DOSING AND ADVERSE REACTION MANAGEMENT GUIDE

For LENVIMA®

*For Treatment of **Advanced Renal Cell Carcinoma***

RECOGNIZE ARs that may occur with LENVIMA + everolimus

Understand possible ARs with LENVIMA + everolimus to help you and your patients prepare for the treatment journey

MONITOR ARs that may occur with LENVIMA + everolimus

Identify points in treatment when ARs emerged in Study 205, so you can provide timely management

MANAGE ARs that may occur with LENVIMA + everolimus

Consider ways to approach ARs to help your patients on treatment

AR=adverse reaction.

INDICATION

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

SELECTED SAFETY INFORMATION

Warnings and Precautions

Hypertension. In DTC (differentiated thyroid cancer), hypertension occurred in 73% of patients on LENVIMA (44% grade 3-4). In RCC (renal cell carcinoma), 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 (hepatocellular carcinoma), hypertension occurred in 45% of LENVIMA-treated patients (24% grade 3). Grade 4 hypertension was not reported in HCC.

Serious complications of poorly controlled hypertension have been reported. Control blood pressure prior to initiation. 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 reduced dose when hypertension is controlled or permanently discontinue based on severity.

Please see additional Selected Safety Information throughout and full Prescribing Information.

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

National Comprehensive Cancer Network® (NCCN®)-recommended subsequent therapy option for advanced clear cell renal cell carcinoma

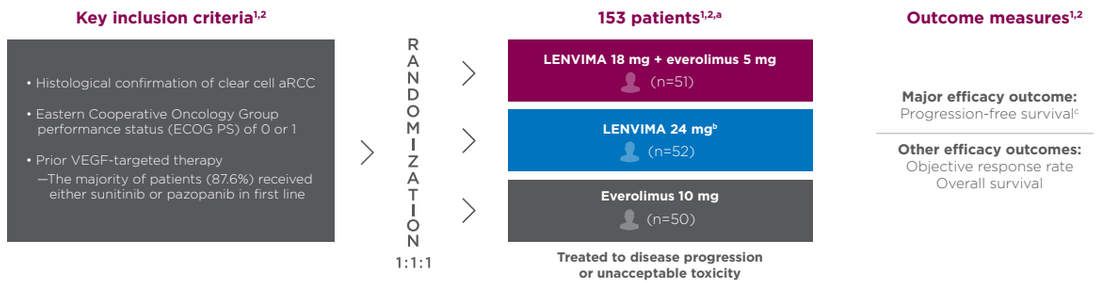
Lenvatinib (LENVIMA®) + everolimus has a NCCN category 2A other recommended regimen as a subsequent therapy option for patients with relapse or stage IV clear cell RCC*†

*Category 2A: Based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

†Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V.4.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed January 18, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Study 205: Combination vs monotherapy trial

A multicenter, randomized, phase 2 trial in patients with advanced or metastatic RCC who had received 1 prior anti-angiogenic therapy[1-3]

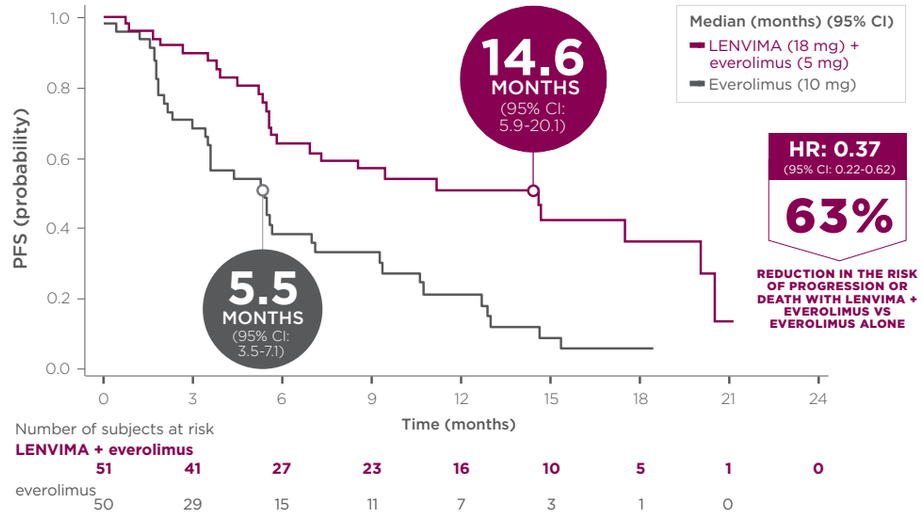


- An independent imaging follow-up assessment was performed at the request of the FDA to corroborate the investigator assessment[1,3]
- In Study 205, objective responses were confirmed at the next scheduled assessment 8 weeks later[2]
  - Objective responses were confirmed according to RECIST 1.1 (≥4 weeks after the criteria for response were met)[1,4]

