

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-----

Dosage and Administration (2.5)	11/2020
Warnings and Precautions (5.14)	2/2020
Warnings and Precautions (5.15)	12/2020

-----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)
- In combination with pembrolizumab, for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial. (1.4)

-----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)
- Endometrial Carcinoma: The recommended dosage is 20 mg orally once daily in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks. (2.5)
- Modify the recommended daily dose for certain patients with renal or hepatic impairment. (2.7, 2.8)

-----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. (2.6, 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. (2.6, 5.2)
- **Arterial Thromboembolic Events:** Discontinue following an arterial thromboembolic event. (2.6, 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. (2.6, 5.4)
- **Renal Failure or Impairment:** Withhold or discontinue for Grade 3 or 4 renal failure or impairment. (2.6, 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. (2.6, 5.6)
- **Diarrhea:** May be severe and recurrent. Promptly initiate management for severe diarrhea. Withhold or discontinue based on severity. (2.6, 5.7)
- **Fistula Formation and Gastrointestinal Perforation:** Discontinue in patients who develop Grade 3 or 4 fistula or any Grade gastrointestinal perforation. (2.6, 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. (2.6, 5.9)
- **Hypocalcemia:** Monitor blood calcium levels at least monthly and replace calcium as necessary. Withhold or discontinue based on severity. (2.6, 5.10)
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** Withhold for RPLS until fully resolved or discontinue. (2.6, 5.11)
- **Hemorrhagic Events:** Withhold or discontinue based on severity. (2.6, 5.12)
- **Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction:** Monitor thyroid function prior to treatment and monthly during treatment. (5.13)
- **Impaired Wound Healing:** Withhold LENVIMA for at least 1 week before elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of LENVIMA after resolution of wound healing complications has not been established. (5.14)
- **Osteonecrosis of the Jaw:** Consider preventive dentistry prior to treatment with LENVIMA. Avoid invasive dental procedures, if possible, particularly in patients at higher risk. (5.15)
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.16, 8.1, 8.3)

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

- In DTC, the most common adverse reactions (incidence $\geq 30\%$) 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 $\geq 30\%$) 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 $\geq 20\%$) 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)
- In Endometrial Carcinoma, the most common adverse reactions (incidence $\geq 20\%$) for LENVIMA and pembrolizumab are fatigue, hypertension, musculoskeletal pain, diarrhea, decreased appetite, hypothyroidism, nausea, stomatitis, vomiting, decreased weight, abdominal pain, headache, constipation, urinary tract infection, dysphonia, hemorrhagic events, hypomagnesemia, palmar-plantar erythrodysesthesia, dyspnea, cough, and rash. (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: 12/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE**
 - 1.1 Differentiated Thyroid Cancer
 - 1.2 Renal Cell Carcinoma
 - 1.3 Hepatocellular Carcinoma
 - 1.4 Endometrial Carcinoma
- 2 DOSAGE AND ADMINISTRATION**
 - 2.1 Important Dosage Information
 - 2.2 Recommended Dosage for Differentiated Thyroid Cancer (DTC)
 - 2.3 Recommended Dosage for Renal Cell Carcinoma (RCC)
 - 2.4 Recommended Dosage for Hepatocellular Carcinoma (HCC)
 - 2.5 Recommended Dosage for Endometrial Carcinoma
 - 2.6 Dosage Modifications for Adverse Reactions
 - 2.7 Dosage Modifications for Severe Renal Impairment
 - 2.8 Dosage Modifications for Severe Hepatic Impairment
 - 2.9 Preparation and Administration
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Hypertension
 - 5.2 Cardiac Dysfunction
 - 5.3 Arterial Thromboembolic Events
 - 5.4 Hepatotoxicity
 - 5.5 Renal Failure or Impairment
 - 5.6 Proteinuria
 - 5.7 Diarrhea
 - 5.8 Fistula Formation and Gastrointestinal Perforation
 - 5.9 QT Interval Prolongation
 - 5.10 Hypocalcemia
 - 5.11 Reversible Posterior Leukoencephalopathy Syndrome
 - 5.12 Hemorrhagic Events
 - 5.13 Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction
 - 5.14 Impaired Wound Healing
 - 5.15 Osteonecrosis of the Jaw (ONJ)
 - 5.16 Embryo-Fetal Toxicity
- 6 ADVERSE REACTIONS**
 - 6.1 Clinical Trials Experience
 - 6.2 Postmarketing Experience
- 7 DRUG INTERACTIONS**
 - 7.1 Drugs That Prolong the QT Interval
- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy
 - 8.2 Lactation
 - 8.3 Females and Males of Reproductive Potential
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use
 - 8.6 Renal Impairment
 - 8.7 Hepatic Impairment
- 10 OVERDOSAGE**
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
 - 12.1 Mechanism of Action
 - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY**
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES**
 - 14.1 Differentiated Thyroid Cancer
 - 14.2 Renal Cell Carcinoma
 - 14.3 Hepatocellular Carcinoma
 - 14.4 Endometrial Carcinoma (EC)
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
- 17 PATIENT COUNSELING INFORMATION**

