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

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

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

LENVIMA is a kinase inhibitor indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (1).

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

- Recommended dose: 24 mg orally, once daily (2.1).
- In patients with severe renal or hepatic impairment, the dose is 14 mg once daily (2.1).

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

- Capsules: 4 mg and 10 mg (3).

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

None (4).

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

- Hypertension: Control blood pressure prior to treatment with LENVIMA. Withhold LENVIMA for Grade 3 hypertension despite optimal hypertensive therapy. Discontinue for life-threatening hypertension (5.1).
- Cardiac Failure: Monitor for clinical symptoms or signs of cardiac decompensation. Withhold LENVIMA for Grade 3 cardiac dysfunction. Discontinue for Grade 4 cardiac dysfunction (5.2).
- Arterial Thromboembolic Events: Discontinue LENVIMA following an arterial thromboembolic event (5.3).
- Hepatotoxicity: Monitor liver function tests before initiation of LENVIMA and periodically throughout treatment. Withhold LENVIMA for Grade 3 or greater liver impairment. Discontinue for hepatic failure (5.4).
- Proteinuria: Monitor for proteinuria before initiation of, and periodically throughout, treatment with LENVIMA. Withhold LENVIMA for ≥2 grams of proteinuria for 24 hours. Discontinue for nephrotic syndrome (5.5).
- Renal Failure and Impairment: Withhold LENVIMA for Grade 3 or 4 renal failure/impairment (5.6).
- Gastrointestinal Perforation and Fistula Formation: Discontinue LENVIMA in patients who develop gastrointestinal perforation or life-threatening fistula (5.7).
- QT Interval Prolongation: Monitor and correct electrolyte abnormalities in all patients. Withhold LENVIMA for the development of Grade 3 or greater QT interval prolongation (5.8).
- Hypocalcemia: Monitor blood calcium levels at least monthly and replace calcium as necessary (5.9).
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Withhold LENVIMA for RPLS until fully resolved (5.10).
- Hemorrhagic Events: Withhold LENVIMA for Grade 3 hemorrhage. Discontinue for Grade 4 hemorrhage (5.11).
- Impairment of Thyroid Stimulating Hormone Suppression: Monitor TSH levels monthly and adjust thyroid replacement medication as needed in patients with DTC (5.12).
- Embryofetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception (5.13, 8.1, 8.3).

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

The most common adverse reactions (incidence greater than or equal to 30%) for LENVIMA are hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, and dysphonia (6).

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

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

- Lactation: Discontinue breastfeeding (8.2).

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

Revised: 02/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended daily dose of LENVIMA is 24 mg (two 10 mg capsules and one 4 mg capsule) orally taken once daily with or without food [*see Clinical Pharmacology (12.3)*]. Continue LENVIMA until disease progression or until unacceptable toxicity occurs.

Take LENVIMA at the same time each day. If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration.

Severe Renal or Hepatic Impairment

The recommended dose of LENVIMA is 14 mg taken orally once daily in patients with severe renal impairment (creatinine clearance [CLcr] less than 30 mL/min calculated by the Cockroft-Gault equation) or severe hepatic impairment (Child-Pugh C) [*see Warning and Precaution (5.4, 5.6), Use in Specific Populations (8.6, 8.7)*].

2.2 Dose Modifications

Hypertension

- Assess blood pressure prior to and periodically during treatment. Initiate or adjust medical management to control blood pressure prior to and during treatment.
- Withhold LENVIMA for Grade 3 hypertension that persists despite optimal antihypertensive therapy; resume at a reduced dose (*see Table 1*) when hypertension is controlled at less than or equal to Grade 2.
- Discontinue LENVIMA for life-threatening hypertension.

Cardiac dysfunction or hemorrhage

- Discontinue for a Grade 4 event.
- Withhold LENVIMA for development of Grade 3 event until improved to Grade 0 or 1 or baseline.
- Either resume at a reduced dose (*see Table 1*) or discontinue LENVIMA depending on the severity and persistence of the adverse event.

Arterial thrombotic event

- Discontinue LENVIMA following an arterial thrombotic event.

Renal failure and impairment or hepatotoxicity

- Withhold LENVIMA for development of Grade 3 or 4 renal failure/impairment or hepatotoxicity until resolved to Grade 0 to 1 or baseline.

- Either resume at a reduced dose (*see Table 1*) or discontinue LENVIMA depending on the severity and persistence of renal impairment or hepatotoxicity.
- Discontinue LENVIMA for hepatic failure.

Proteinuria
- Withhold LENVIMA for ≥2 grams of proteinuria/24 hours.
- Resume at a reduced dose (*see Table 1*) when proteinuria is <2 gm/24 hours.
- Discontinue LENVIMA for nephrotic syndrome.

Gastrointestinal perforation or fistula formation
- Discontinue LENVIMA in patients who develop gastrointestinal perforation or life-threatening fistula.

QT prolongation
- Withhold LENVIMA for the development of Grade 3 or greater QT interval prolongation.
- Resume LENVIMA at a reduced dose (*see Table 1*) when QT prolongation resolves to Grade 0 or 1 or baseline.

Reversible posterior leukoencephalopathy syndrome (RPLS)
- Withhold for RPLS until fully resolved.
- Upon resolution, resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of neurologic symptoms.

Manage other adverse reactions according to the instructions in Table 1. 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 1 Recommended Dose Modifications for Persistent and Intolerable Grade 2 or Grade 3 Adverse Reactions or Grade 4 Laboratory Abnormalities[a]

Adverse Reaction	Modification	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

[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 mg, 20 mg, or 14 mg per day)

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

3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension

In Study 1 hypertension was reported in 73% of LENVIMA-treated patients and 16% of patients in the placebo group [*see Adverse Reactions (6.1)*]. The median time to onset of new or worsening hypertension 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.

Control blood pressure prior to treatment with LENVIMA. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment with LENVIMA. Withhold LENVIMA for Grade 3 hypertension 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 Dosage and Administration (2.2)*].

5.2 Cardiac Dysfunction

In Study 1, cardiac dysfunction, defined as decreased left or right ventricular function, cardiac failure, or pulmonary edema, was reported in 7% of LENVIMA-treated patients (2% Grade 3 or greater) and 2% (no Grade 3 or greater) of patients in the placebo group. The majority of these cases in LENVIMA-treated patients (14 of 17 cases) were based on findings of decreased ejection fraction as assessed by echocardiography. Six of 261 (2%) LENVIMA-treated patients in Study 1 had greater than 20% reduction in ejection fraction as measured by echocardiography compared to no patients who received placebo.

Monitor patients 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 Dosage and Administration (2.2)*].

5.3 Arterial Thromboembolic Events

In Study 1, arterial thromboembolic events were reported in 5% of LENVIMA-treated patients and 2% of patients in the placebo group. The incidence of arterial thromboembolic

events of Grade 3 or greater was 3% in LENVIMA-treated patients and 1% in the placebo group.

Discontinue LENVIMA following an arterial thrombotic event. The safety of resuming LENVIMA after an arterial thromboembolic event has not been established and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months [*see Dosage and Administration (2.2)*].

5.4 Hepatotoxicity

In Study 1, 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. Across clinical studies in which 1108 patients received LENVIMA, hepatic failure (including fatal events) was reported in 3 patients and acute hepatitis was reported in 1 patient.

Monitor liver function before initiation of LENVIMA, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Withhold LENVIMA for the development of Grade 3 or greater liver 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 hepatotoxicity. Discontinue LENVIMA for hepatic failure [*see Dosage and Administration (2.2)*].

5.5 Proteinuria

In Study 1, proteinuria was reported in 34% of LENVIMA-treated patients and 3% of patients in the placebo group [*see Adverse Reactions (6.1)*]. The incidence of Grade 3 proteinuria in LENVIMA-treated patients was 11% compared to none in the placebo group.

Monitor for proteinuria before initiation of, and periodically throughout treatment. If urine dipstick proteinuria greater than or equal to 2+ is detected, obtain a 24 hour urine protein. Withhold LENVIMA for ≥2 grams of proteinuria/24 hours and resume at a reduced dose when proteinuria is <2 gm/24 hours. Discontinue LENVIMA for nephrotic syndrome [*see Dosage and Administration (2.2)*].

5.6 Renal Failure and Impairment

In Study 1, events of renal impairment were reported in 14% of LENVIMA-treated patients compared to 2% of patients in the placebo group. The incidence of Grade 3 or greater renal failure or impairment was 3% in LENVIMA-treated patients and 1% in the placebo group. The primary risk factor for severe renal impairment in LENVIMA-treated patients was dehydration/hypovolemia due to diarrhea and vomiting.

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 (2.2)*].

5.7 Gastrointestinal Perforation and Fistula Formation

In Study 1, events of gastrointestinal perforation or fistula were reported in 2% of LENVIMA-treated patients and 0.8% of patients in the placebo group.

Discontinue LENVIMA in patients who develop gastrointestinal perforation or life-threatening fistula [*see Dosage and Administration (2.2)*].

5.8 QT Interval Prolongation

In Study 1, QT/QTc interval prolongation was reported in 9% of LENVIMA-treated patients and 2% of patients 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. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics.

Monitor and correct electrolyte abnormalities in all patients. Withhold LENVIMA for the development of Grade 3 or greater QT interval prolongation. Resume LENVIMA at a reduced dose when QT prolongation resolves to Grade 0 or 1 or baseline [*see Dosage and Administration (2.2), Clinical Pharmacology (12.2)*].

5.9 Hypocalcemia

In Study 1, 9% of LENVIMA-treated patients experienced Grade 3 or greater hypocalcemia compared to 2% in the placebo group. In most cases hypocalcemia responded to replacement and dose interruption/dose reduction [*see Adverse Reactions (6.1)*].

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 (2.2)*].

5.10 Reversible Posterior Leukoencephalopathy Syndrome

Across clinical studies in which 1108 patients received LENVIMA, there were 3 reported events of reversible posterior leukoencephalopathy syndrome (RPLS). Confirm the diagnosis of RPLS with MRI. Withhold for RPLS until fully resolved. Upon resolution, resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of neurologic symptoms [*see Dosage and Administration (2.2)*].

5.11 Hemorrhagic Events

In Study 1, hemorrhagic events occurred in 35% of LENVIMA-treated patients and in 18% of the placebo group. However, the incidence of Grade 3-5 hemorrhage was similar between arms at 2% and 3%, respectively. The most frequently reported hemorrhagic event was epistaxis (11% Grade 1 and 1% Grade 2). Discontinuation due to hemorrhagic events occurred in 1% of LENVIMA-treated patients.

Across clinical studies in which 1108 patients received LENVIMA, Grade 3 or greater hemorrhage was reported in 2% of patients. In Study 1, there was 1 case of fatal intracranial hemorrhage among 16 patients who received lenvatinib and had CNS metastases at baseline.

Withhold LENVIMA for the development of Grade 3 hemorrhage until resolved to Grade 0 to 1. Either resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of hemorrhage. Discontinue LENVIMA in patients who experience Grade 4 hemorrhage [*see Dosage and Administration (2.2)*].

5.12 Impairment of Thyroid Stimulating Hormone Suppression

LENVIMA impairs exogenous thyroid suppression. In Study 1, 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 a normal TSH at baseline, elevation of TSH level above 0.5 mU/L was observed post baseline in 57% of LENVIMA-treated patients as compared with 14% of patients receiving placebo.

Monitor TSH levels monthly and adjust thyroid replacement medication as needed in patients with DTC.

5.13 Embryofetal Toxicity

Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended human dose resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 2 weeks following completion of therapy *[see Use in Specific Populations (8.1, 8.3)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the label:

- Hypertension [*see Warnings and Precautions (5.1)*]
- Cardiac Dysfunction [*see Warnings and Precautions (5.2)*]
- Arterial Thromboembolic Events [*see Warnings and Precautions (5.3)*]
- Hepatotoxicity [*see Warnings and Precautions (5.4)*]
- Proteinuria [*see Warnings and Precautions (5.5)*]
- Renal Failure and Impairment [*see Warnings and Precautions (5.6)*]
- Gastrointestinal Perforation and Fistula Formation [*see Warnings and Precautions (5.7)*]
- QT Interval Prolongation [*see Warnings and Precautions (5.8)*]
- Hypocalcemia [*see Warnings and Precautions (5.9)*]
- Reversible Posterior Leukoencephalopathy Syndrome [*see Warnings and Precautions (5.10)]*
- Hemorrhagic Events [*see Warnings and Precautions (5.11)*]

- Impairment of Thyroid Stimulating Hormone Suppression [*see Warnings and Precautions (5.12)*]

6.1 Clinical Trials Experience

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

Safety data obtained in 1108 patients with advanced solid tumors who received LENVIMA as a single agent across multiple clinical studies was used to further characterize risks of serious adverse drug reactions [*see Warnings and Precautions (5.4, 5.10, 5.11)*]. The median age was 60 years (range 21-89 years). The dose range was 0.2 mg to 32 mg. The median duration of exposure in the entire population was 5.5 months.

The safety data described below are derived from Study 1 which randomized (2:1) patients with radioactive iodine-refractory differentiated thyroid cancer (RAI-refractory DTC) to LENVIMA (n=261) or placebo (n=131) [*see Clinical Studies (14)*]. The median treatment duration was 16.1 months for LENVIMA and 3.9 months for placebo. Among 261 patients who received LENVIMA in Study 1, median age was 64 years, 52% were women, 80% were White, 18% were Asian, and 2% were Black; 4% identified themselves as having Hispanic or Latino ethnicity.

In Study 1, the most common adverse reactions observed in LENVIMA-treated patients (greater than or equal to 30%) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia (PPE) syndrome, abdominal pain, and dysphonia. The most common serious adverse reactions (at least 2%) were pneumonia (4%), hypertension (3%), and dehydration (3%).

Adverse reactions led to dose reductions in 68% of patients receiving LENVIMA 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%).

Table 2 presents the percentage of patients in Study 1 experiencing adverse reactions at a higher rate in LENVIMA-treated patients than patients receiving placebo in the double-blind phase of the DTC study.

Table 2 Adverse Reactions Occurring in Patients with a Between-Group Difference of Greater than or Equal to 5% All Grades or Greater than or Equal to 2% Grades 3 and 4

Adverse Reaction	LENVIMA 24 mg N=261		Placebo N=131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Vascular Disorders				
Hypertension[a]	73	44	16	4
Hypotension	9	2	2	0
Gastrointestinal Disorders				
Diarrhea	67	9	17	0
Nausea	47	2	25	1
Stomatitis[b]	41	5	8	0
Vomiting	36	2	15	0
Abdominal pain[c]	31	2	11	1
Constipation	29	0.4	15	1
Oral pain[d]	25	1	2	0
Dry mouth	17	0.4	8	0
Dyspepsia	13	0.4	4	0
General Disorders and Administration Site Conditions				
Fatigue[e]	67	11	35	4
Edema peripheral	21	0.4	8	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/Myalgia[f]	62	5	28	3
Metabolism and Nutrition Disorders				
Weight decreased	51	13	15	1
Decreased appetite	54	7	18	1
Dehydration	9	2	2	1
Nervous System Disorders				
Headache	38	3	11	1
Dysgeusia	18	0	3	0
Dizziness	15	0.4	9	0
Renal and Urinary Disorders				
Proteinuria	34	11	3	0
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia	32	3	1	0
Rash[g]	21	0.4	3	0
Alopecia	12	0	5	0
Hyperkeratosis	7	0	2	0
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	31	1	5	0
Cough	24	0	18	0
Epistaxis	12	0	1	0
Psychiatric Disorders				
Insomnia	12	0	3	0
Infections and Infestations				
Dental and oral infections[h]	10	1	1	0
Urinary tract infection	11	1	5	0
Cardiac Disorders				
Electrocardiogram QT prolonged	9	2	2	0

Table 2 Adverse Reactions Occurring in Patients with a Between-Group Difference of Greater than or Equal to 5% All Grades or Greater than or Equal to 2% Grades 3 and 4

Adverse Reaction	LENVIMA 24 mg N=261		Placebo N=131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)

[a] Includes hypertension, hypertensive crisis, increased blood pressure diastolic, and increased blood pressure

[b] Includes aphthous stomatitis, stomatitis, glossitis, mouth ulceration, and mucosal inflammation

[c] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, and gastrointestinal pain

[d] Includes oral pain, glossodynia, and oropharyngeal pain

[e] Includes asthenia, fatigue, and malaise

[f] Includes musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia

[g] Includes rash macular, rash maculo-papular, rash generalized, and rash

[h] Includes gingivitis, oral infection, parotitis, pericoronitis, periodontitis, sialoadenitis, tooth abscess, and tooth infection

A clinically important adverse reaction occurring more frequently in LENVIMA-treated patients than patients receiving placebo, but with an incidence of less than 5% was pulmonary embolism (3%, including fatal reports vs 2%, respectively).

Table 3 Laboratory Abnormalities with a Difference of at Least ≥2% in Grade 3 - 4 Events and at a Higher Incidence in LENVIMA-Treated Patients[a]

Laboratory Abnormality	LENVIMA 24 mg N=258[b]	Placebo N=131[b]
	Grades 3-4 (%)	Grades 3-4 (%)
Chemistry		
Creatinine increased	3	0
Alanine aminotransferase (ALT) increased	4	0
Aspartate aminotransferase (AST) increased	5	0
Hypocalcemia	9	2
Hypokalemia	6	1
Lipase increased	4	1
Hematology		
Platelet count decreased	2	0

[a] With at least 1 grade increase from baseline

[b] Subject with at least 1 post baseline laboratory value

In addition the following laboratory abnormalities (all Grades) occurred in greater than 5% of LENVIMA-treated patients and at a rate that was two-fold or higher than in patients who received placebo: hypoalbuminemia, increased alkaline phosphatase, hypomagnesemia, hypoglycemia, hyperbilirubinemia, hypercalcemia, hypercholesterolemia, increased serum amylase, and hyperkalemia.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Lenvatinib

No dose adjustment of LENVIMA is recommended when co-administered with CYP3A, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP) inhibitors and CYP3A and P-gp inducers [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Data

Animal Data

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

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

8.2 Lactation

Risk Summary

It is not known whether LENVIMA is present in human milk. However, lenvatinib and its metabolites are excreted in rat milk at concentrations higher than in maternal plasma *[see*

Data]. Because of the potential for serious adverse reactions in nursing infants from LENVIMA, advise women to discontinue breastfeeding during treatment with LENVIMA.

Data
Animal Data
Following administration of radiolabeled lenvatinib to lactating Sprague Dawley rats, lenvatinib-related radioactivity was approximately 2 times higher (based on AUC) in milk compared to maternal plasma.

8.3 Females and Males of Reproductive Potential

Contraception
Based on its mechanism of action, LENVIMA can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 2 weeks following completion of therapy.

Infertility
Females
LENVIMA may result in reduced fertility in females of reproductive potential *[*see *Nonclinical Toxicology (13.1)]*.

Males
LENVIMA may result in damage to male reproductive tissues leading to reduced fertility of unknown duration *[*see *Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

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

Juvenile Animal Data

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

8.5 Geriatric Use

Of 261 patients who received LENVIMA in Study 1, 118 (45.2%) were greater than or equal to 65 years of age and 29 (11.1%) were greater than or equal to 75 years of age. No overall

differences in safety or effectiveness were observed between these subjects and younger subjects.

8.6 Renal Impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended dose is 14 mg taken once daily. Patients with end stage renal disease were not studied [*see Dosage and Administration (2.1), Warnings and Precautions (5.6), Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

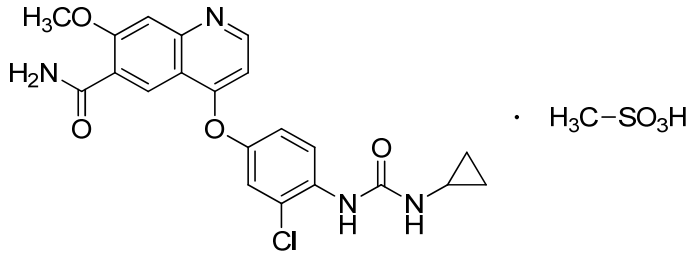
No dose adjustment is recommended in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, the recommended dose is 14 mg taken once daily [*see Dosage and Administration (2.1), Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

There is no specific antidote for overdose with LENVIMA. Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable *[see Clinical Pharmacology (12.3)]*.Adverse reactions in patients receiving single doses of LENVIMA as high as 40 mg were similar to the adverse events reported in the clinical studies at the recommended dose.

11 DESCRIPTION

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



Lenvatinib mesylate is a white to pale reddish yellow powder. It is slightly soluble in water and practically insoluble in ethanol (dehydrated). The dissociation constant (pKa value) of lenvatinib mesylate is 5.05 at 25°C. The partition coefficient (log P value) is 3.30.

Each LENVIMA capsule contains lenvatinib mesylate equivalent to 4 mg or 10 mg of lenvatinib, and the following inactive ingredients: calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, hydroxypropyl cellulose (type H), and talc. The hypromellose capsule shell contains titanium dioxide, ferric oxide yellow, and ferric oxide red. The printing ink contains shellac, black iron oxide, potassium hydroxide, and propylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib also inhibits other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET.

12.2 Pharmacodynamics

Cardiac Electrophysiology

A single 32 mg dose (1.3 times the recommended daily dose) of lenvatinib did not prolong the QT/QTc interval in a thorough QT study in healthy subjects. However, QT prolongation was observed in Study 1 *[see Warnings and Precautions (5.8)]*.

12.3 Pharmacokinetics

Absorption: After oral administration of LENVIMA, time to peak plasma concentration (T_{max}) typically occurred from 1 to 4 hours post-dose. Administration with food did not affect the extent of absorption, but decreased the rate of absorption and delayed the median T_{max} from 2 hours to 4 hours.

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

Distribution: In vitro binding of lenvatinib to human plasma proteins ranged from 98% to 99% (0.3 – 30 μg/mL). In vitro, the lenvatinib blood-to-plasma concentration ratio ranged from 0.589 to 0.608 (0.1 – 10 μg/mL).

Based on in vitro data, lenvatinib is a substrate of P-gp and BCRP but not a substrate for organic anion transporter (OAT) 1, OAT3, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, or the bile salt export pump (BSEP).

Elimination: Plasma concentrations declined bi-exponentially following C_{max}. The terminal elimination half-life of lenvatinib was approximately 28 hours.

Metabolism: CYP3A is one of the main metabolic enzymes of lenvatinib. The main metabolic pathways for lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes.

Excretion: Ten days after a single administration of radiolabeled lenvatinib to 6 patients with solid tumors, approximately 64% and 25% of the radiolabel were eliminated in the feces and urine, respectively.

Specific Populations:

Renal Impairment

The pharmacokinetics of lenvatinib following a single 24 mg dose were evaluated in subjects with mild (CLcr 60-89 mL/min), moderate (CLcr 30-59 mL/min), and severe (CLcr <30 mL/min) renal impairment, and compared to healthy subjects. Subjects with end stage renal disease were not studied. After a single 24 mg oral dose of LENVIMA, the $AUC_{0\text{-}inf}$ for subjects with renal impairment were similar compared to those for healthy subjects [*see Dosage and Administration (2.1), Warnings and Precautions (5.6), Use in Specific Populations (8.6)*].

Hepatic Impairment

The pharmacokinetics of lenvatinib following a single 10 mg dose of LENVIMA were evaluated in subjects with mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment. The pharmacokinetics of a single 5 mg dose were evaluated in subjects with severe (Child Pugh C) hepatic impairment. Compared to subjects with normal hepatic function, the dose-adjusted $AUC_{0\text{-}inf}$ of lenvatinib for subjects with mild, moderate, and severe hepatic impairment were 119%, 107%, and 180%, respectively [*see Dosage and Administration (2.1), Use in Specific Populations (8.7)*].

Effects of Age, Sex, and Race

Based on a population PK analysis, age, sex, and race did not have a significant effect on apparent clearance (Cl/F) of lenvatinib.

Drug Interaction Studies

Effect of Other Drugs on Lenvatinib

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

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

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

Effect of Lenvatinib on Other Drugs

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

In Vitro Studies with CYP or UDP-glucuronosyltransferase (UGT) Substrates: Lenvatinib inhibits CYP2C8, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A, but an increase in lenvatinib exposure that impacts safety is unlikely. Lenvatinib does not inhibit CYP2A6 and CYP2E1.

Lenvatinib induces CYP3A, but a decrease in lenvatinib exposure that impacts efficacy is unlikely. Lenvatinib does not induce CYP1A1, CYP1A2, CYP2B6, and CYP2C9.

Lenvatinib directly inhibits UGT1A1 and UGT1A4. The clinical implication of this finding is unknown. Lenvatinibshows little or no inhibition on UGT1A6, UGT1A9, UGT2B7, or aldehyde oxidase.

Lenvatinib does not induce UGT1A1, UGT1A4, UGT1A6, UGT1A9, or UGT2B7.

In Vitro Studies with Drug Transporter System Substrates: Lenvatinib inhibits OAT1, OAT3, OCT1, OCT2, OATP1B1, and BSEP. The clinical implication of this finding is unknown. Lenvatinib shows little or no inhibition on OATP1B3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

14 CLINICAL STUDIES

A multicenter, randomized (2:1), double-blind, placebo-controlled trial was conducted in 392 patients with locally recurrent or metastatic radioactive iodine-refractory differentiated thyroid cancer and radiographic evidence of disease progression within 12 months prior to randomization, confirmed by independent radiologic review. Radioactive iodine-refractory was defined as 1 or more measurable lesions with no iodine uptake on RAI scan, iodine uptake with progression within 12 months of RAI therapy, or having received cumulative RAI activity of >600 mCi (22 GBq) with the last dose administered at least 6 months prior to study entry. Patients were randomized to receive LENVIMA 24 mg once daily (n=261) or placebo (n=131) until disease progression. Randomization was stratified by geographic

region, prior VEGF/VEGFR-targeted therapy, and age. The major efficacy outcome measure was progression-free survival as determined by blinded independent radiologic review using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Independent review confirmation of disease progression was required prior to discontinuing patients from the randomization phase of the study. Other efficacy outcome measures included objective response rate and overall survival. Patients in the placebo arm could receive lenvatinib following independent review confirmation of disease progression.

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

A statistically significant prolongation in PFS was demonstrated in LENVIMA-treated patients compared to those receiving placebo (see Table 4 and Figure 1). Upon confirmation of progression, 109 (83%) patients randomly assigned to placebo crossed over to receive open-label LENVIMA.

Table 4 Efficacy Results for Study 1

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

[a] Independent radiologic review

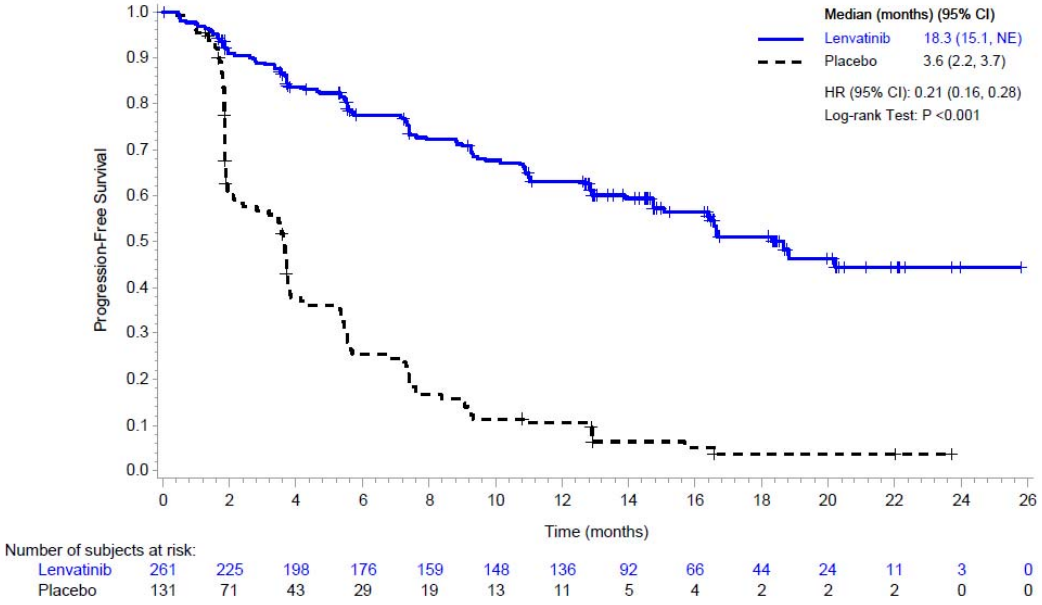
[b] Estimated with Cox proportional hazard model stratified by region (Europe vs North America vs other), age group (≤65 year vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs 1)

[c] Log-rank test stratified by region (Europe vs North America vs other), age group (≤65 years vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs 1)

[d] Cochran-Mantel-Haenszel chi-square test

[e] NE = Not estimable

Figure 1 Kaplan-Meier Plot of Progression-Free Survival



16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

- NDC 62856-724-30: 24 mg, carton with 6 cards NDC 62856-724-05 (ten 10 mg capsules and five 4 mg capsules per card).
- NDC 62856-720-30: 20 mg, carton with 6 cards NDC 62856-720-05 (ten 10 mg capsules per card).
- NDC 62856-714-30: 14 mg, carton with 6 cards NDC 62856-714-05 (five 10 mg capsules and five 4 mg capsules per card).
- NDC 62856-710-30: 10 mg, carton with 6 cards NDC 62856-710-05 (five 10 mg capsules per card).

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

17 PATIENT COUNSELING INFORMATION

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

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

Cardiac Dysfunction:
Advise patients that LENVIMA can cause cardiac dysfunction and to immediately contact their healthcare provider if they experience any clinical symptoms of cardiac dysfunction such as shortness of breath or swelling of ankles [*see Warnings and Precautions (5.2)*].

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

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

Proteinuria and Renal Failure/Impairment:
Advise patients that they will need to undergo regular lab tests to monitor for kidney function and protein in the urine [*see Warnings and Precautions (5.5, 5.6)]*.

Gastrointestinal perforation or fistula formation:
Advise patients that LENVIMA can increase the risk of gastrointestinal perforation or fistula and to seek immediate medical attention for severe abdominal pain [*see Warnings and Precautions (5.7)*].

Hemorrhagic Events:
Advise patients that LENVIMA can increase the risk for bleeding and to contact their health care provider for bleeding or symptoms of severe bleeding [*see Warnings and Precautions (5.11)*].

Embryofetal Toxicity:
Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.13), Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 2 weeks following completion of therapy *[see Use in Specific Populations (8.3)]*.

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

Manufactured by:
Patheon Inc.
Mississauga, Ontario, Canada

Distributed by:
Eisai Inc.
Woodcliff Lake, NJ 07677

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PATIENT INFORMATION

LENVIMA™ (lehn-veema)
(lenvatinib)
capsules

Read this Patient Information leaflet before you start taking LENVIMA and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is LENVIMA?

LENVIMA is a prescription medicine used to treat people with differentiated thyroid cancer (DTC, a type of thyroid cancer) that can no longer be treated with radioactive iodine and is progressing.

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

What should I tell my healthcare provider before taking LENVIMA?

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

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

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

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

How should I take LENVIMA?

- Take LENVIMA exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much LENVIMA to take and when to take it. Your healthcare provider may change your dose during treatment, stop treatment for some time, or completely stop treatment with LENVIMA if you have side effects.
- Take LENVIMA 1 time each day at the same time, with or without food.
- If you miss a dose of LENVIMA, take it as soon as you remember. If your next dose is due within 12 hours, skip the missed dose and take the next dose at your regular time.
- If you take too much LENVIMA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of LENVIMA?

LENVIMA may cause serious side effects, including:

- **high blood pressure (hypertension).** High blood pressure is a common side effect of LENVIMA and can be serious. Your blood pressure should be well controlled before you start taking LENVIMA. Your healthcare provider should check your blood pressure regularly during treatment with LENVIMA. If you develop blood pressure problems, your healthcare provider may prescribe medicine to treat your high blood pressure, lower your dose of LENVIMA, or stop your treatment with LENVIMA.
- **heart problems.** Call your healthcare provider right away if you get symptoms of heart problems, such as shortness of breath or swelling of your ankles.
- **problem with blood clots in your blood vessels (arteries).** Get emergency medical help right away if you get any of the following symptoms:
  - severe chest pain or pressure
  - pain in your arms, back, neck or jaw
  - shortness of breath
  - numbness or weakness on one side of your body
  - trouble talking
  - sudden severe headache
  - sudden vision changes
- **liver problems.** LENVIMA may cause liver problems that may lead to liver failure and death. Your healthcare provider will check your liver function before and during treatment with LENVIMA. Tell your healthcare provider right away if you have any of the following symptoms:
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark “tea colored” urine
  - light-colored bowel movements (stools)
- **increased protein in your urine (proteinuria).** Proteinuria is a common side effect of LENVIMA and can be serious. Your healthcare provider should check your urine for protein before and during your treatment with LENVIMA.

If you develop protein in your urine, your healthcare provider may decrease your dose of LENVIMA or stop your treatment.

- **kidney problems.** Kidney failure has happened with LENVIMA treatment. Your healthcare provider should do regular blood tests to check your kidneys.
- **an opening in the wall of your stomach or intestines (perforation) or an abnormal connection between two parts of your gastrointestinal tract (fistula).** Get emergency medical help right away if you have severe stomach (abdomen) pain.
- **changes in the electrical activity of your heart called QT prolongation.** QT prolongation can cause irregular heartbeats that can be life threatening. Your healthcare provider will do blood tests during your treatment with LENVIMA to check the levels of potassium, magnesium, and calcium in your blood, and check the electrical activity of your heart with an ECG.
- **low levels of blood calcium (hypocalcemia).** Your healthcare provider will check your blood calcium levels during treatment with LENVIMA.
- **a condition called Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** Call your healthcare provider right away if you get: severe headache, seizures, weakness, confusion, or blindness or change in vision.
- **bleeding.** Tell your healthcare provider if you have any signs or symptoms of bleeding during treatment with LENVIMA, including:
  - severe and persistent nose bleeds
  - vomiting blood
  - red or black (looks like tar) stools
  - coughing up blood or blood clots
  - heavy or new onset vaginal bleeding
- **change in thyroid hormone levels**. You may have changes in your thyroid hormone levels when taking LENVIMA. Your healthcare provider may need to change your dose of thyroid medicine while you are taking LENVIMA. Your healthcare provider should check your thyroid hormone levels every month during treatment with LENVIMA.

The most common side effects of LENVIMA include:

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

LENVIMA may cause fertility problems in males and females. Talk to your healthcare provider if this is a concern for you.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of LENVIMA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LENVIMA?

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

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

General information about the safe and effective use of LENVIMA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LENVIMA for a condition for which it was not prescribed. Do not give LENVIMA to other people, even if they have the same symptoms you have. It may harm them.

If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about LENVIMA that is written for health professionals.

For more information, call 1-877-873-4724 or go to www.LENVIMA.com.

What are the ingredients in LENVIMA?

Active ingredient: lenvatinib
Inactive ingredients: calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, hydroxypropylcellulose (type H), and talc.
The capsule shell contains: titanium dioxide, ferric oxide yellow, and ferric oxide red. The printing ink contains shellac, black iron oxide, potassium hydroxide, and propylene glycol.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Patheon Inc.
Mississauga, Ontario, Canada

Distributed by:
Eisai Inc.
Woodcliff Lake, NJ 07677

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