NCCN=National Comprehensive Cancer Network® (NCCN®).
aRCC=advanced renal cell carcinoma; VEGF=vascular endothelial growth factor; FDA=US Food and Drug Administration.
[a]Patients were stratified by hemoglobin level (≤13 g/dL vs >13 g/dL for males and ≤11.5 g/dL vs >11.5 g/dL for females) and corrected serum calcium (≥10 mg/dL vs <10 mg/dL).[1,2]
[b]The results for the LENVIMA monotherapy arm were not included in the approved label for this indication.
[c]Investigator-assessed and evaluated according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1.[1]

MAJOR EFFICACY OUTCOME

14.6 months median PFS with the combination[1]



- 26 events (51%) occurred in the LENVIMA + everolimus arm vs 37 events (74%) in the everolimus arm[1]
  - 21 patients (41%) who received LENVIMA + everolimus progressed vs 35 patients (70%) who received everolimus
  - Death occurred in 5 patients (10%) who received LENVIMA + everolimus vs 2 patients (4%) who received everolimus
- The treatment effect of LENVIMA + everolimus on PFS was supported by a retrospective, independent review of radiographs with an observed HR of 0.43 (95% CI: 0.24-0.75) compared with the everolimus arm[1]

PFS=progression-free survival; CI=confidence interval; HR=hazard ratio.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

Cardiac Dysfunction. Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, 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 upon recovery or permanently discontinue based on severity.

OTHER EFFICACY OUTCOME

Greater than 2 years median OS with the combination[1]

Greater than 2 years median OS: 25.5-month median OS (95% CI: 16.4-32.1) with LENVIMA® + everolimus vs 15.4 months (95% CI: 11.8-20.6) with everolimus alone; HR: 0.67 (95% CI: 0.42-1.08)

- At the time of analysis, 63% of deaths (32 patients) had occurred in the LENVIMA + everolimus arm and 74% of deaths (37 patients) had occurred in the everolimus arm

OTHER EFFICACY OUTCOME

37% response rate with the combination[1]

37% response rate: 35% PR (n=18/51) and 2% CR (n=1/51) with LENVIMA + everolimus (95% CI: 24%-52%) vs 6% PR (n=3/50) and 0% CR with everolimus alone (95% CI: 1%-17%)

- The ORR was supported by a retrospective, blinded, independent radiologic review of scans[1,3]
- Tumor assessments were based on RECIST v1.1 criteria for progression but only confirmed responses are included for ORR[1]

OS=overall survival; CI=confidence interval; HR=hazard ratio; CR=complete response; PR=partial response; ORR=objective response rate; RECIST=Response Evaluation Criteria In Solid Tumors.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

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.

Among patients receiving LENVIMA with pembrolizumab, arterial thrombotic events of any severity occurred in 5% of patients in CLEAR, including myocardial infarction (3.4%) and cerebrovascular accident (2.3%).

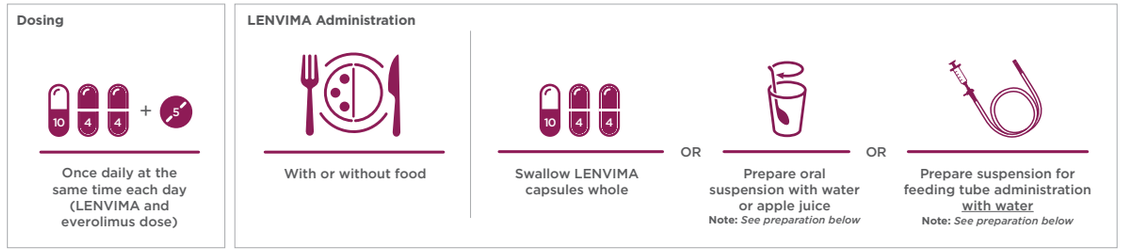
Permanently discontinue following an arterial thrombotic event. The safety of resuming after an arterial thromboembolic event has not been established, and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

Hepatotoxicity. Across clinical studies enrolling 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 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.

Once a Day. Every Day. With or Without Food[1]

Recommended dose: 18 mg LENVIMA (one 10-mg capsule and two 4-mg capsules) + one 5-mg tablet of everolimus



Capsules pictured are not actual size. Refer to the everolimus prescribing information for recommended everolimus dosing information.

Continue LENVIMA until disease progression or unacceptable toxicity.

The approved combination contains **half** of the 10-mg dose that was used in the everolimus monotherapy arm of Study 205. The half-life of LENVIMA is approximately 28 hours.

If a patient misses a dose and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration.

Preparation of suspension:

- Place the required number of capsules, up to a maximum of 5, in a small container (approximately 20 mL capacity) or syringe (20 mL). Do not break or crush capsules
- Add 3 mL of liquid to the container or syringe. Wait 10 minutes for the capsule shell (outer surface) to disintegrate, then stir or shake the mixture for 3 minutes until capsules are fully disintegrated and administer the entire contents
- Next, add an additional 2 mL of liquid to the container or syringe using a second syringe or dropper, swirl or shake and administer. Repeat this step at least once and until there is no visible residue to ensure all of the medication is taken
- If 6 capsules are required for a dose, follow these instructions using 3 capsules at a time

If LENVIMA suspension is not used at the time of preparation, LENVIMA suspension may be stored in a refrigerator at 36°F to 46°F (2°C to 8°C) for a maximum of 24 hours in a covered container. If not administered within 24 hours, the suspension should be discarded.

Note: Compatibility has been confirmed for polypropylene syringes and for feeding tubes of at least 5 French diameter (polyvinyl chloride or polyurethane tube) and at least 6 French diameter (silicone tube).

Everolimus is not distributed by Eisai Inc.

Recognize ARs That May Occur With LENVIMA® + everolimus

Adverse Reactions in Study 205

Most common ARs (≥30%) observed in LENVIMA + everolimus–treated patients[1]

- Diarrhea (81%), fatigue (73%), arthralgia/myalgia (55%), decreased appetite (53%), vomiting (48%), nausea (45%), stomatitis/oral inflammation (44%), hypertension (42%), peripheral edema (42%), cough (37%), abdominal pain (37%), dyspnea (35%), rash (35%), decreased weight (34%), hemorrhagic events (32%), and proteinuria (31%)[1]

Most common serious ARs (≥5%) in LENVIMA + everolimus–treated patients[1]

- Renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%)[1]

Most common grade 3-4 ARs (≥5%)[1]

Adverse reaction	LENVIMA 18 mg + everolimus 5 mg (n=62)	everolimus 10 mg (n=50)
Diarrhea	19%	2%
Fatigue[a]	18%	2%
Hypertension/increased blood pressure	13%	2%
Renal failure event[b]	10%	2%
Proteinuria/urine protein present	8%	2%
Vomiting	7%	0%
Hemorrhagic events[c]	6%	2%
Nausea	5%	0%
Decreased appetite	5%	0%
Arthralgia/myalgia[d]	5%	0%
Dyspnea/exertional dyspnea	5%	8%

Study 205 was not designed to demonstrate a statistically significant difference in AR rates for LENVIMA in combination with everolimus, as compared to everolimus alone.[1]

AR=adverse reaction.
[a]Includes asthenia, fatigue, lethargy, and malaise.
[b]Includes blood creatinine increased, blood urea increased, creatinine renal clearance decreased, nephropathy toxic, renal failure, renal failure acute, and renal impairment.
[c]Includes hemorrhagic diarrhea, epistaxis, gastric hemorrhage, hemarthrosis, hematoma, hematuria, hemoptysis, lip hemorrhage, renal hematoma, and scrotal hematocele.
[d]Includes arthralgia, back pain, extremity pain, musculoskeletal pain, and myalgia.

LENVIMA + everolimus AR profile (>15%)[1]*

Adverse reaction	LENVIMA 18 mg + everolimus 5 mg (n=62)		everolimus 10 mg (n=50)	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Endocrine				
Hypothyroidism	24	0	2	0
Gastrointestinal				
Constipation	16	0	18	0
Diarrhea	81	19	34	2
Dyspepsia/gastroesophageal reflux	21	0	12	0
Abdominal pain[a]	37	3	8	0
Nausea	45	5	16	0
Oral pain[b]	23	2	4	0
Stomatitis/oral inflammation[c]	44	2	50	4
Vomiting	48	7	12	0
General				
Fatigue[d]	73	18	40	2
Peripheral edema	42	2	20	0
Pyrexia/increased body temperature	21	2	10	2
Metabolism and nutrition				
Decreased appetite	53	5	18	0
Decreased weight	34	3	8	0

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*The safety data are derived from Study 205 and an additional 11 patients in the dose escalation portion of the study who received LENVIMA 18 mg + everolimus 5 mg.
[a]Includes abdominal discomfort, gastrointestinal pain, lower abdominal pain, and upper abdominal pain.
[b]Includes gingival pain, glossodynia, and oropharyngeal pain.
[c]Includes aphthous stomatitis, gingival inflammation, glossitis, and mouth ulceration.
[d]Includes asthenia, fatigue, lethargy, and malaise.

Recognize ARs That May Occur With LENVIMA® + everolimus

LENVIMA + everolimus AR profile (>15%)[1]* (cont'd)

	LENVIMA 18 mg + everolimus 5 mg (n=62)		everolimus 10 mg (n=50)	
Adverse reaction	**Grade 1-4 (%)**	**Grade 3-4 (%)**	**Grade 1-4 (%)**	**Grade 3-4 (%)**
Musculoskeletal and connective tissue				
Arthralgia/myalgia[e]	55	5	32	0
Musculoskeletal chest pain	18	2	4	0
Nervous system				
Headache	19	2	10	2
Psychiatric				
Insomnia	16	2	2	0
Renal and urinary				
Proteinuria/urine protein present	31	8	14	2
Renal failure event[f]	18	10	12	2
Respiratory, thoracic, and mediastinal				
Cough	37	0	30	0
Dyspnea/exertional dyspnea	35	5	28	8
Dysphonia	18	0	4	0
Skin and subcutaneous tissue				
Rash[g]	35	0	40	0
Vascular				
Hemorrhagic events[h]	32	6	26	2
Hypertension/increased blood pressure	42	13	10	2

[e]Includes arthralgia, back pain, extremity pain, musculoskeletal pain, and myalgia.
[f]Includes blood creatinine increased, blood urea increased, creatinine renal clearance decreased, nephropathy toxic, renal failure, renal failure acute, and renal impairment.
[g]Includes erythema, erythematous rash, genital rash, macular rash, maculopapular rash, papular rash, pruritic rash, pustular rash, and septic rash.
[h]Includes hemorrhagic diarrhea, epistaxis, gastric hemorrhage, hemarthrosis, hematoma, hematuria, hemoptysis, lip hemorrhage, renal hematoma, and scrotal hematocele.

Grade 3-4 laboratory abnormalities in ≥3% of patients in the LENVIMA + everolimus arm[1†‡]

Laboratory abnormality	LENVIMA 18 mg + everolimus 5 mg % (n=62)	everolimus 10 mg % (n=50)
Chemistry		
Increased aspartate aminotransferase (AST)	3	0
Increased alanine aminotransferase (ALT)	3	2
Increased alkaline phosphatase	3	0
Hyperkalemia	6	2
Hypokalemia	6	2
Hyponatremia	11	6
Hypocalcemia	6	2
Hypophosphatemia	11	6
Hyperglycemia	3	16
Hypertriglyceridemia	18	18
Hypercholesterolemia	11	0
Increased creatine kinase	3	4
Increased lipase	13	12
Hematology		
Anemia	8	16
Thrombocytopenia	5	0
Lymphopenia	10	20

Study 205 was not designed to demonstrate a statistically significant difference in AR rates for LENVIMA in combination with everolimus, as compared to everolimus alone.[1]

AR=adverse reaction.
†With at least 1 grade increase from baseline.
‡Subject with at least 1 post-baseline laboratory value.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

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 DTC 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).

Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at reduced dose upon recovery or permanently discontinue for renal failure or impairment based on severity.

Monitor Select ARs That May Occur With LENVIMA® + everolimus

Regular check-ins with your patients help inform you of any ARs that may need to be managed[1]

- Decreased appetite
- Decreased weight
- Diarrhea
- Fatigue
- Hypertension
- Nausea
- Proteinuria

This is not an all-inclusive list of ARs that may occur with LENVIMA. For more information, please see accompanying full Prescribing Information.