*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).

1.4 Endometrial Carcinoma

LENVIMA, in combination with pembrolizumab, is indicated for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.

This indication is approved under accelerated approval based on tumor response rate and durability of response [*see Clinical Studies (14.4)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage Information

- Reduce the dose for certain patients with renal or hepatic impairment [*see Dosage and Administration (2.7, 2.8)*].
- 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 Recommended Dosage for Endometrial Carcinoma

The recommended dosage of LENVIMA is 20 mg orally once daily, in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks, until unacceptable toxicity or disease progression.

Refer to the pembrolizumab prescribing information for other pembrolizumab dosing information.

2.6 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 [<i>see Warnings and Precautions (5.1)</i>]	Grade 3	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Permanently discontinue.
Cardiac Dysfunction [<i>see Warnings and Precautions (5.2)</i>]	Grade 3	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Permanently discontinue.
Arterial Thromboembolic Event [<i>see Warnings and Precautions (5.3)</i>]	Any Grade	<ul style="list-style-type: none"> Permanently discontinue.
Hepatotoxicity [<i>see Warnings and Precautions (5.4)</i>]	Grade 3 or 4	<ul style="list-style-type: none"> 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 [<i>see Warnings and Precautions (5.5)</i>]	Grade 3 or 4	<ul style="list-style-type: none"> 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.

Table 1. Recommended Dosage Modifications for LENVIMA for Adverse Reactions		
Adverse Reaction	Severity^a	Dosage Modifications for LENVIMA
Proteinuria [<i>see Warnings and Precautions (5.6)</i>]	2 g or greater proteinuria in 24 hours	<ul style="list-style-type: none"> • 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 [<i>see Warnings and Precautions (5.8)</i>]	Any Grade	<ul style="list-style-type: none"> • Permanently discontinue.
Fistula Formation [<i>see Warnings and Precautions (5.8)</i>]	Grade 3 or 4	<ul style="list-style-type: none"> • Permanently discontinue.
QT Prolongation [<i>see Warnings and Precautions (5.9)</i>]	Greater than 500 ms or greater than 60 ms increase from baseline	<ul style="list-style-type: none"> • Withhold until improves to less than or equal to 480 ms or baseline. • Resume at a reduced dose.
Reversible Posterior Leukoencephalopathy Syndrome [<i>see Warnings and Precautions (5.11)</i>]	Any Grade	<ul style="list-style-type: none"> • Withhold until fully resolved. • Resume at a reduced dose or discontinue depending on severity and persistence of neurologic symptoms.
Other Adverse Reactions [<i>see Warnings and Precautions (5.7, 5.10, 5.12)</i>]	Persistent or intolerable Grade 2 or 3 adverse reaction	<ul style="list-style-type: none"> • Withhold until improves to Grade 0 to 1 or baseline. • Resume at reduced dose.
	Grade 4 laboratory abnormality	
	Grade 4 adverse reaction	<ul style="list-style-type: none"> • 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
Endometrial Carcinoma	14 mg once daily	10 mg once daily	8 mg once daily
HCC			
• Actual weight 60 kg or greater	8 mg once daily	4 mg once daily	4 mg every other day
• Actual weight less than 60 kg	4 mg once daily	4 mg every other day	Discontinue

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.

When administering LENVIMA in combination with pembrolizumab for the treatment of endometrial carcinoma, interrupt one or both drugs or dose reduce LENVIMA as appropriate. No dose reductions are recommended for pembrolizumab. Withhold or discontinue pembrolizumab in accordance with the instructions in the pembrolizumab prescribing information.

2.7 Dosage Modifications for Severe Renal Impairment

The recommended dosage of LENVIMA for patients with DTC, RCC, or endometrial carcinoma 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
- Endometrial carcinoma: 10 mg orally once daily

2.8 Dosage Modifications for Severe Hepatic Impairment

The recommended dosage of LENVIMA for patients with DTC, RCC, or endometrial carcinoma 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
- Endometrial carcinoma: 10 mg orally once daily

2.9 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 “C” on cap and “LENV 4 mg” on body.
- 10 mg: yellow body and yellowish-red cap, marked in black ink with “C” 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 (2.6)*].

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 (2.6)*].

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 (2.6)*]. 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 (2.6)*].

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 (2.6)*].

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 (2.6)*].

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 (2.6)*].

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 (2.6)*].

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 (2.6)*].

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 (2.6)*].

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 (2.6)*].

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 (2.6)*].

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 Impaired Wound Healing

Impaired wound healing has been reported in patients who received LENVIMA [see *Adverse Reactions (6.2)*].

Withhold LENVIMA for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of LENVIMA after resolution of wound healing complications has not been established.

5.15 Osteonecrosis of the Jaw

Osteonecrosis of the Jaw (ONJ) has been reported in patients receiving LENVIMA [see *Adverse Reactions (6.1)*]. Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease or invasive dental procedures, may increase the risk of ONJ.

Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA treatment. Advise patients regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk. Withhold LENVIMA for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold LENVIMA if ONJ develops and restart based on clinical judgement of adequate resolution.

5.16 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)*]
- Hepatotoxicity [see *Warnings and Precautions (5.4)*]
- Renal Failure and Impairment [see *Warnings and Precautions (5.5)*]
- Proteinuria [see *Warnings and Precautions (5.6)*]
- Diarrhea [see *Warnings and Precautions (5.7)*]
- Fistula Formation and Gastrointestinal Perforation [see *Warnings and Precautions (5.8)*]

- QT Interval Prolongation [*see Warnings and Precautions (5.9)*]
- Hypocalcemia [*see Warnings and Precautions (5.10)*]
- Reversible Posterior Leukoencephalopathy Syndrome [*see Warnings and Precautions (5.11)*]
- Hemorrhagic Events [*see Warnings and Precautions (5.12)*]
- Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction [*see Warnings and Precautions (5.13)*]
- Impaired Wound Healing [*see Warnings and Precautions (5.14)*]
- Osteonecrosis of the Jaw (ONJ) [*see Warnings and Precautions (5.15)*]

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.

The data in the Warnings and Precautions reflect exposure to LENVIMA as a single agent in 261 patients with DTC (SELECT) and 476 patients with HCC (REFLECT), LENVIMA with pembrolizumab in 94 patients with endometrial carcinoma (Study 111), and LENVIMA with everolimus in 62 patients with RCC (Study 205). Safety data obtained in 1823 patients with advanced solid tumors who received LENVIMA as a single agent across multiple clinical studies was used to further characterize the risks of serious adverse reactions. Among the 1823 patients who received LENVIMA as a single agent, the median age was 61 years (20 to 89 years), the dose range was 0.2 mg to 32 mg daily, and the median duration of exposure was 5.6 months.

The data below reflect exposure to LENVIMA in 893 patients enrolled in randomized, active-controlled trials (REFLECT; Study 205), a randomized, placebo-controlled trial (SELECT) and a single arm trial (Study 111). The median duration of exposure to LENVIMA across these four studies ranged from 6 to 16 months. The demographic and exposure data for each clinical trial population are described in the subsections below.

Differentiated Thyroid Cancer

The safety of LENVIMA was evaluated in SELECT, in which patients with radioactive iodine-refractory differentiated thyroid cancer were randomized (2:1) to LENVIMA (n=261) or placebo (n=131) [*see Clinical Studies (14.1)*]. The median treatment duration was 16.1 months for LENVIMA. Among 261 patients who received LENVIMA, median age was 64 years, 52% were females, 80% were White, 18% were Asian, and 2% were Black; and 4% were Hispanic/Latino.

The most common adverse reactions observed in LENVIMA-treated patients ($\geq 30\%$) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, decreased weight, 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; 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 $\geq 5\%$ in All Grades or $\geq 2\%$ 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 (%)
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
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				

In Table 6, Grade 3-4 laboratory abnormalities occurring in $\geq 3\%$ of patients in the LENVIMA with everolimus arm are presented.

Table 6: Grade 3-4 Laboratory Abnormalities Occurring in $\geq 3\%$ of Patients in the LENVIMA with Everolimus Arm^{a,b} in Study 205 (RCC)		
Laboratory Abnormality	LENVIMA 18 mg with Everolimus 5 mg	Everolimus 10 mg
	Grades 3-4 (%)	Grades 3-4 (%)
Chemistry		
Hypertriglyceridemia	18	18
Increased lipase	13	12
Hypercholesterolemia	11	0
Hyponatremia	11	6
Hypophosphatemia	11	6
Hyperkalemia	6	2
Hypocalcemia	6	2
Hypokalemia	6	2
Increased aspartate aminotransferase (AST)	3	0
Increased alanine aminotransferase (ALT)	3	2
Increased alkaline phosphatase	3	0
Hyperglycemia	3	16
Increased creatine kinase	3	4
Hematology		
Lymphopenia	10	20
Anemia	8	16
Thrombocytopenia	5	0
<p>a With at least 1 grade increase from baseline</p> <p>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 with Everolimus (n = 62), Everolimus (n = 50).</p>		

Hepatocellular Carcinoma

The safety of LENVIMA was evaluated in REFLECT, which randomized (1:1) patients with unresectable hepatocellular carcinoma (HCC) to LENVIMA (n=476) or sorafenib (n=475) [see *Clinical Studies (14.3)*]. The dose of LENVIMA was 12 mg orally once daily for patients with a baseline body weight of ≥ 60 kg and 8 mg orally once daily for patients with a baseline body weight of < 60 kg. The dose of sorafenib was 400 mg orally twice daily. Duration of treatment was ≥ 6 months in 49% and 32% of patients in the LENVIMA and sorafenib groups, respectively. Among the 476 patients who received LENVIMA in REFLECT, the median age was 63 years, 85% were men, 28% were White and 70% were Asian.

The most common adverse reactions observed in the LENVIMA-treated patients ($\geq 20\%$) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic events, hypothyroidism, and nausea.

The most common serious adverse reactions ($\geq 2\%$) in LENVIMA-treated patients were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%).

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

Treatment discontinuation due to adverse reactions occurred in 20% of patients in the LENVIMA-treated group. The most common adverse reactions ($\geq 1\%$) resulting in discontinuation of LENVIMA were fatigue (1%), hepatic encephalopathy (2%), hyperbilirubinemia (1%), and hepatic failure (1%).

Table 7 summarizes the adverse reactions that occurred in $\geq 10\%$ of patients receiving LENVIMA in REFLECT. REFLECT was not designed to demonstrate a statistically significant reduction in adverse reaction rates for LENVIMA, as compared to sorafenib, for any specified adverse reaction listed in Table 7.

Table 7: Adverse Reactions Occurring in $\geq 10\%$ of Patients in the LENVIMA Arm in REFLECT (HCC)				
Adverse Reaction	LENVIMA 8 mg/12 mg N=476		Sorafenib 800 mg N=475	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Endocrine				
Hypothyroidism ^a	21	0	3	0
Gastrointestinal				
Diarrhea	39	4	46	4
Abdominal pain ^b	30	3	28	4
Nausea	20	1	14	1
Vomiting	16	1	8	1
Constipation	16	1	11	0
Ascites ^c	15	4	11	3
Stomatitis ^d	11	0.4	14	1
General				
Fatigue ^e	44	7	36	6
Pyrexia ^f	15	0	14	0.2
Peripheral edema	14	1	7	0.2
Metabolism and Nutrition				
Decreased appetite	34	5	27	1
Decreased weight	31	8	22	3
Musculoskeletal and Connective Tissue				
Arthralgia/Myalgia ^g	31	1	20	2
Nervous System				
Headache	10	1	8	0
Renal and Urinary				
Proteinuria ^h	26	6	12	2
Respiratory, Thoracic and Mediastinal				
Dysphonia	24	0.2	12	0

Table 7: Adverse Reactions Occurring in $\geq 10\%$ of Patients in the LENVIMA Arm in REFLECT (HCC)				
Adverse Reaction	LENVIMA 8 mg/12 mg N=476		Sorafenib 800 mg N=475	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia syndrome	27	3	52	11
Rash ⁱ	14	0	24	2
Vascular				
Hypertension ^j	45	24	31	15
Hemorrhagic events ^k	23	4	15	4
<p>a Includes hypothyroidism, blood thyroid stimulating hormone increased.</p> <p>b Includes abdominal discomfort, abdominal pain, abdominal tenderness, epigastric discomfort, gastrointestinal pain, lower abdominal pain, and upper abdominal pain</p> <p>c Includes ascites and malignant ascites</p> <p>d Includes aphthous ulcer, gingival erosion, gingival ulceration, glossitis, mouth ulceration, oral mucosal blistering, and stomatitis</p> <p>e Includes asthenia, fatigue, lethargy and malaise</p> <p>f Includes increased body temperature, pyrexia</p> <p>g Includes arthralgia, back pain, extremity pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, and myalgia</p> <p>h Includes proteinuria, increased urine protein, protein urine present</p> <p>i Includes erythema, erythematous rash, exfoliative rash, genital rash, macular rash, maculo-papular rash, papular rash, pruritic rash, pustular rash and rash</p> <p>j Includes increased diastolic blood pressure, increased blood pressure, hypertension and orthostatic hypertension</p> <p>k Includes all hemorrhage terms. Hemorrhage terms that occurred in 5 or more subjects in either treatment group include: epistaxis, hematuria, gingival bleeding, hemoptysis, esophageal varices hemorrhage, hemorrhoidal hemorrhage, mouth hemorrhage, rectal hemorrhage and upper gastrointestinal hemorrhage</p>				

In Table 8, Grade 3-4 laboratory abnormalities occurring in $\geq 2\%$ of patients in the LENVIMA arm in REFLECT (HCC) are presented.

Table 8: Grade 3-4 Laboratory Abnormalities Occurring in $\geq 2\%$ of Patients in the LENVIMA Arm^{a,b} in REFLECT (HCC)		
Laboratory Abnormality	Lenvatinib (%)	Sorafenib (%)
Chemistry		
Increased GGT	17	20
Hyponatremia	15	9
Hyperbilirubinemia	13	10
Increased aspartate aminotransferase (AST)	12	18
Increased alanine aminotransferase (ALT)	8	9
Increased alkaline phosphatase	7	5
Increased lipase	6	17
Hypokalemia	3	4
Hyperkalemia	3	2
Decreased albumin	3	1
Increased creatinine	2	2

Table 8: Grade 3-4 Laboratory Abnormalities Occurring in $\geq 2\%$ of Patients in the LENVIMA Arm^{a,b} in REFLECT (HCC)		
Laboratory Abnormality	Lenvatinib (%)	Sorafenib (%)
Hematology		
Thrombocytopenia	10	8
Lymphopenia	8	9
Neutropenia	7	3
Anemia	4	5
<small>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=278 to 470) and sorafenib (n=260 to 473)</small>		

Endometrial Carcinoma

The safety of LENVIMA (20 mg orally once daily) in combination with pembrolizumab (200 mg intravenously every 3 weeks) was evaluated in Study 111, a single-arm, multicenter, open-label trial in 94 patients with endometrial carcinoma whose tumors had progressed following one line of systemic therapy and were not MSI-H or dMMR [see *Clinical Studies (14.4)*]. The median duration of study treatment was 7 months (range: 0.03 to 37.8 months).

Pembrolizumab was continued for a maximum of 24 months; however, treatment with LENVIMA could be continued beyond 24 months.

Fatal adverse reactions occurred in 3% of patients treated with LENVIMA and pembrolizumab, including gastrointestinal perforation, RPLS with intraventricular hemorrhage, and intracranial hemorrhage.

Serious adverse reactions occurred in 52% of patients receiving LENVIMA and pembrolizumab. Serious adverse reactions in $\geq 3\%$ of patients were hypertension (9%), abdominal pain (6%), musculoskeletal pain (5%), hemorrhage (4%), fatigue (4%), nausea (4%), confusional state (4%), pleural effusion (4%), adrenal insufficiency (3%), colitis (3%), dyspnea (3%), and pyrexia (3%).

Permanent discontinuation due to adverse reaction (Grade 1-4) occurred in 21% of patients who received LENVIMA and pembrolizumab. The most common adverse reactions ($>2\%$) resulting in discontinuation of LENVIMA were gastrointestinal perforation or fistula (2%), muscular weakness (2%), and pancreatitis (2%).

Adverse reactions led to dose reduction or interruption in 88% of patients receiving LENVIMA. The most common adverse reactions ($\geq 5\%$) resulting in dose reduction or interruption of LENVIMA were fatigue (32%), hypertension (26%), diarrhea (18%), nausea (13%), palmar-plantar erythrodysesthesia (13%), vomiting (13%), decreased appetite (12%), musculoskeletal pain (11%), stomatitis (9%), abdominal pain (7%), hemorrhages (7%), renal impairment (6%), decreased weight (6%), rash (5%), headache (5%), increased lipase (5%), and proteinuria (5%).

Table 9 presents the adverse reactions in $\geq 20\%$ of patients with LENVIMA in combination with pembrolizumab.

Table 9: Adverse Reactions in $\geq 20\%$ of Patients on LENVIMA plus Pembrolizumab in Study 111		
	LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=94	
Adverse Reactions	All Grades (%)	Grade 3-4 (%)
General		
Fatigue ^a	65	17
Musculoskeletal and Connective Tissue		
Musculoskeletal pain ^b	65	3
Vascular		
Hypertension ^c	65	38
Hemorrhagic events ^d	28	4
Gastrointestinal		
Diarrhea ^e	64	4
Nausea	48	5
Stomatitis ^f	43	0
Vomiting	39	0
Abdominal pain ^g	33	6
Constipation	32	0
Metabolism		
Decreased appetite ^h	52	0
Hypomagnesaemia	27	3
Endocrine		
Hypothyroidism ⁱ	51	1
Investigations		
Decreased weight	36	3
Nervous System		
Headache	33	1
Infections		
Urinary tract infection ^j	31	4
Respiratory, Thoracic and Mediastinal		
Dysphonia	29	0
Dyspnea ^k	24	2
Cough	21	0
Skin and Subcutaneous Tissue		
Palmar-plantar erythrodysesthesia syndrome	26	3
Rash ^l	21	3

Table 9: Adverse Reactions in $\geq 20\%$ of Patients on LENVIMA plus Pembrolizumab in Study 111		
	LENVIMA 20 mg in combination with Pembrolizumab 200 mg N=94	
Adverse Reactions	All Grades (%)	Grade 3-4 (%)
a	Includes asthenia, fatigue, and malaise	
b	Includes arthralgia, arthritis, back pain, breast pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity	
c	Includes essential hypertension, hypertension, and hypertensive encephalopathy	
d	Includes catheter site bruise, contusion, epistaxis, gastrointestinal hemorrhage, hematemesis, hematuria, hemorrhage intracranial, injection site hemorrhage, intraventricular hemorrhage, large intestinal hemorrhage, metrorrhagia, mouth hemorrhage, uterine hemorrhage, and vaginal hemorrhage	
e	Includes diarrhea, gastroenteritis, gastrointestinal viral infection, and viral diarrhea	
f	Includes glossitis, mouth ulceration, oral discomfort, oral mucosal blistering, oropharyngeal pain, and stomatitis	
g	Includes abdominal discomfort, abdominal pain, lower abdominal pain, and upper abdominal pain	
h	Includes decreased appetite and early satiety	
i	Includes increased blood thyroid stimulating hormone and hypothyroidism	
j	Includes cystitis and urinary tract infection	
k	Includes dyspnea and exertional dyspnea	
l	Includes rash, rash generalized, rash macular, and rash maculo-papular	

Table 10 presents, laboratory abnormalities in $\geq 20\%$ (All Grades) or $\geq 3\%$ (Grades 3-4) of patients with LENVIMA in combination with pembrolizumab.

Table 10: Laboratory Abnormalities in $\geq 20\%$ (All Grades) or $\geq 3\%$ (Grades 3-4) of Patients on LENVIMA plus Pembrolizumab in Study 111		
	LENVIMA 20 mg plus Pembrolizumab 200 mg	
Laboratory Abnormality^a	All Grades %^b	Grade 3-4 %^b
Chemistry		
Increased creatinine	80	7
Hypertriglyceridemia	58	4
Hyperglycemia	53	1
Hypercholesteremia	49	6
Hypoalbuminemia	48	0
Hypomagnesemia	47	2
Increased aspartate aminotransferase	43	4
Hyponatremia	42	13
Increased lipase	42	18
Increased alanine aminotransferase	35	3
Increased alkaline phosphatase	32	1
Hypokalemia	27	5
Increased amylase	19	6
Hypocalcemia	14	3
Hypermagnesemia	4	3
Hematology		
Thrombocytopenia	48	0
Leukopenia	38	2
Lymphopenia	36	7

Table 10: Laboratory Abnormalities in $\geq 20\%$ (All Grades) or $\geq 3\%$ (Grades 3-4) of Patients on LENVIMA plus Pembrolizumab in Study 111		
	LENVIMA 20 mg plus Pembrolizumab 200 mg	
Laboratory Abnormality^a	All Grades %^b	Grade 3-4 %^b
Anemia	35	1
Increased INR	21	3
Neutropenia	12	3
^a With at least 1 grade increase from baseline ^b Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post baseline laboratory measurement for each parameter (range: 71 to 92 patients)		

6.2 Postmarketing Experience

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

Gastrointestinal: pancreatitis, increased amylase

General: impaired wound healing

Hepatobiliary: cholecystitis

Renal and Urinary: nephrotic syndrome

Vascular: arterial (including aortic) aneurysms, dissections, and rupture

7 DRUG INTERACTIONS

7.1 Drugs That Prolong the QT Interval

LENVIMA has been reported to prolong the QT/QTc interval. Avoid coadministration of LENVIMA with medicinal products with a known potential to prolong the QT/QTc interval [*see Warnings and Precautions (5.9)*].

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 doses 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.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

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)*].

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction

Advise patients that LENVIMA can cause hypothyroidism and that their thyroid function should be monitored regularly during treatment [*see Warnings and Precautions (5.13)*].

Impaired Wound Healing

Advise patients that LENVIMA may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure [*see Warnings and Precautions (5.14)*].

Osteonecrosis of the Jaw (ONJ)

Advise patients regarding good oral hygiene practices and to have preventive dentistry performed prior to treatment with LENVIMA and throughout treatment with LENVIMA. Inform patients being treated with LENVIMA, particularly those who are at high risk for ONJ, to avoid invasive dental procedures, if possible, and to inform their healthcare provider of any planned dental procedures [*see Warnings and Precautions (5.15)*]. Advise patients to immediately contact their healthcare provider for signs or symptoms associated with ONJ.

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 (5.16), 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)*].

Distributed by:

Eisai Inc.

Woodcliff Lake, NJ 07677

LENVIMA® is a registered trademark of Eisai R&D Management Co., Ltd. and is licensed to Eisai Inc.

© 2020 Eisai Inc.

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.
- LENVIMA is used along with another medicine called pembrolizumab to treat advanced endometrial carcinoma, a type of uterine cancer:
 - that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), **and**
 - that has progressed after treatment with anti-cancer medicine, **and**
 - that cannot be treated with surgery or radiation.

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
- plan to have surgery, a dental procedure, or have had a recent surgery. You should stop taking LENVIMA at least 1 week before planned surgery. See **“What are the possible side effects of LENVIMA?”**
- 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.

Especially tell your healthcare provider if you are taking, or have taken, an osteoporosis medicine.

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.
- **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	○ trouble talking
○ pain in your arms, back, neck or jaw	○ sudden severe headache
○ shortness of breath	○ sudden vision changes
○ numbness or weakness on one side of your body	
- **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.
- **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.** Your healthcare provider should check your thyroid hormone levels before starting and every month during treatment with LENVIMA.
- **wound healing problems.** Wound healing problems have happened in some people who take LENVIMA. Tell your healthcare provider if you plan to have any surgery before or during treatment with LENVIMA.
 - You should stop taking LENVIMA at least 1 week before planned surgery.
 - Your healthcare provider should tell you when you may start taking LENVIMA again after surgery.
- **severe jaw bone problems (osteonecrosis).** Severe jaw bone problems have happened in some people who take LENVIMA. Certain risk factors such as taking a bisphosphonate medicine or the medicine denosumab, having dental disease, or an invasive dental procedure may increase your risk of getting jaw bone problems. Your healthcare provider should examine your mouth before you start and during treatment with LENVIMA. Tell your dentist that you are taking LENVIMA. It is important for you to practice good mouth care during treatment with LENVIMA. Tell your healthcare provider right away if you get signs or symptoms of jaw bone problems during treatment with LENVIMA, including jaw pain, toothache, or sores on your gums. Tell your healthcare provider if you plan to have any dental procedures before or during treatment with LENVIMA. You should avoid having invasive dental procedures if possible, during treatment with LENVIMA. Stopping your bisphosphonate medicine before an invasive dental procedure may help decrease your risk of getting these jaw problems.
 - You should stop taking LENVIMA at least 1 week before planned dental surgery or invasive dental procedures.
 - Your healthcare provider should tell you when you may start taking LENVIMA again after dental procedures.

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

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

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

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

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

- | | |
|-------------------------|--|
| • tiredness | • rash, redness, itching, or peeling of your skin on your hands and feet |
| • decreased appetite | • hoarseness |
| • joint and muscle pain | • bleeding |
| • weight loss | |

- stomach (abdomen) pain
- change in thyroid hormone levels
- nausea

The most common side effects of LENVIMA when given with pembrolizumab in people treated for uterine cancer include:

- tiredness
- joint and muscle pain
- decreased appetite
- change in thyroid hormone levels
- nausea
- mouth sores
- vomiting
- weight loss
- stomach (abdomen) pain
- headache
- constipation
- urinary tract infection
- hoarseness
- bleeding
- low magnesium level
- rash, redness, itching, or peeling of your skin on your hands and feet
- trouble breathing
- cough
- rash

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, hydroxypropyl cellulose, low-substituted hydroxypropylcellulose, mannitol, microcrystalline cellulose, and talc.

The capsule shell contains: ferric oxide red, ferric oxide yellow, hypromellose, and titanium dioxide. The printing ink contains black iron oxide, potassium hydroxide, propylene glycol, and shellac.

Distributed by: Eisai Inc., Woodcliff Lake, NJ 07677

LENVIMA® is a registered trademark of Eisai R&D Management Co., Ltd. and is licensed to Eisai Inc.

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: 12/2020