LENVIMA® and Everolimus: A Second-Line Combination Following Prior Anti-Angiogenic Therapy in Advanced Renal Cell Carcinoma

**INDICATIONS**
LENVIMA® is indicated:
- For the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (RAI-refractory DTC).
- In combination with everolimus for the treatment of patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy.
- For the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC).

**SELECTED SAFETY INFORMATION**

**Hypertension.** In DTC, hypertension occurred in 73% of patients on LENVIMA® + everolimus (13% grade 3). In RCC, hypertension occurred in 42% of patients on LENVIMA + everolimus (13% grade 3). Systolic blood pressure ≥160 mmHg occurred in 29% of patients, and 21% had diastolic blood pressure ≥100 mmHg. In HCC, hypertension occurred in 45% of LENVIMA®-treated patients (24% grade 3).

**Cardiac Dysfunction.** Serious and fatal cardiovascular dysfunction can occur with LENVIMA®. Across clinical trials in 799 patients with RCC, RCC, and HCC, grade 3 or higher cardiac dysfunction occurred in 3% of LENVIMA®-treated patients. Monitor for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at reduced dose when hypertension is controlled or permanently discontinue based on severity.

**Arterial Thromboembolic Events.** Among patients receiving LENVIMA® or LENVIMA® + everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in RCC and HCC and 5% in DTC. Grade 3-5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials. Permanently discontinue following an arterial thromboembolic event. The safety of resuming 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.

**Hepatotoxicity.** Across clinical studies enrolling 1,327 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 HCC, hepatic encephalopathy occurred in 8% of LENVIMA®-treated patients (5% grade 3-5). Grade 3-5 hepatic failure occurred in 3% of LENVIMA®-treated patients. 2% of patients discontinued LENVIMA® due to hepatic encephalopathy and 1% discontinued due to hepatic failure. Monitor liver function prior to initiation, 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 reduced dose upon recovery or permanently discontinue based on severity.

**Renal Failure or Impairment.** Serious including fatal renal failure or impairment can occur with LENVIMA®. Renal impairment was reported in 14% and 7% of LENVIMA®-treated patients in DTC and HCC, respectively. Grade 3-5 renal failure or impairment occurred in 3% of patients with RCC and 2% of patients with HCC, including 1 fatal event in each study. In RCC, renal impairment or renal failure was reported in 18% of LENVIMA® + everolimus-treated patients (10% grade 3).

**Proteinuria.** In DTC and RCC, proteinuria was reported in 31% and 26% of LENVIMA®-treated patients, respectively. Grade 3 proteinuria occurred in 11% and 8% in DTC and RCC, respectively. In HCC, proteinuria occurred in 31% of patients receiving LENVIMA® + everolimus (8% grade 3). Monitor for proteinuria prior to initiation and periodically during treatment. If urine dipstick proteinuria ≥2+ is detected, obtain a 24-hour urine protein. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

**Diabetes.** Of the 737 LENVIMA®-treated patients in DTC and RCC, diabetes occurred in 49% (8% grade 3). In RCC, diabetes occurred in 81% of LENVIMA® + everolimus-treated patients (19% grade 3). Diabetes was the most frequent cause of dose interruption/reduction, and diabetes recurred despite dose reduction. Promptly initiate management of diabetes. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

**PLEASE SEE SELECTED SAFETY INFORMATION THROUGHOUT AND ACCOMPANYING FULL PRESCRIBING INFORMATION.**
Warnings and Precautions

Fistula Formation and Gastrointestinal Perforation. Of the 799 patients treated with LENVIMA or LENVIMA + everolimus in DTC, RCC, and HCC, fistula or gastrointestinal perforation occurred in 2%. Permanently discontinue in patients who develop gastrointestinal perforation of any severity or grade 3-4 fistula.

QT Interval Prolongation. In DTC, RCC, and HCC clinical trials, QT interval prolongation of >500 ms occurred in 2% in RCC, >500 ms occurred in 1% of patients receiving LENVIMA + everolimus and >500 ms occurred in 2% of LENVIMA-treated patients. In RCC, QTc interval increases of >60 ms occurred in 11% of patients receiving LENVIMA + everolimus and QTc interval >500 ms occurred in 6%. In RCC, 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 upon recovery based on severity.

Hypothyroidism. According to standard medical practice.

60% of LENVIMA + everolimus-treated patients in RCC.

LENVIMA impairs exogenous thyroid suppression. In DTC, 88% of patients had baseline thyroid stimulating hormone (TSH) level ≤0.5 mU/L. In patients with normal TSH at baseline, elevation of TSH level >0.5 mU/L was observed post baseline in 57% of LENVIMA-treated patients. In RCC and HCC, grade 1 or 2 hypothyroidism occurred in 24% of LENVIMA + everolimus-treated patients and 21% of LENVIMA-treated patients, respectively. In patients with normal or low TSH at baseline, elevation of TSH was observed post baseline in 70% of LENVIMA-treated patients in RCC and 60% of LENVIMA + everolimus-treated patients in RCC.

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

Impaired Wound Healing. Impaired wound healing has been reported in patients who received LENVIMA. 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.

Embryo-fetal Toxicity. Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to pregnant women. 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, and advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 30 days after the last dose.

Adverse Reactions

In DTC, the most common adverse reactions (≥30%) observed in LENVIMA-treated patients were hypertension (73%), fatigue (67%), diarrhea (67%), arthralgia/myalgia (62%), decreased appetite (64%), decreased weight (51%), nausea (47%), stomatitis (41%), headache (38%), vomiting (36%), proteinuria (34%), palmar-plantar erythrodysesthesia syndrome (32%), abdominal pain (31%), and dysphonia (31%). The most common serious adverse reactions (≥2%) were pneumonia (4%), hypertension (3%), and dehydration (3%). Adverse reactions led to dose reductions in 68% of LENVIMA-treated patients; 18% discontinued LENVIMA. The most common adverse reactions (≥10%) resulting in dose reductions were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions (≥1%) resulting in discontinuation of LENVIMA were hypertension (1%) and asthma (1%). In RCC, the most common adverse reactions (≥30%) observed in LENVIMA + everolimus-treated patients were diarrhea (81%), fatigue (73%), arthralgia/myalgia (55%), decreased appetite (53%), vomiting (40%), nausea (45%), stomatitis (44%), hypertension (42%), peripheral edema (42%), cough (37%), abdominal pain (37%), dyspepsia (35%), rash (35%), decreased weight (34%), hypocalcemia (32%), and proteinuria (31%). The most common serious adverse reactions (≥5%) were renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspepsia (5%). Adverse reactions led to dose reductions or interruption in 89% of patients. The most common adverse reactions (≥5%) resulting in dose reductions were diarrhea (21%), fatigue (8%), thrombocytopenia (8%), vomiting (8%), nausea (6%), and proteinuria (5%). Treatment discontinuation due to an adverse reaction occurred in 29% of patients.

In HCC, the most common adverse reactions (≥30%) observed in LENVIMA-treated patients were hypertension (45%), fatigue (44%), diarrhea (39%), decreased appetite (34%), arthralgia/myalgia (31%), decreased weight (31%), abdominal pain (30%), palmar-plantar erythrodysesthesia syndrome (27%), proteinuria (26%), dysphonia (24%), hypocalcemia (23%), hypothyroidism (21%), and nausea (20%). The most common serious adverse reactions (≥2%) were hepatic encephalopathy (5%), hepatic failure (5%), ascites (5%), and decreased appetite (4%). Adverse reactions led to dose reductions or interruption in 62% of patients. The most common adverse reactions (≥5%) resulting in dose reductions were fatigue (9%), decreased appetite (8%), diarrhea (8%), proteinuria (7%), hypertension (6%), and palmar-plantar erythrodysesthesia syndrome (5%). Treatment discontinuation due to an adverse reaction occurred in 20% of patients. The most common adverse reactions (≥1%) resulting in discontinuation of LENVIMA were fatigue (11%), hepatic encephalopathy (2%), hyperbilirubinemia (1%), and hepatic failure (1%).

Use in Specific Populations

Because of the potential for serious adverse reactions in breastfed infants, advise women to discontinue breastfeeding during treatment and for at least 1 week after last dose. LENVIMA may impair fertility in males and females of reproductive potential.

No dose adjustment is recommended for patients with mild (CLcr 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment. LENVIMA concentrations may increase in patients with DTC or RCC and severe (CLcr 15-29 mL/min) renal impairment. In RCC, severe renal impairment (CLcr <15 mL/min) is an indication for discontinuation of LENVIMA.

No dose adjustment is recommended for patients with mild (CLcr 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment. LENVIMA concentrations may increase in patients with DTC or RCC and severe (CLcr 15-29 mL/min) renal impairment. In RCC, severe renal impairment (CLcr <15 mL/min) is an indication for discontinuation of LENVIMA.

No dose adjustment is recommended for patients with mild (CLcr 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment. LENVIMA concentrations may increase in patients with DTC or RCC and severe (CLcr 15-29 mL/min) renal impairment. In RCC, severe renal impairment (CLcr <15 mL/min) is an indication for discontinuation of LENVIMA.

If you are a licensed healthcare professional in NJ, MN, or VT, employed by U.S. Dept. of Veterans Affairs or Defense or other jurisdiction that may prohibit meals, please identify yourself to an Eisai representative.