AR=adverse reaction.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

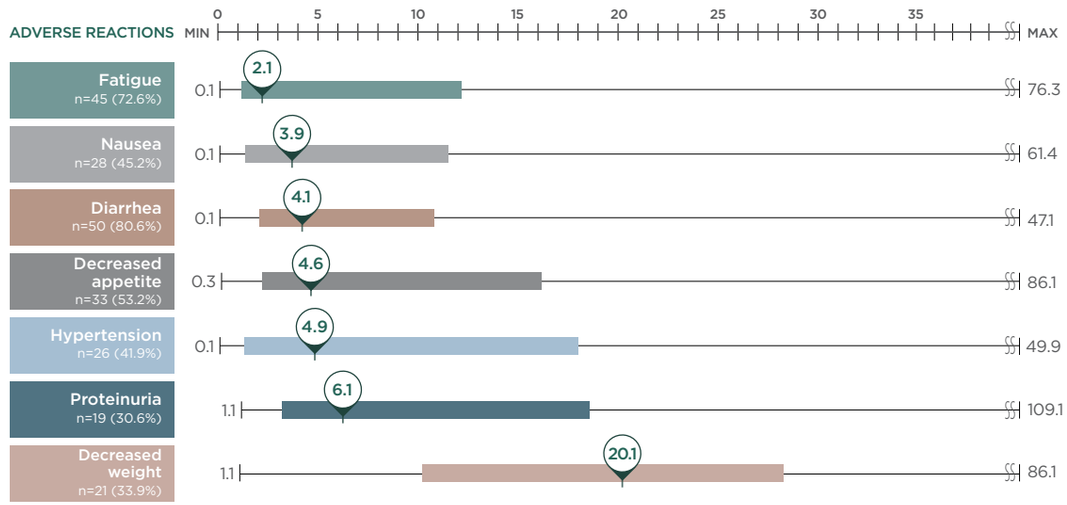
Proteinuria. In DTC and HCC, proteinuria was reported in 34% and 26% of LENVIMA-treated patients, respectively. Grade 3 proteinuria occurred in 11% and 6% in DTC and HCC, respectively. In RCC, proteinuria occurred in 31% of patients receiving LENVIMA + everolimus (8% grade 3). Monitor for proteinuria 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.

Diarrhea. Of the 737 LENVIMA-treated patients in DTC and HCC, diarrhea occurred in 49% (6% grade 3). In RCC, diarrhea occurred in 81% of LENVIMA + everolimus–treated patients (19% grade 3). Diarrhea was the most frequent cause of dose interruption/reduction, and diarrhea recurred despite dose reduction. Promptly initiate management of diarrhea. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Monitor Select ARs That May Occur With LENVIMA + everolimus

Post hoc analysis of time to first onset of select ARs[2]

- Identify points in treatment when ARs emerged with LENVIMA + everolimus in Study 205



Median weeks; (n=62)*

- Monitor your patients for ARs throughout treatment with LENVIMA + everolimus

Limitation: This is a post hoc exploratory analysis for descriptive purposes only; no conclusion can be drawn.

*The bar represents the time to first onset of select ARs for the middle 50% of the patients who experienced that AR from quartile 1 to 3.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

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.

Help Manage Select ARs: **Decreased Appetite**

PI-guided strategies to help manage decreased appetite[1]

Grade 2 (persistent or intolerable) or **Grade 3**

↓

Withhold until improved to grade 0 to 1, or baseline

↓

Resume at a reduced dose

Grade 4

↓

Permanently discontinue

AR=adverse reaction.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

QT Interval Prolongation. In DTC, QT/QTc interval prolongation occurred in 9% of LENVIMA-treated patients and QT interval prolongation of >500 ms occurred in 2%. 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 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 upon recovery based on severity

Hypocalcemia. In DTC, grade 3-4 hypocalcemia occurred in 9% of LENVIMA-treated patients. In 65% of cases, hypocalcemia improved or resolved following calcium supplementation with or without dose interruption or dose reduction. In RCC, grade 3-4 hypocalcemia occurred in 6% of LENVIMA + everolimus–treated patients. In HCC, grade 3 hypocalcemia occurred in 0.8% of LENVIMA-treated patients. 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 depending on severity.

Help Manage Select ARs: **Decreased Weight**

PI-guided strategies to help manage decreased weight[1]

Grade 2 (persistent or intolerable) or **Grade 3**

↓

Withhold until improved to grade 0 to 1, or baseline

↓

Resume at a reduced dose

CTCAE v4.0 does not define grade 4 decreased weight. Permanently discontinue for grade 4 adverse reactions.

CTCAE=Common Terminology Criteria for Adverse Events.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

Reversible Posterior Leukoencephalopathy Syndrome (RPLS). Across clinical studies of 1823 patients who received LENVIMA as a single agent, RPLS occurred in 0.3%. Confirm diagnosis of RPLS with MRI. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity and persistence of neurologic symptoms.

Help Manage Select ARs: **Diarrhea**

PI-guided strategies to help manage diarrhea[1]

Grade 2 (persistent or intolerable) or **Grade 3**

↓

Withhold until improved to grade 0 to 1, or baseline

↓

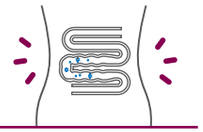
Resume at a reduced dose

Grade 4

↓

Permanently discontinue

Promptly initiate management of diarrhea. Withhold and resume at a reduced dose upon recovery, or permanently discontinue LENVIMA® based on severity.[1]



AR=adverse reaction.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

Hemorrhagic Events. Serious including fatal hemorrhagic events can occur with LENVIMA. In DTC, RCC, and HCC clinical trials, 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 DTC, grade 3-5 hemorrhage occurred in 2% of LENVIMA-treated patients, including 1 fatal intracranial hemorrhage among 16 patients who received LENVIMA and had CNS metastases at baseline. In RCC, grade 3-5 hemorrhage occurred in 8% of LENVIMA + everolimus–treated patients, including 1 fatal cerebral hemorrhage. In HCC, grade 3-5 hemorrhage occurred in 5% of LENVIMA-treated patients, including 7 fatal hemorrhagic events. Serious tumor-related bleeds, including fatal hemorrhagic events, occurred in LENVIMA-treated patients in clinical trials and in the postmarketing setting. In postmarketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than other tumors. 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 (eg, carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Help Manage Select ARs: **Fatigue**

PI-guided strategies to help manage fatigue[1]

Grade 2 (persistent or intolerable) or **Grade 3**

↓

Withhold until improved to grade 0 to 1, or baseline

↓

Resume at a reduced dose

CTCAE v4.0 does not define grade 4 fatigue.
Permanently discontinue for grade 4 adverse reactions.

CTCAE=Common Terminology Criteria for Adverse Events.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction. 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 HCC 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.

Help Manage Select ARs: **Hypertension**

PI-guided strategies to help manage hypertension[1]

Control blood pressure prior to initiating treatment

Monitor
Educate patients on importance of self-monitoring (in addition to regular in-office monitoring)

After 1 week of treatment → Every 2 weeks for first 2 months → At least monthly during treatment

Grade 3

Withhold for grade 3 that persists despite optimal antihypertensive therapy

Resume at reduced dose when hypertension is controlled at ≤grade 2

Grade 4

Permanently discontinue

AR=adverse reaction.

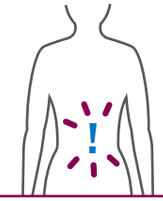
Help Manage Select ARs: **Nausea**

PI-guided strategies to help manage nausea[1]

Grade 2 (persistent or intolerable) or **Grade 3**

Withhold until improved to grade 0 to 1, or baseline

Resume at a reduced dose



CTCAE v4.0 does not define grade 4 nausea.
Permanently discontinue for grade 4 adverse reactions.

CTCAE=Common Terminology Criteria for Adverse Events.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

Osteonecrosis of the Jaw (ONJ). ONJ has been reported in patients receiving LENVIMA. 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 and to consider having preventive dentistry performed prior to treatment with LENVIMA and throughout treatment with LENVIMA.

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.

Help Manage Select ARs: **Proteinuria**

PI-guided strategies to help manage proteinuria[1]

Monitor
For proteinuria prior to starting treatment and periodically during treatment

If ≥2+ g/24 hr on urine dipstick

↓

Obtain 24-hour urine protein sample

↓

Withhold for >2 g/24 hr

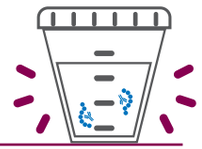
↓

Resume at reduced dose upon recovery or permanently discontinue based on severity

For nephrotic syndrome
Disorder characterized by symptoms that include severe edema, proteinuria, and hypoalbuminemia; it is indicative of renal dysfunction[5]

↓

Permanently discontinue



AR=adverse reaction.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

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 30 days after the last dose.

Dose Modifications for LENVIMA®

If your patients are experiencing ARs, you may be able to help them manage their ARs with an established plan for dose reductions, dose interruptions, and/or discontinuation of treatment

Dose reductions or interruptions with LENVIMA + everolimus in Study 205

- ARs led to dose reductions or interruptions in 89% of patients receiving LENVIMA + everolimus[1]
- The most common ARs (≥5%) resulting in dose reductions in the LENVIMA + everolimus–treated group were diarrhea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%)[1]

Treatment discontinuations with LENVIMA + everolimus in Study 205

- Treatment discontinuation due to ARs occurred in 29% of patients taking LENVIMA + everolimus[1]
- The most common ARs (≥1%) resulting in discontinuation of LENVIMA + everolimus were thrombocytopenia (4%), alanine aminotransferase increased (2%), arthralgia (2%), aspartate aminotransferase increased (2%), cerebral hemorrhage (2%), confusional state (2%), convulsion (2%), diarrhea (2%), dyspnea (2%), gastric hemorrhage (2%), hepatic pain (2%), hyperkalemia (2%), hypokalemia (2%), penile edema (2%), proteinuria (2%), and weight decreased (2%)[2]

SELECTED SAFETY INFORMATION

Adverse Reactions
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 (48%), nausea (45%), stomatitis (44%), hypertension (42%), peripheral edema (42%), cough (37%), abdominal pain (37%), dyspnea (35%), rash (35%), decreased weight (34%), hemorrhagic events (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 dyspnea (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 (6%), vomiting (6%), nausea (5%), and proteinuria (5%). Treatment discontinuation due to an adverse reaction occurred in 29% of patients.

How to Dose Modify With 2 Therapies[1,a]

Recommended LENVIMA dose	1st dosage reduction to	2nd dosage reduction to[b]	3rd dosage reduction to[b]
 **18 mg** ONCE DAILY (one 10-mg capsule + two 4-mg capsules)	 **14 mg** ONCE DAILY (one 10-mg capsule + one 4-mg capsule)	 **10 mg** ONCE DAILY (one 10-mg capsule)	 **8 mg** ONCE DAILY (two 4-mg capsules)

Capsules pictured are not actual size.

Review the full Prescribing Information for everolimus for recommended dosing information and dose modifications [1,c]

For toxicities thought to be related to		
	Everolimus alone	Modify the everolimus dose in accordance with the everolimus Package Insert
	OR	
	LENVIMA + everolimus	First reduce LENVIMA and then everolimus

Proactively plan to manage nausea, vomiting, or diarrhea with concomitant medications as necessary prior to interruption or dose reduction of LENVIMA.

- ARs led to dose reductions and interruption in 89% of patients receiving LENVIMA + everolimus[1]
- Treatment discontinuation due to ARs occurred in 29% of patients receiving LENVIMA + everolimus[1]

Recommended dose of LENVIMA for renal or hepatic impairment[1]

- No dose adjustment is recommended in patients with mild or moderate renal or hepatic impairment. Patients with end-stage renal disease were not studied

In patients with:	Recommended dose:
Severe renal impairment (CrCl <30 mL/min)[d]	**10 mg (one 10-mg capsule) once daily**
Severe hepatic impairment (Child-Pugh C)	**10 mg (one 10-mg capsule) once daily**

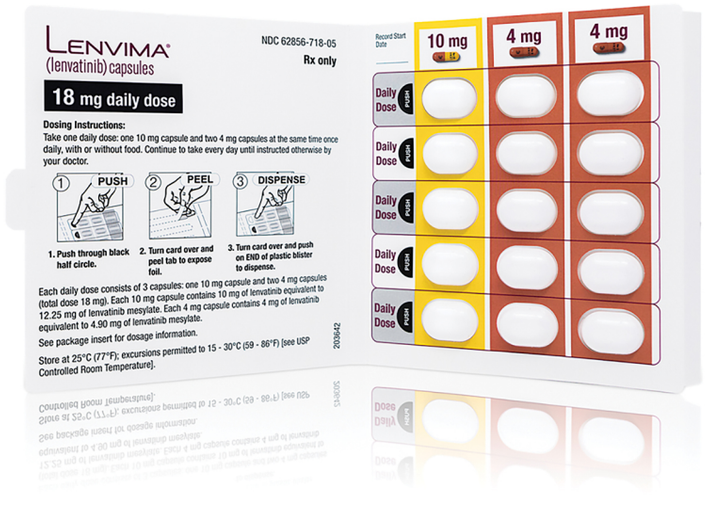
AR=adverse reaction; CrCl=creatinine clearance.
[a]Reduce dose in succession based on the previous dose level (18 mg, 14 mg, 10 mg, or 8 mg per day).
[b]Refers to the same or a different adverse reaction that requires dose modification.
[c]Refer to everolimus Prescribing Information for additional dose modification information.
[d]As calculated by the Cockcroft-Gault equation.

SELECTED SAFETY INFORMATION

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

You Can Modify Dosage With the Existing Blister Pack[1]

Every pack of LENVIMA includes a 30-day treatment supply consisting of 6 individual blister cards. Each blister card contains a 5-day supply. Patients will receive a pack specific to their prescribed dose.



For example, if reducing the dose of LENVIMA from 18 mg to 14 mg, have your patient take one 10-mg capsule and one 4-mg capsule once daily. The recommended reduced dosages for advanced RCC are 14 mg, 10 mg, and 8 mg.*

Two separate prescriptions are required for the combination

Everolimus is not distributed by Eisai Inc.
*The safety data are derived from Study 205 and an additional 11 patients in the dose escalation portion of the study who received LENVIMA 18 mg + everolimus 5 mg.[1]

SELECTED SAFETY INFORMATION

Use in Specific Populations (cont'd)
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, RCC, or EC (endometrial carcinoma) and severe (CLcr 15-29 mL/min) renal impairment. Reduce the dose for patients with DTC, RCC, or EC and severe renal impairment. There is no recommended dose for patients with HCC and severe renal impairment. LENVIMA has not been studied in patients with end-stage renal disease.

No dose adjustment is recommended for patients with HCC and mild hepatic impairment (Child-Pugh A). There is no recommended dose for patients with HCC with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with DTC, RCC, or EC and mild or moderate hepatic impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or EC and severe hepatic impairment. Reduce the dose for patients with DTC, RCC, or EC and severe hepatic impairment.

ACCESS AND SUPPORT INFORMATION

For Patients Prescribed LENVIMA®

Eisai Patient Support

Eisai Patient Support offers access and reimbursement support for patients. By contacting Eisai Patient Support, patients can get help understanding their coverage for LENVIMA through a benefits investigation. They can also request a patient welcome kit. The Patient Assistance Program also provides LENVIMA at no cost to eligible patients with financial need.

Eisai Patient Support

LENVIMA Co-Pay Program

With the LENVIMA Co-Pay Program, eligible commercially insured patients may pay as little as $0 per month.* Annual limits apply. Depending on the insurance plan, patients could have additional financial responsibility. See **www.LENVIMAREIMBURSEMENT.com/hcp** for complete terms and conditions. For assistance, call 1-855-347-2448 or visit **www.LENVIMACopay.com** to enroll eligible patients.

*Not available to patients enrolled in state or federal healthcare programs, including Medicare, Medigap, VA, DoD, or TRICARE.

LENVIMA Dose Exchange Program

Through the LENVIMA Dose Exchange Program, eligible patients that require a dose reduction may exchange qualifying doses. For additional information, including complete terms and conditions, please visit **EisaiReimbursement.com**.

Please visit
www.LENVIMAREIMBURSEMENT.com/hcp
or call **1-866-61-EISAI (1-866-613-4724)**
for more information about access and reimbursement

References: 1. LENVIMA [package insert]. Nutley, NJ: Eisai Inc. **2.** Data on file. Eisai Inc. **3.** Motzer RJ, Hutson TE, Ren M, Dutcus C, Larkin J. Independent assessment of Lenvatinib plus everolimus in patients with metastatic renal cell carcinoma. *Lancet Oncol.* 2016;17(1):e4-e5. **4.** Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247. **5.** Kodner C. Diagnosis and management of nephrotic syndrome in adults. *Am Fam Physician.* 2016;93(6):479-485.

Please visit **https://us.eisai.com/RequiredPriceDisclosures** for price disclosure information

Please see Selected Safety Information throughout and full Prescribing Information.

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LENV-US9682

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg