Help your patients along their treatment journey

AR management plan for the LENVIMA® treatment journey

*For the treatment of **RAI-refractory Differentiated Thyroid Cancer***

RECOGNIZE ARs that may occur with LENVIMA

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

MONITOR ARs that may occur with LENVIMA

Identify points in treatment when ARs emerged in the SELECT study, so you can provide timely management

MANAGE ARs that may occur with LENVIMA

Consider ways to approach ARs to help your patients on treatment

RAI=radioactive iodine; AR=adverse reaction; SELECT=**S**tudy of (**E**7080) **LE**nvatinib in Differentiated **C**ancer of the **T**hyroid.

INDICATION

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

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 accompanying full Prescribing Information.

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

The only NCCN category 1 preferred first-line systemic therapy option

NCCN GUIDELINES® | **PREFERRED** FIRST-LINE SYSTEMIC THERAPY OPTION (NCCN CATEGORY 1)

Lenvatinib (LENVIMA®): THE ONLY NCCN CATEGORY 1 PREFERRED FIRST-LINE SYSTEMIC THERAPY OPTION by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for the treatment of locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (RAI-refractory DTC)*†

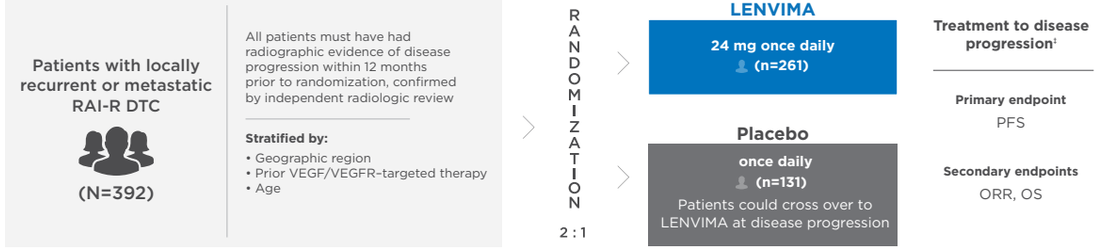
- **Category 1** recommendation is based on high-level evidence. There is uniform NCCN consensus that the intervention is appropriate

*Preferred intervention=interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

†Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Thyroid Carcinoma V.3.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed July 18, 2024. 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.

The SELECT study design

A phase 3, multicenter, randomized, double-blind, placebo-controlled trial in patients with locally recurrent, or metastatic RAI-R DTC[1]



NCCN=National Comprehensive Cancer Network® (NCCN®).
SELECT=**S**tudy of (**E**7080) **LE**nvatinib in Differentiated **C**ancer of the **T**hyroid; RAI-R=radioactive iodine-refractory; DTC=differentiated thyroid cancer; VEGF=vascular endothelial growth factor; VEGFR=vascular endothelial growth factor receptor; PFS=progression-free survival; ORR=objective response rate; OS=overall survival; RECIST=Response Evaluation Criteria In Solid Tumors; CI=confidence interval; NE=not estimable; HR=hazard ratio; PR=partial response; CR=complete response.

‡Determined by blinded, independent, radiologic review using RECIST version 1.1.
§Assessed by independent radiologic review according to RECIST v1.1; ORR=sum of CR and PR.[1-3]
‖CR=disappearance of all target and nontarget lesions.[3]
¶PR=30% or greater decrease in the sum of diameters of target lesions.[3]
#According to the Cochran-Mantel-Haenszel chi-square test.

SELECTED SAFETY INFORMATION

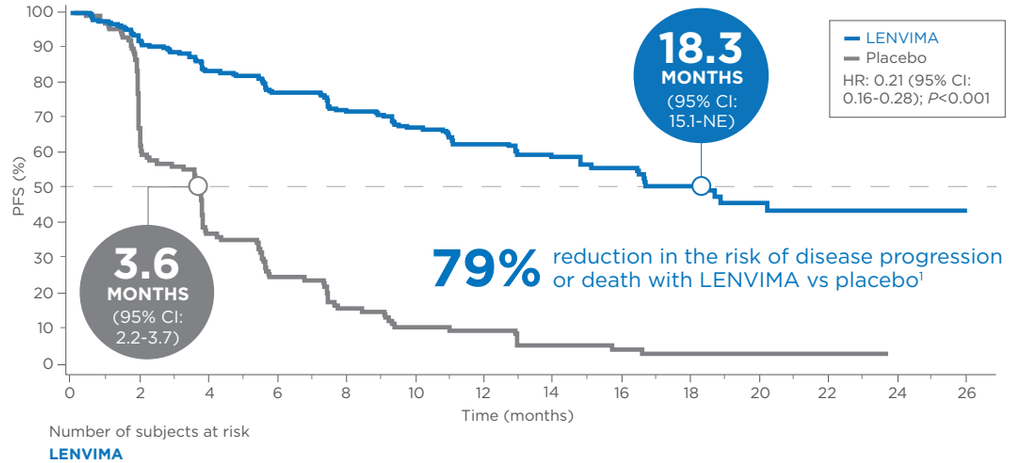
Warnings and Precautions (cont'd)

