 60 kg-appear to have reduced tolerability to LENVIMA

In patients with HCC
The recommended daily dose of LENVIMA is 8 mg (two 4 mg capsules) once daily for patients with a body weight of < 60 kg and 12 mg (three 4 mg capsules) once daily for patients with a body weight of ≥ 60 kg. The daily dose is to be modified, as needed, according to the dose/toxicity management plan.

Race

In patients with DTC and RCC
No adjustment of starting dose is required on the basis of race. Asian race appears to have reduced tolerability.

In patients with HCC
No adjustment of starting dose is required on the basis of race. Caucasian race demonstrated reduced tolerability.

Gender

No adjustment of starting dose is required on the basis of gender. For HCC patients, patients of female gender appear to have reduced tolerability to LENVIMA.

Recommended Dose Modification for Everolimus

See manufacturer's Product Monograph for the coadministered product, everolimus for dose adjustment guidelines in the event of toxicity and other relevant safety information or contraindications. For toxicities thought to be related to everolimus alone, discontinue, interrupt, or use alternate day dosing. For toxicities thought to be related to both LENVIMA and everolimus, first reduce LENVIMA and then everolimus.

Missed Dose

If a patient misses a dose of LENVIMA (DTC/HCC) or LENVIMA + everolimus (RCC), 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.

Administration

Take LENVIMA (DTC, HCC) or LENVIMA + everolimus (RCC) at the same time each day, with or without food. The LENVIMA capsules should be swallowed whole with water. Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.

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

liquid must be swallowed.

OVERDOSAGE

Cases of LENVIMA (lenvatinib) overdose have been reported, including a single administration of 144 mg, 6, 8 or 18 times the recommended daily dose for DTC, RCC or HCC, respectively. These cases were associated with adverse reactions consistent with the known safety profile of LENVIMA (i.e., renal and cardiac failure), or were without adverse reactions. The highest doses of LENVIMA studied clinically were 32 mg and 40 mg per day. Accidental medication errors resulting in single doses of 40 to 48 mg have occurred in clinical trials. The most frequently observed adverse drug reactions at these doses were hypertension, nausea, diarrhea, fatigue, stomatitis, proteinuria, headache, and aggravation of PPE.

There is no specific antidote for overdose with lenvatinib. In case of suspected overdose, LENVIMA should be withheld and supportive care initiated.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Lenvatinib is a targeted antineoplastic agent that belongs to the family of receptor tyrosine kinase (RTK) inhibitors that selectively inhibit 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 had selective, direct antiproliferative activity in hepatocellular cell lines dependent on activated FGFR signaling, which is attributed to the inhibition of FGFR signaling by lenvatinib. Enhanced antiangiogenic and antitumor activity was observed when the combination of lenvatinib and everolimus was studied in nonclinical models.

Pharmacodynamics

Cardiac Electrophysiology and Hemodynamics: A single-dose, randomized, double-blind, placebo- and active-controlled, three-treatment, three–way crossover study was performed in healthy subjects (N=52) to evaluate the potential electrocardiographic effects of LENVIMA 32 mg. ECG data were collected at 1, 2, 3, 4, 5, 6, 12, and 24 h post-dosing.

LENVIMA caused a decrease in heart rate. Heart rate was reduced at all time points from 1 to 24 h post-dosing. The maximum mean difference from placebo was -8.09 bpm (90% CI -9.554, -6.64) at 12 h post-dosing. The proportion of subjects with low heart rate outlier values <50 bpm was higher in the LENVIMA arm (41.2%) than in the placebo arm (16.0%).

LENVIMA resulted in small negative mean differences from placebo in the QTcF interval from 1-12 h post-dosing, inclusive, with 90% confidence intervals excluding zero. The maximum mean difference from placebo was -5.72 ms (90% CI -7.76, -3.69) at 6 h. QTc prolongation was observed, however, during steady-state LENVIMA treatment in the phase 3 clinical trial of DTC. QTc prolongation was also observed in the RCC Phase 2 clinical trial. (see ADVERSE REACTIONS).

A single dose of LENVIMA 32 mg resulted in a delay in atrioventricular conduction. From 1 to 24 h post-dosing the PR interval was prolonged. The maximum mean difference from placebo was 8.45 ms (90% CI 5.96, 10.94) at the 5 h time point.

Blood pressure data were collected predose and at 2, 4, 6, and 8 h post-dosing. From 2-8 h post-dosing LENVIMA 32 mg treatment was associated with a statistically significant pressor effect. The maximum mean increase from baseline was 8.3 mmHg (90% CI 6.1, 10.5) for systolic blood pressure and 8.6 mmHg (90% CI 6.9, 10.4) for diastolic blood pressure, both at the 8 h time point (See WARNINGS & PRECAUTIONS, Cardiovascular & Monitoring and Laboratory Tests, ADVERSE REACTIONS, DRUG INTERACTIONS).

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 to healthy subjects with food, peak plasma concentrations are delayed by 2 hours (2hr to 4hr). Absolute bioavailability has not been determined in humans; however, data from a mass-balance study suggests that it is in the order of 85%. Lenvatinib exhibited good oral bioavailability in dogs (70.4%) and monkeys (78.4%).

Dose proportionality and accumulation: In patients with solid tumors administered single and multiple doses of lenvatinib once daily, exposure to lenvatinib (Cmax and AUC) increased in direct proportion to the administered dose over the range of 3.2 to 32 mg once-daily. 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).

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

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

Lenvatinib is a substrate for P-gp and BCRP. Lenvatinib showed minimal or no inhibitory activities toward P-gp-mediated and BCRP-mediated transport activities. Similarly, no induction of P-gp mRNA expression was observed. Lenvatinib is not a substrate for organic anion transporter (OAT) 1, OAT3, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, multidrug and toxin extrusion MATE1, MATE2-K or the bile salt export pump (BSEP).

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

Metabolism: The main metabolic pathways in humans were identified as oxidation by AO, demethylation via CYP3A4, GSH conjugation with elimination of the *O*-aryl group (chlorbenzyl moiety), and combinations of these pathways. Subsequently, further biotransformations occur (eg, glucuronidation, hydrolysis of the glutathione moiety, degradation of the cysteine moiety, and intramolecular rearrangement of the cysteinylglycine and cysteine conjugates with subsequent dimerization).

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 CYP3A4 (rifampin and ketoconazole, respectively) had a minimal effect on lenvatinib exposure.

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

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

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

Following administration of radiolabeled lenvatinib to 6 subjects with solid tumors, approximately two-thirds and one-fourth of the radiolabel were eliminated in the feces and urine, respectively. The total percentages of the radioactive dose excreted as metabolites M2, M2', and M3' were 4.4%, 11%, and, 17%, respectively. 2.9% of the dose was eliminated as lenvatinib.

Special Populations and Conditions

Pediatrics: No studies have been conducted to investigate the pharmacokinetics of lenvatinib in pediatric patients.

Geriatrics: Based on a population pharmacokinetic analysis of patients receiving up to 24 mg lenvatinib once daily, age had no significant effects on Cl/F.

Gender: Based on a population pharmacokinetic analysis of patients receiving up to 24 mg lenvatinib once daily, gender had no significant effects on apparent clearance Cl/F.

Race: Based on a population pharmacokinetic analysis of patients receiving up to 24 mg lenvatinib once daily, race (Japanese vs other, Caucasian vs other) had no significant effects on Cl/F.

Tumor Type: HCC study 304, patients demonstrated 13.2% lower lenvatinib Cl/F than subjects with other cancer types, including DTC.

Weight
Based on population PK analyses, weight did not have a significant effect on clearance (CL/F) of lenvatinib in DTC and RCC. However, in HCC, lenvatinib PK was affected by body weight. Lenvatinib exposures in HCC subjects (pivotal HCC Phase 3 REFLECT Study 304) were comparable between those weighing < 60 kg with an 8 mg starting dose and ≥ 60 kg with a starting dose of 12 mg (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: The pharmacokinetics of lenvatinib following a single 10 mg dose were evaluated in 6 subjects with mild and moderate hepatic impairment (Child-Pugh A and Child-Pugh B, respectively). A 5 mg dose was evaluated in 6 subjects with severe hepatic impairment (Child-Pugh C). Eight healthy, demographically matched subjects served as controls and received a 10 mg dose.

The median half-life was comparable in subjects with mild, moderate, and severe hepatic impairment as well as those with normal hepatic function and ranged from 26 hr to 31 hr.
The percentage of the dose of lenvatinib excreted in urine was low in all cohorts (<2.16% across treatment cohorts).

Lenvatinib exposure, based on $AUC_{0\text{-}inf}$ data, was 119%, 107%, and 180% for subjects with mild, moderate, and severe hepatic impairment, respectively when compared to patients with normal hepatic function. It is unknown whether there is a change in the plasma protein binding in hepatically impaired subjects. There are not sufficient data for HCC patients with Child-Pugh B (moderate hepatic impairment, 3 patients treated with lenvima in the pivotal trial) and no data available in Child Pugh C HCC patients (severe hepatic impairment). Lenvatinib is mainly eliminated via the liver and exposure might be increased in these patient populations (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency: The pharmacokinetics of lenvatinib following a single 24 mg dose were evaluated in 6 subjects each with mild (Creatinine clearance, CrCl 50 to 80 mL/min), moderate (CrCl 30 to 49 mL/min), and severe (CrCl 15 to 29 mL/min) renal impairment, and compared to 8 healthy (CrCl ≥81 mL/min), demographically matched subjects. Subjects with end stage renal disease were not studied. The lenvatinib dose-adjusted exposure ($AUC_{0\text{-}inf}$) estimates for subjects with mild, moderate, and severe renal impairment were 101%, 90%, and 122%, respectively, compared to patients with normal renal function.

STORAGE AND STABILITY

LENVIMA (lenvatinib) should be stored between 15-30°C.

SPECIAL HANDLING INSTRUCTIONS

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

Do not open the capsule. Avoid repeat exposure to contents of the capsule.

DOSAGE FORMS, COMPOSITION AND PACKAGING

4 mg hard capsule: A hard hypromellose capsule containing lenvatinib mesylate equivalent to 4 mg lenvatinib. 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.

10 mg hard capsule: A hard hypromellose capsule containing lenvatinib mesylate equivalent to 10 mg lenvatinib. 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.

Non-Medicinal Ingredients: Calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, low-substituted hydroxypropylcellulose, talc. Capsules: Hypromellose, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172). The printing ink contains: Shellac, black iron oxide (E172), potassium hydroxide, and propylene glycol.

Packaging: LENVIMA (lenvatinib) capsules are supplied in blisters of PA/Aluminum/PVC with a push through Aluminum foil lidding in the following compliance packaging configurations:

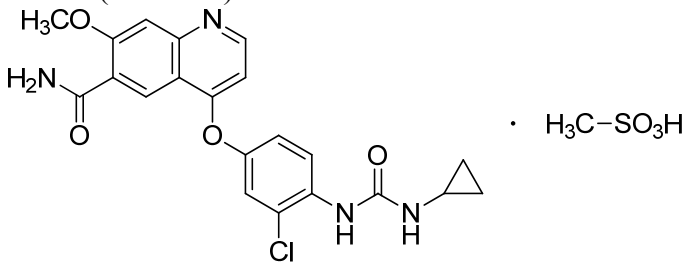
- 24 mg daily-dose carton containing 6 blister cards (each 5-day blister card contains ten 10 mg capsules and five 4 mg capsules)
- 20 mg daily-dose carton containing 6 blister cards (each 5-day blister card contains ten 10 mg capsules)
- 18 mg daily-dose carton containing 6 blister cards (each 5-day blister card contains five 10 mg capsules and ten 4 mg capsules)
- 14 mg daily-dose carton containing 6 blister cards (each 5-day blister card contains five 10 mg capsules and five 4 mg capsules)
- 12 mg daily-dose carton containing 6 blister cards (each 5-day blister card contains fifteen 4 mg capsules)
- 10 mg daily-dose carton containing 6 blister cards (each 5-day blister card contains five 10 mg capsules)
- 8 mg daily-dose carton containing 6 blister cards (each 5-day blister card contains ten 4 mg capsules)
- 4 mg daily-dose carton containing 6 blister cards (each 5-day blister card contains five 4 mg capsules)

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name: Lenvatinib mesylate
Chemical name: 4-[3-chloro-4-(*N'*-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate
Company code: E7080
Molecular formula: $C_{21}H_{19}ClN_4O_4 \cdot CH_4O_3S$
Molecular mass: 522.96 (mesylate)
426.86 (free base)
Structural formula:



Physicochemical properties: **Appearance:** White powder
Solubility: Lenvatinib mesylate is sparingly soluble in acetic acid and slightly soluble in water. In aqueous solutions, lenvatinib mesylate is very slightly soluble in 0.1 mol/L HCL and practically insoluble in Britton-Robinson buffer, pH 3-11
pKa: 5.05
Partition coefficient: Partition constant (log P(o/w)) 3.30
Melting point: 221 to 224°C

CLINICAL TRIALS

The clinical safety and efficacy of LENVIMA have been studied in patients with differentiated thyroid cancer (DTC), renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC).

Differentiated Thyroid Cancer (DTC)

A multicenter, randomized, double-blind, placebo-controlled trial was conducted in 392 patients with radioiodine-refractory differentiated thyroid cancer with radiographic evidence of disease progression within 12 months (+1 month window) prior to randomization. Radioiodine-refractory was defined as one or more measurable lesions either with no iodine uptake on RAI scan or iodine uptake and progression within 12 months of RAI therapy, or having a cumulative RAI activity of >600 mCi or 22 GBq, with the last dose administered at least 6 months prior to study entry. Randomization 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 primary efficacy endpoint was progression-free survival (PFS) as determined by blinded independent radiologic review using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Secondary efficacy endpoints included overall response rate (ORR) and overall survival (OS). Patients in the placebo arm could receive LENVIMA (lenvatinib) treatment after confirmed disease progression.

Eligible patients with measurable disease according to RECIST 1.1 were randomly assigned in a 2:1 ratio 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 assigned to treatment, 23.7% had received 1 prior VEGF/VEGFR-targeted therapy. 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%, and brain in 4.1%. The median cumulative RAI activity administered prior to study entry was 350 mCi (12.95 GBq).

The subject-years of exposure to 24 mg (97.6 years) was greater than for any other dose.

A statistically significant prolongation in PFS was demonstrated in LENVIMA-treated patients compared to 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. In addition, the positive effect on PFS was seen across the subgroups of age, sex, race, histological subtype, and geographic region. Among subjects who achieved a complete or partial response, 70.4% achieved the response on or within 30 days of treatment with the 24 mg dose of LENVIMA. Following independent review confirmation of disease progression, 109 (83%) patients randomly assigned to placebo crossed over to open-label LENVIMA.

Table 14 Efficacy Results (DTC)

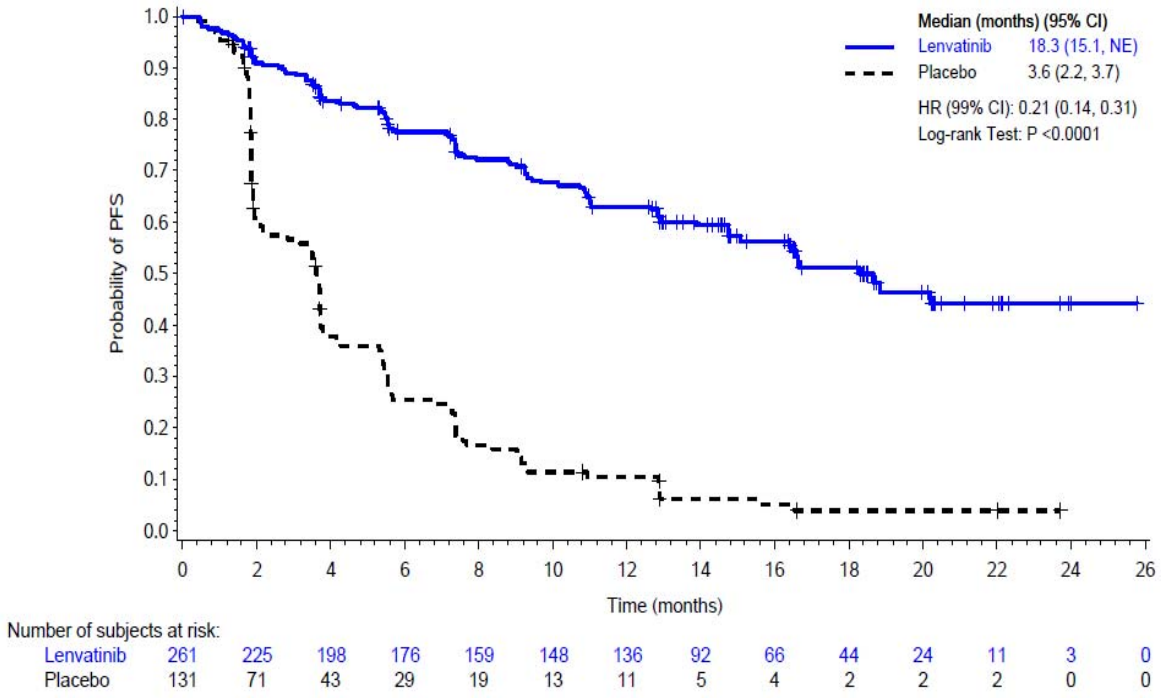
	LENVIMA N = 261	**Placebo N = 131**
Progression-free Survival[a]		
Number of progressions or deaths (%)	107 (41)	113 (86.3)
Median PFS in months (95% CI)	18.3 (15.1, NE)	3.6 (2.2, 3.7)
Hazard ratio (99% CI)[b,c]	0.21 (0.14, 0.31)	
P-value[b]	<0.0001	
Patients who had received 0 prior VEGF/VEGFR-targeted therapy (%)	195 (74.7)	104 (79.4)
Number of progressions or deaths	76	88
Median PFS in months (95% CI)	18.7 (16.4, NE)	3.6 (2.1, 5.3)
Hazard ratio (95% CI)[b,c]	0.20 (0.14, 0.27)	
Patients who had received 1 prior VEGF/VEGFR-targeted therapy (%)	66 (25.3)	27 (20.6)
Number of progressions or deaths	31	25
Median PFS in months (95% CI)	15.1 (8.8, NE)	3.6 (1.9, 3.7)
Hazard ratio (95% CI)[b,c]	0.22 (0.12, 0.41)	

Table 14 Efficacy Results (DTC)

	LENVIMA N = 261	Placebo N = 131
Overall Response Rate[a]		
Number of objective responders (%)	169 (64.8)	2 (1.5)
(95% CI)	(59.0, 70.5)	(0.0, 3.6)
Number of complete responses (%)	4 (1.5)	0
Number of partial responses (%)	165 (63.2)	2 (1.5)
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,d]	0.73 (0.50, 1.07)	
P-value[b,d]	0.1032	

[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] Not adjusted for crossover effect
NE = Not estimable

Figure 1 Kaplan-Meier Plot of Progression-Free Survival (DTC)



Renal Cell Carcinoma (RCC)

A multicenter, randomized, 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 RCC. The study consisted of a Phase 1b dose finding and a Phase 2 portion. The phase 1b portion included patients who received the combination of LENVIMA 18 mg + everolimus 5 mg. The Phase 2 portion enrolled a total of 153 patients with unresectable advanced or metastatic renal cell carcinoma (RCC) following 1 prior VEGF-targeted treatment. A total of 62 patients received the combination of LENVIMA and everolimus at the recommended dose. Patients were required, among others, to have histological confirmation of predominant clear cell RCC, radiographic evidence of disease progression according to Response Evaluation Criteria in Solid Tumor Version 1.1 (RECIST 1.1), one prior VEGF-targeted therapy and Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.

Patients were randomly allocated to one of 3 arms: LENVIMA 18 mg + everolimus 5 mg , LENVIMA 24 mg, or everolimus 10 mg using a 1:1:1 ratio. Patients were stratified by hemoglobin level (≤13 g/dL vs. >13 g/dL for males and ≤11.5 g/dL vs >11.5 g/dL for females) and corrected serum calcium (≥10 mg/dL vs. <10 mg/dL).

Of the 101 patients randomly allocated to the LENVIMA + everolimus arm and everolimus monotherapy arm, 72% were male, the median age was 60 years, 31% were older than 65 years, 96% were White. Metastases were present in 95% of the patients and unresectable advanced disease was present in 5%. All patients had a baseline ECOG PS of either 0 (54%) or 1 (46%) with similar distribution across the 2 treatment arms. Memorial Sloan Kettering Cancer Center (MSKCC) favorable, intermediate, and poor risk was observed respectively in 24%, 37%, and 39% of patients in the LENVIMA + everolimus arm, and 24%, 38%, and 38% of patients in the everolimus arm. The median time from diagnosis to first dose was 32 months in the LENVIMA + everolimus-treatment arm, and 26 months in the everolimus arm. All patients had been treated with 1 prior VEGF inhibitor; 65% with sunitinib, 23% with pazopanib, 4% with tivozanib, 3% with bevacizumab, and 2% each with sorafenib or axatinib.

The primary efficacy outcome measure was investigator-assessed progression-free survival (PFS) evaluated according to RECIST 1.1. Efficacy results from RCC Phase 2 Study 205 are summarized in Table 10 and Figures 2 and 3.

The treatment effect of the combination on PFS was supported by a retrospective independent blinded review of scans.

Table 15: Efficacy Results in Renal Cell Carcinoma

	LENVIMA 18 mg + Everolimus 5 mg (N=51)	Everolimus 10 mg (N=50)
Progression-Free Survival (PFS)[a]		
Number of events, n (%)	26 (51)	37 (74)
Progressive disease	21 (41)	35 (70)
Death	5 (10)	2 (4)
Median PFS in months (95% CI)	14.6 (5.9, 20.1)	5.5 (3.5, 7.1)
Hazard Ratio (95% CI)[b] LENVIMA + Everolimus vs Everolimus	0.40 (0.24, 0.68)	
P Value LENVIMA + Everolimus vs Everolimus	0.0005	-
Overall Survival (OS)		
Number of deaths (%)	19 (37)	26 (52)
Median OS in months (95% CI)	25.5 (20.8, 25.5)	17.5 (11.8, NE)
Hazard Ratio (95% CI)[b] LENVIMA + Everolimus vs Everolimus	0.55 (0.30, 1.01)	-
P Value LENVIMA + Everolimus vs Everolimus	0.0623	-
Objective Response Rate		
Objective Response Rate (%)	22 (43)	3 (6)
Number of complete responses (%)	1 (2)	0
Number of partial responses (%)	21 (41)	3 (6)
Number of stable disease (%)	21 (41)	31 (62)
Number of progressive disease (%)	2 (4)	12 (24)
Duration of response, months, median (95% CI)	13.0 (3.7, NE)	8.5 (7.5, 9.4)

Tumor assessment was based on RECIST 1.1 criteria. Data cutoff date = 13 Jun 2014
Percentages are based on the total number of subjects in the Full Analysis Set within relevant treatment group.
CI = confidence interval, NE = not estimable
a Point estimates are based on Kaplan-Meier method and 95% CIs are based on the Greenwood formula using log-log transformation.
b Stratified hazard ratio is based on a stratified Cox regression model including treatment as a covariate factor and hemoglobin and corrected serum calcium as strata. The Efron method was used for correction for tied events.

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

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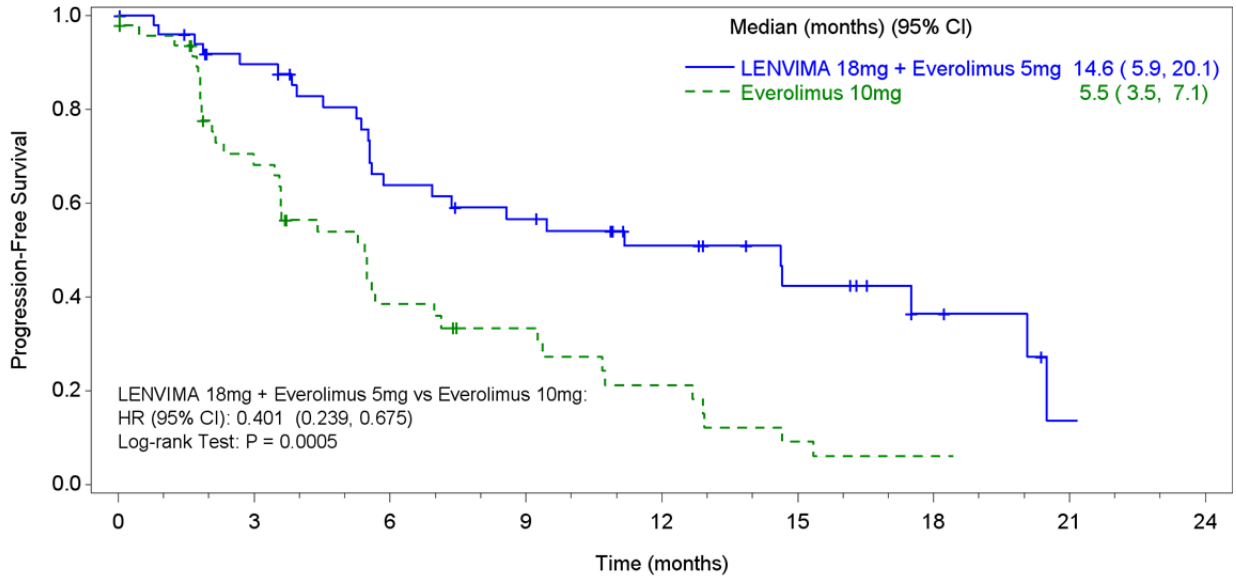
Page 1 of 1

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



Number of Subjects at risk:

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

L(18mg) + E(5mg)=LENVIMA 18mg + Everolimus 5mg; E(10mg)=Everolimus 10mg.
Hazard ratio is based on a stratified Cox regression model including treatment as a factor and hemoglobin and corrected serum calcium as strata.
The Efron method was used for correction for tied events.
Median survival is based on Kaplan-Meier method and 95% confidence interval is based on the Greenwood Formula using log-log transformation.
Data Cutoff Date: 13JUN2014

Figure 3: Kaplan-Meier Plot of Overall Survival (RCC)

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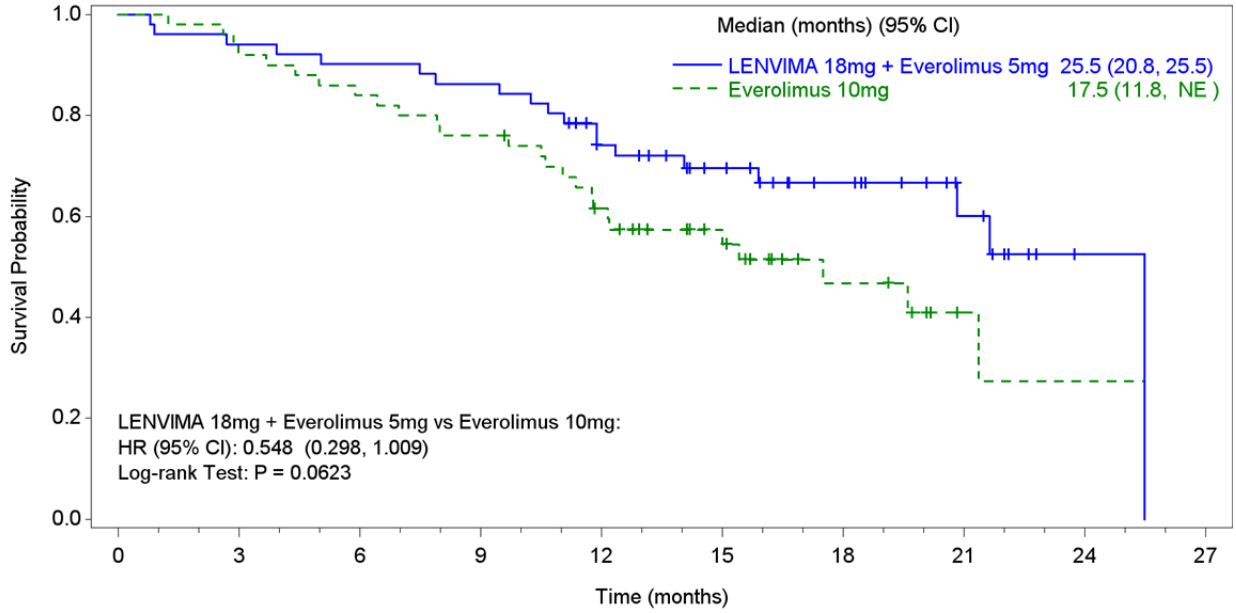
Figure 3: Kaplan-Meier Plot of Overall Survival (RCC)



Number of Subjects at risk:

L(18mg) + E(5mg)	51	48	46	44	34	26	18	9	1	0
E(10mg)	50	46	42	38	29	20	10	3	1	0

L(18mg) + E(5mg)=LENVIMA 18mg + Everolimus 5mg; E(10mg)=Everolimus 10mg.
Hazard ratio is based on a stratified Cox regression model including treatment as a factor and hemoglobin and corrected serum calcium as strata.
The Efron method was used for correction for tied events.
Median survival is based on Kaplan-Meier method and 95% confidence interval is based on the Greenwood Formula using log-log transformation.
Data Cutoff Date: 13JUN2014

Hepatocellular Carcinoma (HCC)

The efficacy of LENVIMA was evaluated in an open-label, multicenter study (Phase 3 REFLECT Study 304), that was conducted in 954 adult patients with previously untreated, unresectable hepatocellular carcinoma. The study enrolled patients Child-Pugh A (score 5 or 6) and Barcelona Clinic Liver Cancer (BCLC) Stage C or B HCC who were not amenable to local liver-directed therapy; had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1. Patients had received no prior systemic therapy for HCC, and had at least one measureable target hepatic/nonhepatic lesion according to modified RECIST (mRECIST), and had adequate liver, bone marrow, blood coagulation, renal, and pancreatic function. Target lesions previously treated with radiotherapy or locoregional therapy had to show radiographic evidence of disease progression. Patients with ≥50% liver occupation, clear invasion into the bile duct or a main branch of the portal vein (Vp4) on imaging were also excluded.

Randomization was stratified by region (Western vs Asia Pacific), presence or absence of macroscopic portal vein invasion (MPVI), or extrahepatic spread (EHS) or both, ECOG PS 0 or 1, and body weight (<60 kg or ≥60 kg).

Patients were randomized to LENVIMA given orally once daily or sorafenib 400 mg (two 200 mg tablets) given orally twice daily, until radiological disease progression or unacceptable toxicity. Patients receiving LENVIMA were assigned to the dose by body weight, 12 mg for baseline body weight ≥60 kg or 8 mg for baseline body weight <60 kg. The median treatment duration was 6 months for LENVIMA and 4 months for sorafenib.

Study demographics and baseline disease characteristics

	LENVIMA Total (n=478)
Median age (years)	62
Gender	
Male	84%
Female	16%
Race:	
Caucasian	29%
Asian	69%
Black or African American:	1.4%
Body weight:	
<60 kg	31%
60-80 kg	50%
>80 kg	19%
ECOG Performance Status (ECOG PS):	
0	63%
1	37%
Child-Pugh A	99%
Child-Pugh B	1%
Etiology:	
Hepatitis B	50%
Hepatitis C	23%
Alcohol	6%
Absence of macroscopic portal vein invasion (MPVI):	79%

Absence of MPVI, extra-hepatic tumour spread (EHS) or both	30%
Underlying cirrhosis (by independent imaging review)	75%
Barcelona Clinic Liver Cancer (BCLC) Stage:	
Stage B	20%
Stage C	80%
Prior treatments:	
Hepatectomy	28%
Radiotherapy	11%
Loco-regional therapies including transarterial (chemo) embolization	52%
Radiofrequency ablation	21%
Percutaneous ethanol injection	4%

REFLECT was designed to demonstrate the non-inferiority of LENVIMA to sorafenib for the primary endpoint of Overall Survival (OS), and surrogate outcome measures progression-free survival (PFS) and overall response rate (ORR) using mRECIST. Blinded independent imaging review of surrogate endpoints was also conducted to corroborate the efficacy results.

Efficacy results from the HCC Phase 3 Study 304 are summarized in Table 16 and Figure 4.

For the primary efficacy endpoint, LENVIMA was non-inferior for overall survival (OS) to sorafenib with HR = 0.92 (95% CI of (0.79, 1.06) and a median OS of 13.6 months vs 12.3 months. Treatment with LENVIMA resulted in statistically significant (P<0.00001) and clinically meaningful improvement over sorafenib in the secondary endpoints of ORR.

Table 16: Efficacy Results in Hepatocellular Carcinoma pivotal HCC Phase 3 REFLECT Study 304

	LENVIMA (N= 478)	**Sorafenib (N=476)**
Overall Survival (OS)		
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)	
Per Independent Radiological Review (mRECIST)		
Progression-Free Survival (PFS)		
Median PFS in months (95% CI) [a]	7.3 (5.6, 7.5)	3.6 (3.6, 3.7)
Hazard Ratio (95% CI) [b,c]	0.64 (0.55, 0.75)	
P-value [c,d]	<0.00001	
Objective response rate (ORR) [eg]		
%	40.6%	12.4%
95% CI	(36.2%, 45.0%)	(9.4%, 15.4%)
Complete Response; n (%)	10 (2.1)	4 (0.8)
Partial Response, n (%)	184 (38.5)	55 (11.6)
P-value	<0.001	
Per Independent Radiological Review (RECIST 1.1)		
Progression-Free Survival (PFS)		
Median PFS in months (95% CI) [a]	7.3 (5.6, 7.5)	3.6 (3.6, 3.9)
Hazard Ratio (95% CI) [b,c]	0.65 (0.56, 0.77)	
Objective response rate (ORR) [fg]		
%	18.8	6.5
95% CI	(15%, 22%)	(4%, 9%)
Complete Response; n (%)	2 (0.4)	2 (0.4)
Partial Response, n (%)	88 (18.4)	30 (6.3)

Table 16: Efficacy Results in Hepatocellular Carcinoma pivotal HCC Phase 3 REFLECT Study 304

	LENVIMA (N= 478)	Sorafenib (N=476)

Data cutoff date: 13 Nov 2016.

The noninferiority margin for the HR of lenvatinib 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;

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 lenvatinib 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).

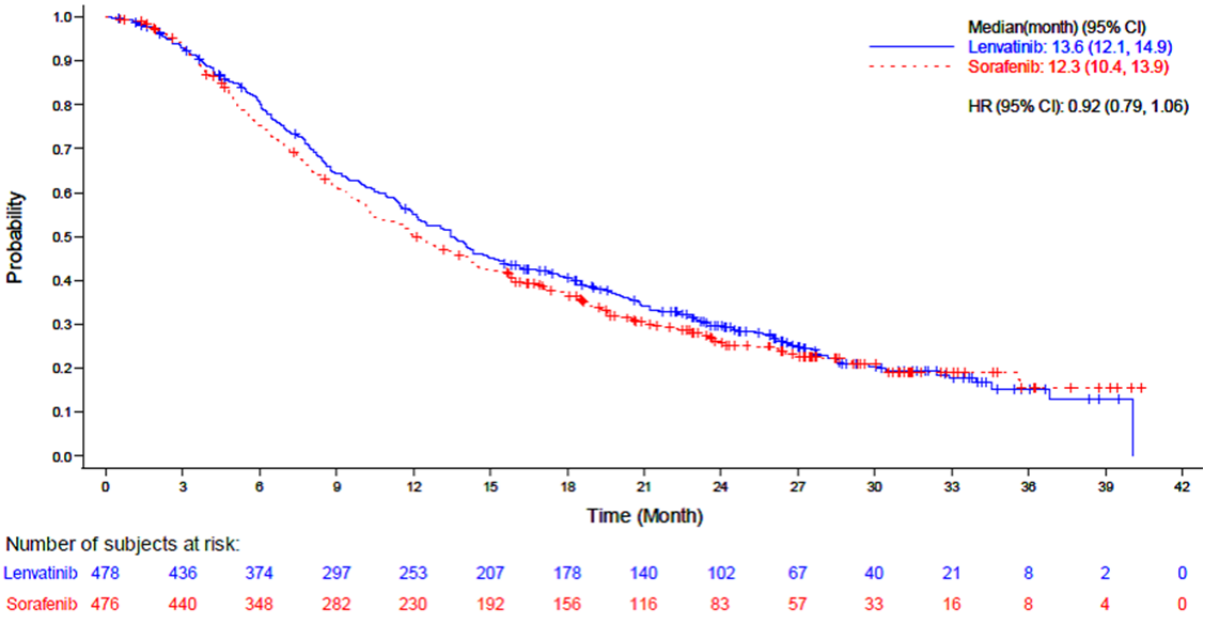
d P-value is for the superiority test of lenvatinib versus sorafenib.

e Per retrospective independent radiological review. The median duration of objective response was 7.3 (95% CI 5.6, 7.4) months in the LENVIMA arm and 6.2 (95% CI 3.7, 11.2) months in the sorafenib arm.

f Per retrospective independent radiological review. The median duration of objective response was 7.4 (95% CI 5.6, 9.2) months in the LENVIMA arm and 15.8 (95% CI 5.9, NE) months in the sorafenib arm.

g Results are based on confirmed and unconfirmed responses.

Figure 4: Kaplan-Meier Curve and Analysis of Overall Survival in HCC – Full Analysis Set



Footnotes for Figure 7:
Data cutoff date = 13 Nov 2016.
Noninferiority margin for hazard ratio (HR: lenvatinib 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

In subgroup analyses by stratification factors (presence or absence of MPVI or EHS or both, ECOG PS 0 or 1, BW <60 kg or ≥60 kg and region) the HR consistently favoured LENVIMA over sorafenib, with the exception of Western region [HR of 1.08 (95% CI 0.82, 1.42)], patients without EHS [HR of 1.01 (95% CI 0.78, 1.30)] and patients without MPVI, EHS or both [HR of 1.05 (0.79, 1.40)]. The results of subgroup analyses should be interpreted with caution.

The median duration of treatment was 5.7 months (Q1: 2.9, Q3: 11.1) in the LENVIMA arm and 3.7 months (Q1: 1.8, Q3: 7.4) in the sorafenib arm.

In both treatment arms in the REFLECT study, median OS was approximately 9 months longer in subjects who received post-treatment anticancer therapy than in those who did not. In the LENVIMA arm, median OS was 19.5 months (95% CI: 15.7, 23.0) for subjects who received post-treatment anticancer therapy (43%) and 10.5 months (95% CI: 8.6, 12.2) for those who did not. In the sorafenib arm, median OS was 17.0 months (95% CI: 14.2, 18.8) for subjects who received posttreatment anticancer therapy (51%) and 7.9 months (95% CI: 6.6, 9.7) for those who did not. Median OS was longer by approximately 2.5 months in the LENVIMA arm compared with the sorafenib arm in both subsets of subjects (with or without post-treatment anticancer therapy).

DETAILED PHARMACOLOGY

Primary Pharmacodynamics

VEGF has been identified as a crucial regulator of both physiologic and pathologic angiogenesis, with increased expression being associated with a poor prognosis in many human tumor types. Elevated levels of VEGF have been found in thyroid tumors, and the intensity of VEGF expression in papillary thyroid cancer (PTC) has been correlated with a higher risk of metastasis and shorter disease-free survival.

Kinase inhibition profiling studies targeting 66 protein kinases demonstrated that lenvatinib selectively inhibited tyrosine kinase activities of VEGF receptors (VEGFR1 – 3) and RET with inhibition constant (K_i) values of approximately 1 nmol/L. Lenvatinib also inhibited other proangiogenic and oncogenic pathway-related RTKs including FGFR1 – 4, PDGFRα, and KIT, with half-maximal inhibitory concentration (IC_{50}) values below 100 nmol/L. The equilibrium dissociation constant (K_d) of lenvatinib against VEGFR2 was 2.1 nmol/L. X-ray analysis for the crystal structure of VEGFR2-lenvatinib complex and the FGFR1-lenvatinib complex demonstrated that lenvatinib binds to the adenosine triphosphate (ATP)-binding site and the neighboring allosteric region in the kinase domain adopting an "aspartic acid-phenylalanine-glycine (DFG)-in" conformation.

In cell-based assays, lenvatinib inhibited VEGF-driven VEGFR2 phosphorylation, proliferation, and tube formation in human umbilical vein endothelial cell (HUVEC) models with half-maximal inhibitory concentration (IC_{50}) values of 0.25, 3.4 and 2.1 nmol/L, respectively.

Lenvatinib also inhibited the FGF-driven tube formation of HUVECs with an IC_{50} value of 7.3 nmol/L, indicating that lenvatinib inhibits both VEGF- and FGF-driven angiogenesis in vitro. Analysis of the phosphorylation status of signal transduction molecules in HUVECs revealed that lenvatinib inhibited both the mitogen activated kinase (MAPK) pathway and the PI3K-AKT-mTOR-S6K-S6 signal transduction pathway (hereafter referred as mTOR-S6K-S6 pathway) triggered by activated VEGFR and FGFR, both of which are important for stimulating angiogenesis in tumors.

In a mouse model in which angiogenesis was generated in the skin by VEGF or FGF secreted from the KP-1 tumor cells in a Millipore chamber embedded in a dorsal air sac, lenvatinib significantly inhibited both VEGF- and FGF-induced in vivo angiogenesis compared with each respective control group. Plasma FGF23, a protein hormone regulating mineral metabolism recognized as a pharmacodynamic marker for FGFR inhibition in vivo, was significantly elevated in mice 24 hours after a single oral administration of lenvatinib, demonstrating that this regimen is able to inhibit the FGFR signaling pathway in mice. These results demonstrated that lenvatinib could inhibit angiogenesis driven by either VEGF or FGF in both in vitro and in vivo models.

Lenvatinib showed antiproliferative activity against human HCC cell lines Hep 3B2.1-7 and HuH-7 with continuously activated FGFR signaling due to an autocrine loop of overexpressed FGF19 and FGFR4 with IC_{50} values of 230 and 420 nmol/L (86 and 160 nmol/L as the [protein-

free] form), respectively, accompanied by the inhibition of FGFR signaling in these cells. Lenvatinib showed weak antiproliferative activity against human HCC cell line PLC/PRF/5, where enhanced FGFR signaling is not reported, with an IC_{50} value exceeding 10,000 nmol/L. In contrast, lenvatinib exhibited weak, direct antiproliferative activity in vitro against human cancer cell line H460 (NSCLC) and Colo205 (colorectal cancer), A-498 (RCC), and 9 of 11 human thyroid cancer cell lines with IC_{50} values above 10 µmol/L. In contrast, the direct antitumor activity of lenvatinib was greater in cancer cell lines naturally expressing the RET-fusion protein CCDC6-RET or where RET is constitutively activated.

Antitumor activity of lenvatinib, in vivo, was evaluated in various human tumor xenograft models in athymic mice, including 4 human HCC xenograft models, 2 of which were patient-derived xenografts (PDXs) in athymic mice. Orally administered lenvatinib showed significant tumor growth inhibition (TGI) with good tolerability at all models tested, including the Hep 3B2.1-7 and PDX-derived LIXC-012 HCC xenograft models with continuously activated FGFR signaling due to an autocrine loop of overexpressed FGF19 and FGFR4. In the LIXC-012 xenograft model, lenvatinib, showed less body weight loss (BWL) compared to vehicle control at dose levels of 10 and 30 mg/kg, indicating that the TGI alleviated cachexia-induced BWL in the lenvatinib-treated mice.

Lenvatinib showed greater TGI against BNL 1ME A.7R.1 murine HCC isografts in immunocompetent mice than that in athymic mice. Flow cytometric analysis revealed that orally administered lenvatinib (10 mg/kg) decreased the population of tumor associated macrophages (TAM) in the tumor, and increased activated cytotoxic T cells in the draining lymph node of the treated mice suggesting that an immunostimulatory effect of lenvatinib may also contribute to its antitumor activity in immunocompetent mice.

Orally administered lenvatinib significantly inhibited tumor growth of K1 (papillary thyroid carcinoma), R082-W-1 (follicular thyroid carcinoma), 8305C (anaplastic thyroid carcinoma), SW579 (squamous thyroid carcinoma), TT (medullary thyroid carcinoma), PLC/PRF/5 (hepatocellular carcinoma [HCC]), Colo205 (colorectal cancer), MKN-74 (gastric cancer), H460 and A549 (NSCLC), A375 (melanoma), SEKI (melanoma), IM95m (gastric cancer), A2780 (ovarian carcinoma), A-498 RCC, and Caki-1 RCC human tumor xenografts at doses between 1 and 100 mg/kg (as lenvatinib mesylate). In addition, orally administered lenvatinib significantly inhibited growth of recombinant KP-1 cells expressing human VEGF (KP-1/VEGF) and recombinant KP-1 cells expressing murine FGF (KP-1/FGF) xenografts in athymic mouse models where secretion of excess VEGF or FGF from the respective recombinant KP-1/VEGF or KP-1/FGF cells was expected to enhance VEGF- or FGF-induced tumor angiogenesis. The body weight loss in mice was not severe in most models.

In the 8305C model, the decrease in endothelial vessels was well correlated to tumor growth inhibition, suggesting that lenvatinib exerted an antitumor effect through its antiangiogenesis activity. In the TT model, marked inhibition of receptor tyrosine kinase oncogene (RET) autophosphorylation in the xenograft was observed at all doses at which lenvatinib exhibited antitumor activity. Since the growth of TT cells is strongly driven by a constitutive active mutant of RET (C634W), this RET inhibition is postulated to contribute to the antitumor effect of lenvatinib in this model.

Secondary Pharmacodynamics

To evaluate the potential secondary pharmacodynamic effects of lenvatinib, binding to a panel of 50 nonkinase receptors (ExpresSProfile) known to play significant biological roles was determined at lenvatinib concentrations of 1 and 10 μmol/L. No significant binding (>50% inhibition) of lenvatinib to any receptor of the ExpresSProfile was observed at the observed concentrations, except for the 5-hydroxytryptamine receptor 1B (58%) and human norepinephrine transporter (50%) at 10 μmol/L.

Safety Pharmacology

The effects of lenvatinib on the cardiovascular, respiratory, and central nervous system (CNS) were evaluated in rats and dogs. The effect of lenvatinib on hERG tail currents recorded from stably transfected HEK293 cells (4 cells/treatment) was evaluated using the whole-cell patch-clamp method. Lenvatinib inhibited hERG tail current in a concentration-dependent manner, with an IC_{50} value of 11.89 μmol/L (based on target concentrations).

Effects on action potential parameters were evaluated in isolated guinea pig papillary muscle (6/treatment) using the glass microelectrode method. No effects on action potential parameters were observed at lenvatinib target concentrations of 1 and 10 μmol/L.

Lenvatinib mesylate was administered orally by gavage, as a single dose to male and female dogs (3/sex/treatment) at doses of 6 and 30 mg/kg to evaluate the effects on the cardiovascular system. Heart rate, mean blood pressure, and electrocardiogram (ECG [PR interval, QRS duration, and QT interval]) were measured predose, and at 1, 2, 4, and 8 hours after oral administration of lenvatinib using telemetry. Lenvatinib at 6 and 30 mg/kg had no significant effect on heart rate, mean blood pressure, or ECG parameters.

Drug metabolizing enzyme and transporter inhibition

In vitro, lenvatinib exhibited an inhibitory effect on CYP2C8 (half-maximal inhibitory concentration [IC_{50}]: 10.1 μmol/L), weak inhibitory effects on CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A, and virtually no inhibitory effects on CYP2A6 and CYP2E1 in human liver microsomes. Time dependent inhibition of the formation of 1′-hydroxymidazolam from midazolam (CYP3A) by lenvatinib was observed.

In human liver microsomes, lenvatinib directly inhibited 5′-diphospho-glucuronosyl-transferase (UGT) 1A1 and UGT1A4 but showed little or no evidence of inhibition on UGT1A6, UGT1A9, and UGT2B7. Treatment of cultured human hepatocytes with up to 3 μmol/L lenvatinib did not induce UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 enzyme activities or their mRNA expressions.

Lenvatinib showed minimal or no inhibitory activities toward P-gp-mediated and BCRP-mediated transport activities.

Lenvatinib showed inhibitory effects on organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT) 1, OCT2, organic anion transporting polypeptide (OATP) 1B1, and the 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 (AO) activity (IC_{50} >100 μmol/L).

Drug metabolizing enzyme and transporter induction

Treatment of cultured human hepatocytes with up to 3 μmol/L of lenvatinib slightly increased CYP3A enzyme activity (≤1.54-fold) and CYP3A4 mRNA expression (≤1.65-fold). No effects on CYP1A1, CYP1A2, CYP2B6, and CYP2C9 enzyme activities or mRNA expression were observed.

In vitro, lenvatinib did not induce UGT1A1, UGT1A4, UGT1A6, UGT1A9, or UGT2B7 enzyme activities or mRNA expressions.

Treatment of cultured human hepatocytes with up to 3 μmol/L of lenvatinib showed no induction potency on P-gp mRNA expression.

TOXICOLOGY

Carcinogenicity studies have not been conducted with lenvatinib. Lenvatinib was not mutagenic in the in vitro Ames and mouse lymphoma tests, and was not clastogenic in an in vivo micronucleus assay in rats.

In the repeated-dose toxicity studies (up to 39 weeks), lenvatinib caused toxicologic changes in various organs and tissues related to the expected pharmacologic effects of lenvatinib as a VEGF receptor tyrosine kinase inhibitor and via the inhibition of angiogenesis including testicular hypocellularity, ovarian follicular atresia, and arterial (arterial fibrinoid necrosis, medial degeneration, or hemorrhage) lesions in rats, dogs, and cynomolgus monkeys. Reversibility of the toxicologic changes was observed at the end of a 4-week recovery period in all animal species investigated. In repeat-dose studies in adult monkeys, lenvatinib (>0.5mg/kg/day) led to bone effects at AUC levels about 0.6 times those observed in humans following the recommended human dose.

The target organs in juvenile rats administered lenvatinib at doses up to 10 mg/kg were the same as in adult rats although mortality in the juvenile rats at 10 mg/kg was observed earlier compared to adult rats administered the same dose level. Growth retardation and secondary delay of physical development was also observed in juvenile rats. The results of animal studies suggest the potential for lenvatinib to effect growth plates in children. Hence, lenvatinib should not be used in children younger than 2 years (see INDICATION AND CLINICAL USE, Pediatrics).

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 below the anticipated clinical exposure (based on AUC) at the maximum recommended human dose. Thus lenvatinib may result in decreased male and female fertility (see WARNINGS AND PRECAUTIONS, Sexual Function/Reproduction, Fertility).

Administration of lenvatinib during organogenesis resulted in embryolethality and teratogenicity in both rats and rabbits at exposures below the clinical exposure (based on AUC) at the maximum recommended human dose. Fetal external and skeletal anomalies were observed at doses of 0.1 mg/kg and greater in rats, and a fetal NOAEL was not identified in rats. Fetal external, visceral, or skeletal anomalies were noted at 0.1 and 0.5 mg/kg in rabbits. The fetal NOAEL in the rabbit study was 0.03 mg/kg. These findings indicate that lenvatinib has a teratogenic potential, likely related to the pharmacologic activity of lenvatinib as an antiangiogenic agent, thus pregnant women must be advised of potential risk of fetal harm (see WARNINGS AND PRECAUTIONS; Special Populations, Pregnant Women).

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

[Pr]LENVIMA®
Lenvatinib capsules

Read this carefully before you start taking LENVIMA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about LENVIMA.

Serious Warnings and Precautions

This drug should be prescribed and managed only by a doctor experienced in anticancer drugs.

Serious side-effects can include:

- High blood pressure, and its complications, including separation of the layers of the aortic wall
- Heart failure
- Blood clots
- Gastrointestinal perforation (tears in the stomach or intestinal wall) or fistula (abnormal connection between two or more body parts)
- Liver injury
- Kidney injury
- Bleeding
- A condition called Posterior Reversible Encephalopathy Syndrome

What is LENVIMA used for?

- LENVIMA is used alone to treat a type of thyroid cancer that can no longer be treated with radio-active iodine.
- LENVIMA is used with another medicine, everolimus, to treat a type of kidney cancer.
- LENVIMA is used alone to treat a type of liver cancer that cannot be removed with surgery.

How does LENVIMA work?

LENVIMA targets a group of proteins known to be involved in the growth and spread of certain types of cancer. These proteins start the process of creating new blood vessels that allow certain types of tumours to grow. LENVIMA works by blocking the creation of these proteins in tumour cells, which slows down the growth of new blood vessels in these tumours. This cuts off the supply of nutrients and oxygen to the tumour, which slows or prevents its growth. LENVIMA also acts directly on cancer cells in other ways to kill them or slow down their rate of growth.

What are the ingredients in LENVIMA?

Medicinal ingredients: lenvatinib mesylate
Non-medicinal ingredients: black iron oxide, calcium carbonate, ferric oxide red, ferric oxide

yellow, hydroxypropylcellulose, low-substituted hydroxypropylcellulose, mannitol, microcrystalline cellulose, potassium hydroxide, propylene glycol, shellac, talc, and titanium dioxide.

LENVIMA comes in the following dosage forms:
Capsules containing lenvatinib mesylate equivalent to 4 mg and 10 mg of lenvatinib.

Do not use LENVIMA if:
- you are allergic to:
  - lenvatinib,
  - or any of the other ingredients in it.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LENVIMA. Talk about any health conditions or problems you may have, including if you:
- have high blood pressure
- have heart problems
- abnormal heart rhythm (also known as **QT-prolongation**)
- a family history of abnormal heart rate
- have headaches, seizures, or vision problems (symptoms of a condition called **Posterior Reversible Encephalopathy Syndrome**)
- have or have had kidney problems
- have or have had liver problems
- have any bleeding problems
- have a history of blood clots in your arteries, including stroke, heart attack, or change in vision
- have diarrhea
- have a **gastrointestinal perforation.**
- have a **fistula.**
- recently had a surgery
- are pregnant or plan to become pregnant. It is not known if LENVIMA will harm your unborn baby. Avoid becoming pregnant while taking LENVIMA and for at least one month after your last dose.
  - You should use effective methods of birth control while taking LENVIMA. Continue to use birth control for at least one month after taking your last dose.
  - Oral contraceptives may not work as well if taken with LENVIMA. If you are taking an oral contraceptive, you should also use a barrier method such as a condom.
  - Talk with your healthcare provider about birth control methods to prevent pregnancy while you are taking LENVIMA.
  - Tell your healthcare provider right away if you become pregnant or think you are pregnant while taking LENVIMA.
- are breastfeeding or plan to breastfeed. It is not known if LENVIMA passes into your breast milk. You and your healthcare provider should decide if you will take LENVIMA or breastfeed. You should not do both.
- plan to father a child. Men must not get a woman pregnant while taking LENVIMA. Use a

barrier method (such as a condom) together with a spermicide.

Fertility: For both men and women, LENVIMA may decrease your ability to have a child. Talk to your doctor about this if you want to have a child.

Other warnings you should know about:
Your blood pressure should be well controlled before you start taking LENVIMA. Your doctor or nurse should check your blood pressure regularly when you take LENVIMA. If blood pressure becomes a problem, your doctor may prescribe medicine to treat your high blood pressure. Your doctor may also lower your dose of LENVIMA, or stop your treatment with LENVIMA.

LENVIMA should be stopped before major surgery. This is to be sure the wound can heal.

Problem with blood clots in your arteries. Get emergency help and call your healthcare provider if you get any of the following symptoms:
- chest pain or pressure;
- pain in your arms, back, neck or jaw;
- shortness of breath;
- numbness or weakness on one side of your body;
- trouble talking;
- sudden severe headache; or
- sudden vision changes.

Kidney failure has happened with LENVIMA treatment. Drink fluids during treatment with LENVIMA to help prevent too much fluid loss (dehydration). Call your healthcare provider if you have diarrhea or vomiting.

Changes in the electrical activity of your heart can happen with LENVIMA treatment. This is called **QT prolongation**. These can cause changes in your heartbeat that can be life threatening. Your doctor will decide if you need heart monitoring or blood tests during your treatment with LENVIMA.

The following patients may be less able to tolerate LENVIMA:
- Patients 75 years old, or older
- Patients of Asian race
- Patients with existing high blood pressure, liver or kidney disease
- Patients who weigh less than 60 kg
- Patients who are female

You should not take LENVIMA if you had other anticancer treatments within 4 weeks.

Blood and urine tests:

Your healthcare professional will check your urine regularly while you are taking LENVIMA.

This is to determine how your kidneys are working and whether you have protein in your urine.

Blood tests will be done before you start taking LENVIMA. These will be repeated every two weeks for the first two months and then again at least once a month while you are taking this medicine. This will help your healthcare professional to know if any changes happen to your blood after taking LENVIMA. These blood tests will also check how your liver is working and whether you have too little calcium in your blood (hypocalcemia).

You may have changes in your thyroid hormone levels when taking LENVIMA. Your thyroid medicine dose may need to be changed. Your doctor should check your thyroid hormone level every month during treatment with LENVIMA.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with LENVIMA:

- drugs known to cause heart rhythm changes
- antipsychotic drugs
- antidepressants
- drugs to relieve pain
- antibiotics
- pentamidine
- drugs used to treat malaria
- azole antifungals (e.g., ketoconazole, fluconazole, voriconazole)
- specific drugs for nausea
- drugs to treat cancer
- drugs for asthma and chronic obstructive pulmonary disease
- oral contraceptives. Birth control pills may not work as well if taken with LENVIMA
- thyroid medicine

How to take LENVIMA:

Take LENVIMA:

- exactly as prescribed by your healthcare provider.
- once a day
- at the same time each day
- with or without food.
- continue to take your dose every day unless your doctor tells you to stop or change your dose.

Swallow LENVIMA capsules whole with water. Do NOT open, chew, crush, or split LENVIMA capsules.

If LENVIMA capsule(s) cannot be swallowed whole:

- Use a small cup to measure about 1 tablespoon of water or apple juice.
- Add LENVIMA capsules into the cup of water or apple juice. Be careful not to break or crush the capsules.

- Let the capsules sit in the liquid for about 10 minutes, then stir the contents for another 3 minutes.
- Swallow the mixture.
- After swallowing, rinse the cup with a little more water or apple juice. Swirl the contents around the cup and then swallow the liquid.

Dosing Instructions:
Your doctor will decide the best daily dose for you.

If your daily dose of LENVIMA is:
4 mg: It takes one capsule to make up the dose
8 mg: It takes two capsules to make up the dose
10 mg: It takes one capsule to make up the dose
12 mg: It takes three capsules to make up the dose
14 mg: It takes two capsules to make up the dose
18 mg: It takes three capsules to make up the dose
20 mg: It takes two capsules to make up the dose
24 mg: It takes three capsules to make up the dose

All daily doses of LENVIMA are packaged on cards. This will help you to take the right dose each day. Each card holds 5 doses. Take one dose a day. Each carton contains 6 cards. There are 30 daily doses in a carton. Record the start date on the line above the first dose from each card.

Your doctor may decide to:
- change your dose during treatment,
- change how often you take your dose,
- stop treatment for some time, (then resume at the same or a lower dose), or
- completely stop treatment.

Once your dose is reduced, you should never go back to a higher dose.

Overdose:

If you think you have taken too much LENVIMA, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of LENVIMA, take it as soon as you remember. However, if your next dose is due within 12 hours, then skip the missed dose and take the next dose at your regular time.

What are possible side effects from using LENVIMA?

These are not all the possible side effects you may feel when taking LENVIMA. If you experience any side effects not listed here, contact your healthcare professional. Please also see the **Serious Warnings and Precautions** box.

The most common side effects of LENVIMA include:

- decreased appetite and weight
- nausea, vomiting, diarrhea, abdominal pain
- tiredness, headache
- mouth sores, hoarseness
- trouble breathing, cough
- protein in your urine
- rash, redness, itching, or peeling of your skin on your hands and feet
- muscle and joint pain
- swelling in hands or feet

LENVIMA can cause abnormal test results. Your doctor will decide when to perform tests. Your doctor will decide if you need heart monitoring (electrocardiogram or ECG), blood or urine tests. The doctor will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON **High blood pressure (hypertension):** Headaches, vision disorders, nausea, and vomiting			X
Bleeding: Black, tarry, or bloody stools, or coughing up of blood			X
COMMON **Liver problems:** Yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, bleeding or bruising more easily than normal, itchiness, or feeling very tired.			X
Hypothyroidism (low level of thyroid hormone in the blood): changes in heart rate, appetite or weight; tiredness; feeling cold; swelling at front of the neck		X	
Hypocalcemia (low level of calcium in the blood): muscle aches, cramps or stiffness; tingling in lips, fingers and feet; fast heartrate			X
Blood clots: Chest pain or pressure; pain in your arms, back, neck or jaw; shortness of breath; numbness or weakness on one side of your body; trouble talking; sudden severe headache; or sudden vision changes			X

Wound complications (a wound that does not heal)		X	
Perforation (tear in your stomach or intestinal wall) or fistula (an abnormal connection between two or more body parts): Severe abdominal pain, chills, fever, nausea, vomiting, or a leak of air from your lung into the chest causing sudden chest pain and/or difficulty breathing.			X
Ascites (an abnormal build-up of fluid in the abdomen): sudden weight gain, swollen belly, belly pain, nausea, vomiting, heartburn.			X
Kidney problems: Nausea, vomiting, swelling (hands, feet, or around your eyes), foamy urine and fatigue.			X
QT prolongation (an abnormal heart signal): Fainting, seizures or fits. Sudden death.			X
Infections (including pneumonia and sepsis): fever, chills, shivering, fast heartrate, rapid breathing.			X
RARE **Heart failure (heart does not pump as well as it should):** Shortness of breath; swelling of ankles and feet.			X
Posterior Reversible Encephalopathy Syndrome (PRES): Headache, seizures, weakness, confusion, high blood pressure, blindness or change in vision, or problems thinking.			X
VERY RARE **Aortic Dissection (separation of the layers of the aortic wall):** Sudden severe pain in the back, chest or abdomen.			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store LENVIMA at 15°C to 30°C.

Do not use LENVIMA that is out of date or no longer needed. Ask your healthcare provider or pharmacist how to safely throw away LENVIMA capsules.

Keep out of reach and sight of children.

If you want more information about LENVIMA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.eisai.ca, or by calling 1-877-873-4724.

This leaflet was prepared by Eisai Limited, Mississauga, ON L5N 7K2

Last Revised December 19, 2018

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