HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

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

Indications and Usage, Hepatocellular Carcinoma (1.3)	8/2018
Dosage and Administration, Recommended Dose for HCC (2.4)	8/2018
Warnings and Precautions (5.1, 5.14)	8/2018

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

LENVIMA is a kinase inhibitor that is indicated:

- For the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC). (1.1)
- In combination with everolimus, for the treatment of patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy. (1.2)
- For the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC). (1.3)

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

- DTC: The recommended dosage is 24 mg orally once daily. (2.2)
- RCC: The recommended dosage is 18 mg orally once daily with everolimus 5 mg orally once daily. (2.3)
- HCC: The recommended dosage is based on actual body weight:
  - 12 mg orally once daily for patients greater than or equal to 60 kg
  - 8 mg orally once daily for patients less than 60 kg. (2.4)
- Modify the recommended daily dose for certain patients with renal or hepatic impairment. (2.6, 2.7)

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

Capsules: 4 mg and 10 mg. (3)

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

None. (4)

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

- Hypertension: Control blood pressure prior to treatment and monitor during treatment. Withhold for Grade 3 hypertension despite optimal antihypertensive therapy. Discontinue for Grade 4 hypertension. (2.5, 5.1)
- Cardiac Dysfunction: Monitor for clinical symptoms or signs of cardiac dysfunction. Withhold or discontinue for Grade 3 cardiac dysfunction. Discontinue for Grade 4 cardiac dysfunction. (2.5, 5.2)
- Arterial Thromboembolic Events: Discontinue following an arterial thromboembolic event. (2.5, 5.3)
- Hepatotoxicity: Monitor liver function prior to treatment and periodically during treatment. Withhold or discontinue for Grade 3 or 4 hepatotoxicity. Discontinue for hepatic failure. (2.5, 5.4)
- Renal Failure or Impairment: Withhold or discontinue for Grade 3 or 4 renal failure or impairment. (2.5, 5.5)
- Proteinuria: Monitor for proteinuria prior to treatment and periodically during treatment. Withhold for 2 or more grams of proteinuria per 24 hours. Discontinue for nephrotic syndrome. (2.5, 5.6)
- Diarrhea: May be severe and recurrent. Promptly initiate management for severe diarrhea. Withhold or discontinue based on severity. (2.5, 5.7)
- Fistula Formation and Gastrointestinal Perforation: Discontinue in patients who develop Grade 3 or 4 fistula or any Grade gastrointestinal perforation. (2.5, 5.8)
- QT Interval Prolongation: Monitor and correct electrolyte abnormalities. Withhold for QT interval greater than 500 ms or for 60 ms or greater increase in baseline QT interval. (2.5, 5.9)
- Hypocalcemia: Monitor blood calcium levels at least monthly and replace calcium as necessary. Withhold or discontinue based on severity. (2.5, 5.10)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Withhold for RPLS until fully resolved or discontinue. (2.5, 5.11)
- Hemorrhagic Events: Withhold or discontinue based on severity. (2.5, 5.12)
- Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction: Monitor thyroid function prior to treatment and monthly during treatment. (5.13)
- Wound Healing Complications: Withhold LENVIMA before surgery. Discontinue in patients with wound healing complications. (5.14)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.15, 8.1, 8.3)

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

In DTC, the most common adverse reactions (incidence ≥30%) for LENVIMA are hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, decreased weight, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, and dysphonia. (6.1)

In RCC, the most common adverse reactions (incidence ≥30%) for LENVIMA and everolimus are diarrhea, fatigue, arthralgia/myalgia, decreased appetite, vomiting, nausea, stomatitis/oral inflammation, hypertension, peripheral edema, cough, abdominal pain, dyspnea, rash, decreased weight, hemorrhagic events, and proteinuria. (6.1)

In HCC, the most common adverse reactions (incidence ≥20%) for LENVIMA are hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic events, hypothyroidism, and nausea. (6.1)

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

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

- Lactation: Advise not to breastfeed. (8.2)

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

Revised: 12/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Differentiated Thyroid Cancer

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

1.2 Renal Cell Carcinoma

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

1.3 Hepatocellular Carcinoma

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage Information

- Reduce the dose for certain patients with renal or hepatic impairment *[see Dosage and Administration (2.6, 2.7)]*.
- Take LENVIMA once daily, with or without food, at the same time each day *[see Clinical Pharmacology (12.3)]*. If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration.

2.2 Recommended Dosage for Differentiated Thyroid Cancer (DTC)

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

2.3 Recommended Dosage for Renal Cell Carcinoma (RCC)

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

Refer to everolimus prescribing information for recommended everolimus dosing information.

2.4 Recommended Dosage for Hepatocellular Carcinoma (HCC)

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

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

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

2.5 Dosage Modifications for Adverse Reactions

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

Table 1. Recommended Dosage Modifications for LENVIMA for Adverse Reactions

Adverse Reaction	**Severity** [a]	**Dosage Modifications for LENVIMA**
Hypertension *[see Warnings and Precautions (5.1)]*	Grade 3	• Withhold for Grade 3 that persists despite optimal antihypertensive therapy. • Resume at reduced dose when hypertension is controlled at less than or equal to Grade 2.
	Grade 4	• Permanently discontinue.
Cardiac Dysfunction *[see Warnings and Precautions (5.2)]*	Grade 3	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at a reduced dose or discontinue depending on the severity and persistence of adverse reaction.
	Grade 4	• Permanently discontinue.
Arterial Thromboembolic Event *[see Warnings and Precautions (5.3)]*	Any Grade	• Permanently discontinue.
Hepatotoxicity *[see Warnings and Precautions (5.4)]*	Grade 3 or 4	• Withhold until improves to Grade 0 to 1 or baseline. • Either resume at a reduced dose or discontinue depending on severity and persistence of hepatotoxicity. • Permanently discontinue for hepatic failure.
Renal Failure or Impairment *[see Warnings and Precautions (5.5)]*	Grade 3 or 4	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at a reduced dose or discontinue depending on severity and persistence of renal impairment.
Proteinuria *[see Warnings and Precautions (5.6)]*	2 g or greater proteinuria in 24 hours	• Withhold until less than or equal to 2 grams of proteinuria per 24 hours. • Resume at a reduced dose. • Permanently discontinue for nephrotic syndrome.
Gastrointestinal Perforation *[see Warnings and Precautions (5.8)]*	Any Grade	• Permanently discontinue.
Fistula Formation *[see Warnings and Precautions*	Grade 3 or 4	• Permanently discontinue.

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

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

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

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

2.6 Dosage Modifications for Severe Renal Impairment

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

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

2.7 Dosage Modifications for Severe Hepatic Impairment

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

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

2.8 Preparation and Administration

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

3 DOSAGE FORMS AND STRENGTHS

Capsules:

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension

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

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

Serious complications of poorly controlled hypertension have been reported.

Control blood pressure prior to initiating LENVIMA. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at a reduced dose when hypertension is controlled or permanently discontinue LENVIMA based on severity *[see Dosage and Administration (2.5)]*.

5.2 Cardiac Dysfunction

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

Monitor patients for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity *[see Dosage and Administration (2.5)]*.

5.3 Arterial Thromboembolic Events

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

Permanently discontinue LENVIMA following an arterial thrombotic event *[see Dosage and Administration (2.5)]*. The safety of resuming LENVIMA after an arterial thromboembolic event has not been established and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

5.4 Hepatotoxicity

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

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

Monitor liver function prior to initiating LENVIMA, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Monitor patients with HCC closely for signs of hepatic failure, including hepatic encephalopathy. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity *[see Dosage and Administration (2.5)]*.

5.5 Renal Failure or Impairment

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

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

Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA for renal failure or impairment based on severity *[see Dosage and Administration (2.5)]*.

5.6 Proteinuria

Proteinuria occurred in 34% of LENVIMA-treated patients in SELECT (DTC) and in 26% of LENVIMA-treated patients in REFLECT (HCC). Grade 3 proteinuria occurred in 11% and 6% in SELECT and REFLECT, respectively. In Study 205 (RCC), proteinuria occurred in 31% of patients receiving LENVIMA with everolimus and 14% of patients receiving everolimus. Grade 3 proteinuria occurred in 8% of patients receiving LENVIMA with everolimus compared to 2% of patients receiving everolimus *[see Adverse Reactions (6.1)]*.

Monitor for proteinuria prior to initiating LENVIMA and periodically during treatment. If urine dipstick proteinuria greater than or equal to 2+ is detected, obtain a 24-hour urine protein. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity *[see Dosage and Administration (2.5)]*.

5.7 Diarrhea

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

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

Promptly initiate management of diarrhea. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA based on severity *[see Dosage and Administration (2.5)]*.

5.8 Fistula Formation and Gastrointestinal Perforation

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

Permanently discontinue LENVIMA in patients who develop gastrointestinal perforation of any severity or Grade 3 or 4 fistula *[see Dosage and Administration (2.5)]*.

5.9 QT Interval Prolongation

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

Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Withhold and resume at reduced dose of LENVIMA upon recovery based on severity *[see Dosage and Administration (2.5)]*.

5.10 Hypocalcemia

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

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

Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue LENVIMA depending on severity *[see Dosage and Administration (2.5)]*.

5.11 Reversible Posterior Leukoencephalopathy Syndrome

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

Confirm the diagnosis of RPLS with magnetic resonance imaging. Withhold and resume at a reduced dose upon recovery or permanently discontinue LENVIMA depending on severity and persistence of neurologic symptoms *[see Dosage and Administration (2.5)]*.

5.12 Hemorrhagic Events

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

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

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

Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (e.g. carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue LENVIMA based on the severity *[see Dosage and Administration (2.5)]*.

5.13 Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction

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

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

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

5.14 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.

5.15 Embryo-Fetal Toxicity

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

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

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Hypertension *[see Warnings and Precautions (5.1)]*
- Cardiac Dysfunction *[see Warnings and Precautions (5.2)]*
- Arterial Thromboembolic Events *[see Warnings and Precautions (5.3)]*

palmar-plantar erythrodysesthesia (PPE) syndrome, abdominal pain, and dysphonia. The most common serious adverse reactions (at least 2%) were pneumonia (4%), hypertension (3%), and dehydration (3%).

Adverse reactions led to dose reductions in 68% of patients receiving LENVIMA; 18% of patients discontinued LENVIMA for adverse reactions. The most common adverse reactions (at least 10%) resulting in dose reductions of LENVIMA were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions (at least 1%) resulting in discontinuation of LENVIMA were hypertension (1%) and asthenia (1%).

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

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

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

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

Adverse Reaction	LENVIMA 24 mg N=261		Placebo N=131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hyperkeratosis	7	0	2	0
Respiratory, Thoracic and Mediastinal				
Dysphonia	31	1	5	0
Cough	24	0	18	0
Epistaxis	12	0	1	0
Psychiatric				
Insomnia	12	0	3	0
Infections				
Urinary tract infection	11	1	5	0
Dental and oral infections[h]	10	1	1	0
Cardiac				
Electrocardiogram QT prolonged	9	2	2	0

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

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

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

Table 4: Laboratory Abnormalities with a Difference of ≥ 2% in Grade 3 - 4 Events and at a Higher Incidence in the LENVIMA Arm[a, b] in SELECT (DTC)

Laboratory Abnormality	LENVIMA 24 mg	Placebo
	Grades 3-4 (%)	Grades 3-4 (%)
Chemistry		
Hypocalcemia	9	2
Hypokalemia	6	1
Increased aspartate aminotransferase (AST)	5	0

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

a With at least 1 grade increase from baseline

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

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

Renal Cell Carcinoma

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

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

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

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

Table 5 presents the adverse reactions in >15% of patients in the LENVIMA with everolimus arm. Study 205 was not designed to demonstrate a statistically significant difference in

Reversible Posterior Leukoencephalopathy Syndrome

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

Hemorrhagic Events

Advise patients that LENVIMA can increase the risk for bleeding and to contact their healthcare provider for bleeding or symptoms of severe bleeding *[see Warnings and Precautions (5.12)]*.

Wound Healing Complications

Advise patients that LENVIMA can increase the risk of wound healing complications. Advise patients to inform their healthcare provider of any planned surgical procedure *[see Warnings and Precautions (5.14)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.15), Use in Specific Populations (8.1)]*.

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

Lactation

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

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PATIENT INFORMATION
LENVIMA® (lehn-veema)
(lenvatinib)
capsules

What is LENVIMA?

LENVIMA is a prescription medicine that is used to treat certain kinds of cancer.

- LENVIMA is used by itself to treat differentiated thyroid cancer (DTC), a type of thyroid cancer that can no longer be treated with radioactive iodine and is progressing.
- LENVIMA is used along with another medicine called everolimus to treat advanced renal cell carcinoma (RCC), a type of kidney cancer, after one course of treatment with another anti-cancer medicine.
- LENVIMA is used by itself as the first treatment for a type of liver cancer called hepatocellular carcinoma (HCC) when it cannot be removed by surgery.

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

Before you take LENVIMA, tell your healthcare provider about all of your medical conditions, including if you:

- have high blood pressure
- have heart problems
- have a history of blood clots in your arteries (type of blood vessel), including stroke, heart attack, or change in vision
- have or have had liver or kidney problems
- have a history of a tear (perforation) in your stomach or intestine, or an abnormal connection between two or more body parts (fistula)
- have headaches, seizures, or vision problems
- have any bleeding problems
- are pregnant or plan to become pregnant. LENVIMA can harm your unborn baby.
  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with LENVIMA.
  - You should use an effective method of birth control during treatment with LENVIMA and for at least 30 days after the last dose of LENVIMA. Talk with your healthcare provider about birth control methods you can use during this time. Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with LENVIMA.
- are breastfeeding or plan to breastfeed. It is not known if LENVIMA passes into your breast milk. Do not breastfeed during treatment with LENVIMA and for at least 1 week after the last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Know the medicines you take. Keep a list of your medicines to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take LENVIMA?

- Take LENVIMA exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much LENVIMA to take and when to take it. Your healthcare provider may change your dose during treatment, stop treatment for some time, or completely stop treatment with LENVIMA if you have side effects.
- Take LENVIMA 1 time each day at the same time, with or without food.
- If you miss a dose of LENVIMA, take it as soon as you remember. If your next dose is due within 12 hours, skip the missed dose and take the next dose at your regular time.
- If you cannot swallow LENVIMA capsules whole:
  - Use a medicine cup to measure about one tablespoon of water or apple juice and place into a small glass.
  - Place the LENVIMA capsules into the small glass without breaking or crushing them.
  - Leave the capsules in the liquid for at least 10 minutes.
  - Stir the contents of the glass for at least 3 minutes.
  - Drink the mixture. After drinking, rinse the glass with a small amount of additional water or apple juice and swallow the liquid.
- If you take too much LENVIMA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of LENVIMA?

LENVIMA may cause serious side effects, including:

- **high blood pressure (hypertension).** High blood pressure is a common side effect of LENVIMA and can be serious. Your blood pressure should be well controlled before you start taking LENVIMA. Your healthcare provider should check your blood pressure regularly during treatment with LENVIMA. If you develop blood pressure problems, your healthcare provider may prescribe medicine to treat your high blood pressure, lower your dose of LENVIMA, or stop your treatment with LENVIMA.
- **heart problems.** LENVIMA can cause serious heart problems that may lead to death. Call your healthcare provider right away if you get symptoms of heart problems, such as shortness of breath or swelling of your ankles.
- **problem with blood clots in your blood vessels (arteries).** Get emergency medical help right away if you get any of the following symptoms:
  - severe chest pain or pressure
  - pain in your arms, back, neck or jaw
  - shortness of breath
  - numbness or weakness on one side of your body
  - trouble talking
  - sudden severe headache
  - sudden vision changes
- **liver problems.** LENVIMA may cause liver problems that may lead to liver failure and death. Your healthcare provider will check your liver function before and during treatment with LENVIMA. Tell your healthcare provider right away if you have any of the following symptoms:
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark “tea colored” urine
  - light-colored bowel movements (stools)
  - feeling drowsy, confused or loss of consciousness
- **kidney problems.** Kidney failure, which can lead to death, has happened with LENVIMA treatment. Your healthcare provider should do regular blood tests to check your kidneys.
- **increased protein in your urine (proteinuria).** Proteinuria is a common side effect of LENVIMA and can be serious. Your healthcare provider should check your urine for protein before and during your treatment with LENVIMA. If you develop protein in your urine, your healthcare provider may decrease your dose of LENVIMA or stop your treatment.
- **diarrhea.** Diarrhea is a common side effect of LENVIMA and can be serious. If you get diarrhea, ask your healthcare provider about what medicines you can take to treat your diarrhea. It is important to drink more water when you get diarrhea. Tell your healthcare provider or go to the emergency room, if you are unable to drink enough liquids and your diarrhea is not able to be controlled.
- **an opening in the wall of your stomach or intestines (perforation) or an abnormal connection between two or more body parts (fistula).** Get emergency medical help right away if you have severe stomach (abdomen) pain.

- **changes in the electrical activity of your heart called QT prolongation.** QT prolongation can cause irregular heartbeats that can be life threatening. Your healthcare provider will do blood tests before and during your treatment with LENVIMA to check the levels of potassium, magnesium, and calcium in your blood, and may check the electrical activity of your heart with an ECG.
- **low levels of blood calcium (hypocalcemia).** Your healthcare provider will check your blood calcium levels during treatment with LENVIMA and may tell you to take a calcium supplement if your calcium levels are low.
- **a condition called Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** Call your healthcare provider right away if you get: severe headache, seizures, weakness, confusion, or blindness or change in vision.
- **bleeding.** LENVIMA may cause serious bleeding problems that may lead to death. Tell your healthcare provider if you have any signs or symptoms of bleeding during treatment with LENVIMA, including:
  - severe and persistent nose bleeds
  - vomiting blood
  - red or black (looks like tar) stools
  - blood in your urine
  - coughing up blood or blood clots
  - heavy or new onset vaginal bleeding
- **change in thyroid hormone levels**. 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 before starting and every month during treatment with LENVIMA.
- **wound healing problems.** If you need to have a surgical procedure, tell your healthcare provider that you are taking LENVIMA. LENVIMA should be stopped until your wound heals.

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

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

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

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

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

- tiredness
- decreased appetite
- joint and muscle pain
- weight loss
- stomach (abdomen) pain
- rash, redness, itching, or peeling of your skin on your hands and feet
- hoarseness
- bleeding
- change in thyroid hormone levels
- nausea

LENVIMA may cause fertility problems in males and females. Talk to your healthcare provider if this is a concern for you.
These are not all the possible side effects of LENVIMA.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LENVIMA?

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

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

General information about the safe and effective use of LENVIMA.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LENVIMA for a condition for which it was not prescribed. Do not give LENVIMA to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about LENVIMA that is written for health professionals.

What are the ingredients in LENVIMA?
Active ingredient: lenvatinib
Inactive ingredients: calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, low-substituted hydroxypropylcellulose, 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.

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

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 12/2018