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.

PRIMARY ENDPOINT

Superior PFS benefit[1]

Median PFS: 18.3 months with LENVIMA vs 3.6 months with placebo



Number of subjects at risk

LENVIMA	**261**	**225**	**198**	**176**	**159**	**148**	**136**	**92**	**66**	**44**	**24**	**11**	**3**	**0**
Placebo	131	71	43	29	19	13	11	5	4	2	2	2	0	0

- 107 events (41%) occurred in the LENVIMA arm vs 113 events (86%) in the placebo arm[1]
  - 93 patients (36%) who received LENVIMA progressed vs 109 patients (83%) who received placebo
  - Death occurred in 14 patients (5%) who received LENVIMA vs 4 patients (3%) who received placebo

SECONDARY ENDPOINTS

Superior response[1,2]

- 65% ORR§ with LENVIMA (including 2% CR‖)[1,2]
  - 65% ORR: (95% CI: 59%-71%) (63% PR,¶ 2% CR) vs 2% ORR with placebo (95% CI: 0%-4%) (2% PR, 0% CR) (no CR); *P*<0.001#

Median OS was not estimable at data cutoff (HR: 0.73 [95% CI: 0.50-1.07]; *P*=0.10)[1]

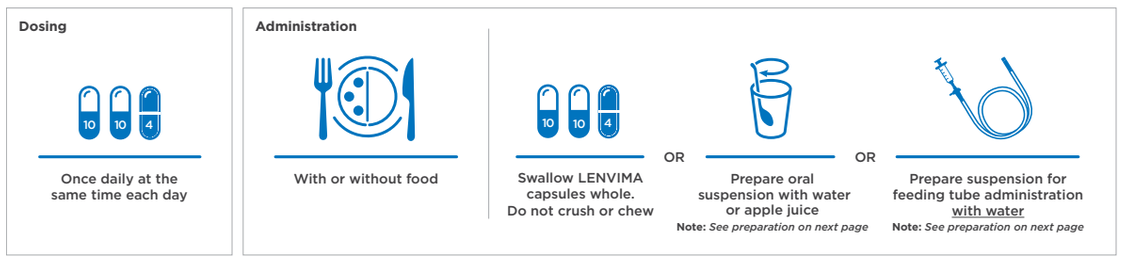
- 83% (109/131) of placebo-treated patients with confirmed disease progression crossed over to receive LENVIMA in the open-label extension phase (data cutoff: November 15, 2013)[1,2]

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.

Once a day. Every day. With or without food[1]



Capsules pictured are not actual size.

The recommended dose of LENVIMA® for RAI-R DTC is **24 mg (two 10-mg capsules and one 4-mg capsule)** taken once a day, with or without food[1]:

- Continue LENVIMA until disease progression or until unacceptable toxicity
- LENVIMA should be taken at the same time each day. 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
- LENVIMA is available as 10-mg and 4-mg capsules

RAI=radioactive iodine.

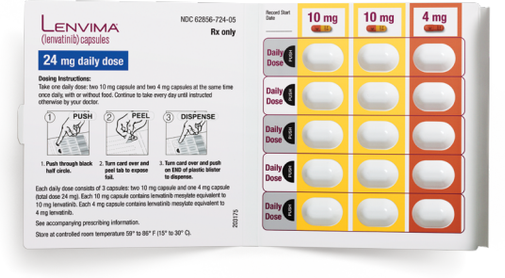
Preparation of suspension[1]:

- 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).

LENVIMA capsules are supplied in cartons of 6 blister cards. Each carton contains a 30-day supply of LENVIMA capsules[1]



Patients will receive a dosing card specific to their prescribed dose.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

Arterial Thromboembolic Events (cont'd). 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.

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.

Recognize ARs that may occur with LENVIMA®

Adverse reactions in the SELECT trial[1]

Most common ARs (≥30%) observed in LENVIMA-treated patients

- Hypertension (73%), fatigue (67%), diarrhea (67%), arthralgia/myalgia (62%), decreased appetite (54%), decreased weight (51%), nausea (47%), stomatitis (41%), headache (38%), vomiting (36%), proteinuria (34%), palmar-plantar erythrodysesthesia syndrome (32%), abdominal pain (31%), and dysphonia (31%)

Most common serious ARs (≥2%) in the LENVIMA arm

- Pneumonia (4%), hypertension (3%), and dehydration (3%)

Most common Grade 3-4 ARs (≥5%)[1]

Adverse reactions included in this table have a between-group difference of ≥2% (Grade 3-4)

Adverse reaction	LENVIMA 24 mg (n=261)	Placebo (n=131)
Hypertension[a]	44%	4%
Decreased weight	13%	1%
Fatigue[b]	11%	4%
Proteinuria	11%	0%
Diarrhea	9%	0%
Decreased appetite	7%	1%
Arthralgia/myalgia[c]	5%	3%
Stomatitis[d]	5%	0%

No Grade 4 diarrhea, hand-foot skin reaction, fatigue, or proteinuria.[4]

- No overall differences in safety or effectiveness were observed between older patients (≥65 years) and younger patients[1]
- Clinically important adverse reactions occurring more frequently in LENVIMA-treated patients than patients receiving placebo, but with an incidence of <5% were pulmonary embolism (3%, including fatal reports vs 2%, respectively) and osteonecrosis of the jaw (0.4% vs 0%, respectively)[1]

RAI=radioactive iodine; ARs=adverse reactions; SELECT=**S**tudy of (**E**7080) **LE**nvatinib in Differentiated **C**ancer of the **T**hyroid.

[a]Includes hypertension, hypertensive crisis, increased blood pressure diastolic, and increased blood pressure.
[b]Includes asthenia, fatigue, and malaise.
[c]Includes musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia.
[d]Includes aphthous stomatitis, stomatitis, glossitis, mouth ulceration, and mucosal inflammation.

LENVIMA AR profile[1]

Adverse reactions occurring in patients with a between-group difference of ≥5% (all grades) or ≥2% (Grade 3-4) in SELECT

		LENVIMA 24 mg (n=261)		Placebo (n=131)	
Adverse reaction		**All grades (%)**	**Grade 3-4 (%)**	**All grades (%)**	**Grade 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

[a]Includes hypertension, hypertensive crisis, increased blood pressure diastolic, and increased blood pressure.
[b]Includes aphthous stomatitis, stomatitis, glossitis, mouth ulceration, and mucosal inflammation.
[c]Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal pain.
[d]Includes oral pain, glossodynia, and oropharyngeal pain.
[e]Includes asthenia, fatigue, and malaise.
[f]Includes musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia.

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.

Recognize ARs that may occur with LENVIMA®

LENVIMA AR profile (cont'd)[1]

Adverse reactions occurring in patients with a between-group difference of ≥5% (all grades) or ≥2% (Grade 3-4) in SELECT

		LENVIMA 24 mg (n=261)		Placebo (n=131)	
Adverse reaction		**All grades (%)**	**Grade 3-4 (%)**	**All grades (%)**	**Grade 3-4 (%)**
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 syndrome	32	3	1	0
	Rash[a]	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	Insomnia	12	0	3	0
Infections	Urinary tract infection	11	1	5	0
	Dental and oral infections[b]	10	1	1	0
Cardiac	Prolonged electrocardiogram QT	9	2	2	0

RAI=radioactive iodine; SELECT=**S**tudy of (**E**7080) **LE**nvatinib in Differentiated **C**ancer of the **T**hyroid; ALT=alanine aminotransferase; AST=aspartate aminotransferase.

[a]Includes macular rash, maculo-papular rash, generalized rash, and rash.
[b]Includes gingivitis, oral infection, parotitis, pericoronitis, periodontitis, sialadenitis, tooth abscess, and tooth infection.

Grade 3-4 laboratory abnormalities[1,a,b]

With a difference ≥2% in Grade 3-4 events and at a higher incidence in patients treated with LENVIMA in SELECT

		LENVIMA 24 mg (n=258)	Placebo (n=131)
Laboratory abnormality		**Grade 3-4 (%)**	**Grade 3-4 (%)**
Chemistry	Hypocalcemia	9	2
	Hypokalemia	6	1
	AST increased	5	0
	ALT increased	4	0
	Lipase increased	4	1
	Creatinine increased	3	0
Hematology	Thrombocytopenia	2	0

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

[a]With at least 1 grade increase from baseline.
[b]Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post baseline laboratory measurement for each parameter. LENVIMA (n=253 to 258), placebo (n=129 to 131).

SELECTED SAFETY INFORMATION

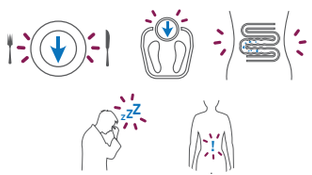
Warnings and Precautions (cont'd)

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.

Help your patients along their treatment journey

Summary of the PI-guided AR management plan

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

AR	Severity[a]	Dose modifications for LENVIMA
Hypertension 	Grade 3	• Withhold for Grade 3 that persists despite optimal antihypertensive therapy • Resume at reduced dose when hypertension is controlled at less than or equal to Grade 2
	Grade 4	• Permanently discontinue
Proteinuria 	2 g or greater proteinuria in 24 hours	• Withhold until less than or equal to 2 grams of proteinuria per 24 hours • Resume at a reduced dose • Permanently discontinue for nephrotic syndrome
Other select ARs (includes decreased appetite, decreased weight, diarrhea, fatigue, and nausea) 	Persistent or intolerable Grade 2 or 3 AR Grade 4 laboratory abnormality	• Withhold until improves to Grade 0 to 1 or baseline • Resume at a reduced dose
	Grade 4 AR	• Permanently discontinue

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

RAI=radioactive iodine; PI=prescribing information; ARs=adverse reactions; SELECT=**S**tudy of (**E**7080) **LE**nvatinib in Differentiated **C**ancer of the **T**hyroid.

SELECTED SAFETY INFORMATION

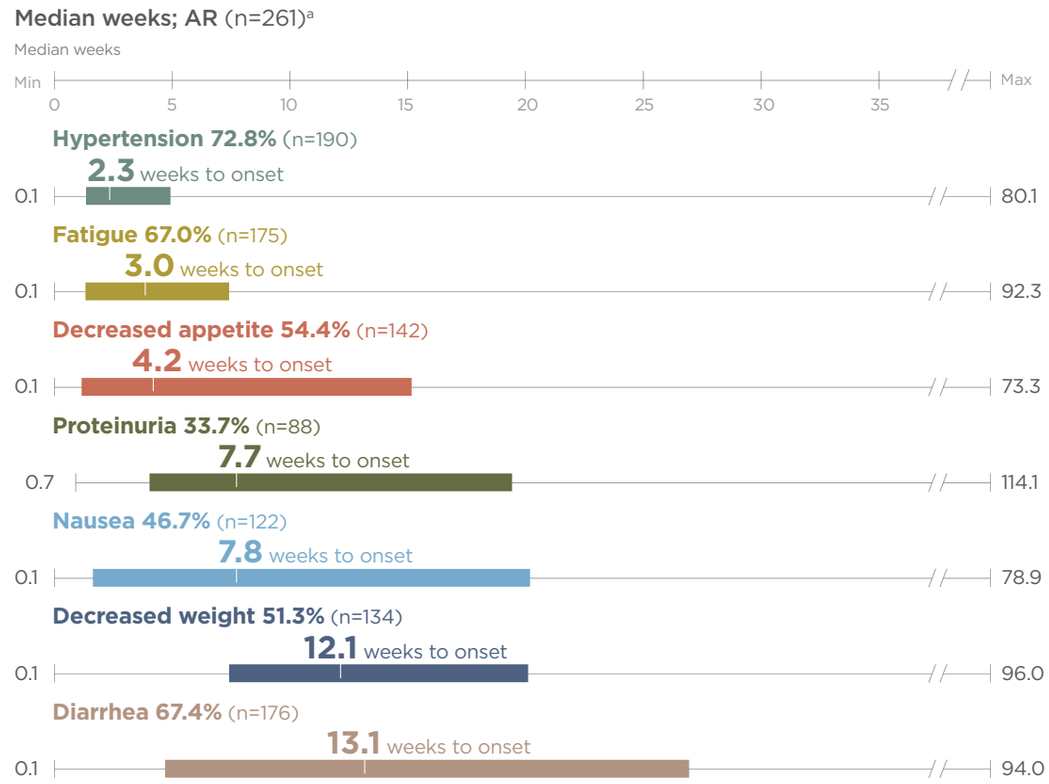
Warnings and Precautions (cont'd)

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.

Monitor certain ARs that may occur with LENVIMA®

Post hoc analysis of time to first onset of certain ARs[5]

- Identify points in treatment when ARs emerged with LENVIMA in the SELECT trial



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

[a]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)

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%.

Help manage diarrhea and decreased appetite with PI-guided strategies[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]

Help manage fatigue, nausea, and decreased weight with PI-guided strategies[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, nausea, and decreased weight. Permanently discontinue for Grade 4 adverse reactions.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

QT Interval Prolongation (cont'd). 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.

Help manage proteinuria with PI-guided strategies[1]

Monitor
For proteinuria prior to starting treatment and periodically during treatment

If ≥2+ g/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[6]

↓

Permanently discontinue

RAI=radioactive iodine; PI=prescribing information; CTCAE=Common Terminology Criteria for Adverse Events.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

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 hypertension with PI-guided strategies[1]

Control BP prior to initiating treatment with LENVIMA®

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	Grade 4
Withhold for Grade 3 that persists despite optimal antihypertensive therapy	**Permanently discontinue**
Resume at reduced dose when hypertension is controlled at ≤Grade 2	

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

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.

Recommended dose and dose modifications[1]

Interrupt, reduce and/or discontinue LENVIMA based on type and/or severity (grade) of adverse reaction

Recommended dose	1st dosage reduction to[a]	2nd dosage reduction to[a]	3rd dosage reduction to[a]
			
24 mg Once daily (two 10-mg capsules + one 4-mg capsule)	**20 mg** Once daily (two 10-mg capsules)[a]	**14 mg** Once daily (one 10-mg capsule + one 4-mg capsule)[a]	**10 mg** Once daily (one 10-mg capsule)[a]

Capsules pictured are not actual size.

[a]Reduce dose in succession based on the previous dose level (20 mg, 14 mg, or 10 mg per day).

Dose reductions in the SELECT trial[1]

- In SELECT, ARs led to dose reductions in 68% of patients receiving LENVIMA
- The most common ARs (≥10%) resulting in dose reductions of LENVIMA were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%)

Treatment discontinuations in the SELECT trial[1]

- Treatment discontinuation due to ARs occurred in 18% of patients taking LENVIMA
- The most common ARs that led to discontinuation in the LENVIMA-treated group were hypertension (1%) and asthenia (1%)

Dose adjustments for renal or hepatic impairment

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

In patients with:	Recommended dose:
Severe renal impairment (CrCl <30 mL/min)[a]	14 mg (one 10-mg capsule + one 4-mg capsule) once daily
Severe hepatic impairment (Child-Pugh C)	14 mg (one 10-mg capsule + one 4-mg capsule) once daily

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

RAI=radioactive iodine; PI=prescribing information; BP=blood pressure; AR=adverse reaction; CrCl=creatinine clearance.

*Mild renal impairment is defined as CrCl 60-89 mL/min and moderate renal impairment is defined as CrCl 30-59 mL/min. Mild and moderate hepatic impairment is defined as Child-Pugh A and Child-Pugh B, respectively.
[a]As calculated by the Cockcroft-Gault equation.

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.

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.

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.

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.

SELECTED SAFETY INFORMATION

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 (54%), 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 asthenia (1%).

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.

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.

References: 1. LENVIMA [package insert]. Nutley, NJ: Eisai Inc. **2.** Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med*. 2015;372(7):621-630. **3.** 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. **4.** Haddad RI, Schlumberger M, Wirth LJ, et al. Incidence and timing of common adverse events in lenvatinib-treated patients from the SELECT trial and their association with survival outcomes. *Endocrine*. 2017;56(1):121-128. **5.** Data on file, Eisai Inc. **6.** Kodner C. Diagnosis and management of nephrotic syndrome in adults. *Am Fam Physician*. 2016;93(6):479-485.

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.EisaiPatientSupport.com/HCP/LENVIMA** 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

Eisai cannot guarantee payment of any claim. Coding, coverage, and reimbursement may vary significantly by payer, plan, patient, and setting of care. Actual coverage and reimbursement decisions are made by individual payers following the receipt of claims. For additional information, customers should consult with their payers for all relevant coding, reimbursement, and coverage requirements. It is the sole responsibility of the provider to select the proper code and ensure the accuracy of all claims used in seeking reimbursement. All services must be medically appropriate and properly supported in the patient medical record.

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

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

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg