



DOSING AND ADVERSE REACTION MANAGEMENT GUIDE

For LENVIMA[®]

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 trial, 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=Study of (E7080) LENVatinib in Differentiated Cancer of the Thyroid.

INDICATION

LENVIMA is indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (RAI-refractory 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 full [Prescribing Information](#).



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

Lenvatinib (LENVIMA®) is the only category 1 preferred first-line systemic therapy option by the National Comprehensive Cancer Network® (NCCN®) for locally recurrent or metastatic, progressive radioactive iodine-refractory differentiated thyroid cancer*

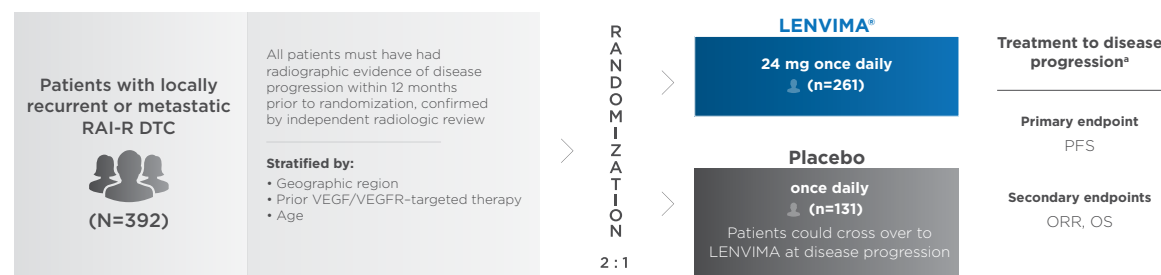


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†Category 1 recommendation is based on high-level evidence. There is uniform NCCN consensus that the intervention is appropriate.

The SELECT trial design

A phase 3, multicenter, randomized, double-blind, placebo-controlled trial in patients with locally recurrent, or metastatic RAI-R DTC¹



SELECT=Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid; 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.

¹Determined by blinded, independent, radiologic review using RECIST version 1.1.

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.

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.

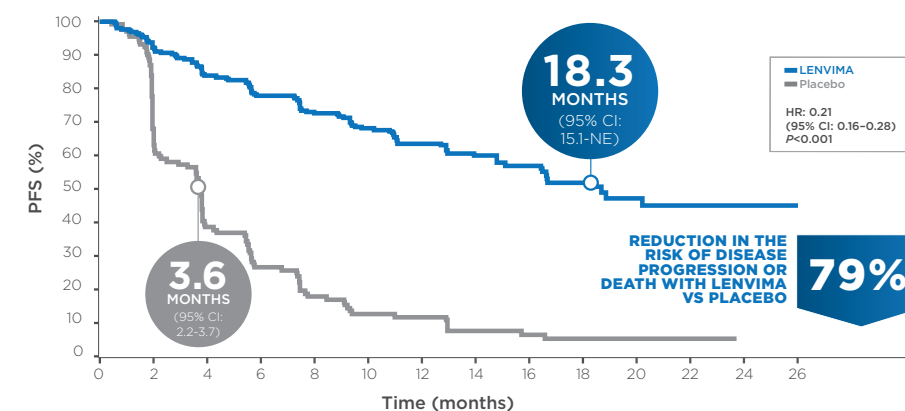
Among patients receiving LENVIMA with pembrolizumab, arterial thrombotic events of any severity occurred in 5% of patients in CLEAR, including myocardial infarction (3.4%) and cerebrovascular accident (2.3%).

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

PRIMARY ENDPOINT

Superior PFS benefit¹

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



Number of subjects at risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26
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 arm¹
 - 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 ENDPOINT

Superior response^{1,2}

- 65% ORR^a with LENVIMA (including 2% CR^b)^{1,2}
 - 65% ORR: (95% CI: 59%-71%) (63% PR, 2% CR) vs 2% ORR (95% CI: 0%-4%) (2% PR, 0% CR) with placebo (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}

CI=confidence interval; HR=hazard ratio; PR=partial response.

^aObjective response rate (ORR)=sum of CR and PR.^{1,3}

^bComplete response (CR)=disappearance of all target and nontarget lesions.³

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

Arterial Thromboembolic Events (cont'd). 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.

Once a Day. Every Day. With or Without Food¹

Orally, once daily, at the same time each day
Capsules pictured are not actual size



With or without food



Swallowed whole with water or dissolved in a tablespoon of water or apple juice

Recommended dose: **24 mg (two 10-mg capsules and one 4-mg capsule)** taken orally once a day, every day, with or without food¹

- 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

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

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.

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.

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 $\geq 2+$ is detected, obtain a 24-hour urine protein. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

For patients who have difficulty swallowing capsules whole

- LENVIMA capsules can be dissolved in a small glass of liquid. Patients should measure 1 tablespoon of water or apple juice and put the capsules into the liquid without breaking or crushing them. The capsules should be left in the liquid for at least 10 minutes. Patients should stir for at least 3 minutes, then they may drink the mixture. After drinking, patients should add the same amount (1 tablespoon) of water or apple juice to the glass and swirl the contents a few times before swallowing the additional liquid

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



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

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.

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, 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.

Recognize ARs That May Occur With LENVIMA®

Adverse reactions in the SELECT trial

Most common ARs (≥30%) observed in LENVIMA-treated patients¹

- 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 arm¹

- 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

RAI=radioactive iodine; AR=adverse reaction; SELECT=Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid.

^aIncludes hypertension, hypertensive crisis, increased blood pressure diastolic, and increased blood pressure.

^bIncludes asthenia, fatigue, and malaise.

^cIncludes musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia.

^dIncludes aphthous stomatitis, stomatitis, glossitis, mouth ulceration, and mucosal inflammation.

LENVIMA AR profile¹

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

Adverse reaction	LENVIMA 24 mg (n=261)		Placebo (n=131)	
	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

^aIncludes hypertension, hypertensive crisis, increased blood pressure diastolic, and increased blood pressure.

^bIncludes aphthous stomatitis, stomatitis, glossitis, mouth ulceration, and mucosal inflammation.

^cIncludes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal pain.

^dIncludes oral pain, glossodynia, and oropharyngeal pain.

^eIncludes asthenia, fatigue, and malaise.

^fIncludes musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia.

Recognize ARs That May Occur With LENVIMA®

Adverse reactions occurring in patients with a between-group difference of $\geq 5\%$ (all grades) or $\geq 2\%$ (grade 3-4) in SELECT¹

Adverse reaction	LENVIMA 24 mg (n=261)		Placebo (n=131)	
	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=Study of (E7080) LENVIMA in Differentiated Cancer of the Thyroid.

^aIncludes macular rash, maculo-papular rash, generalized rash, and rash.

^bIncludes gingivitis, oral infection, parotitis, pericoronitis, periodontitis, sialadenitis, tooth abscess, and tooth infection.

Grade 3-4 laboratory abnormalities

With a difference $\geq 2\%$ in grade 3-4 events and at a higher incidence in patients treated with LENVIMA in SELECT^{1,a,b}

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

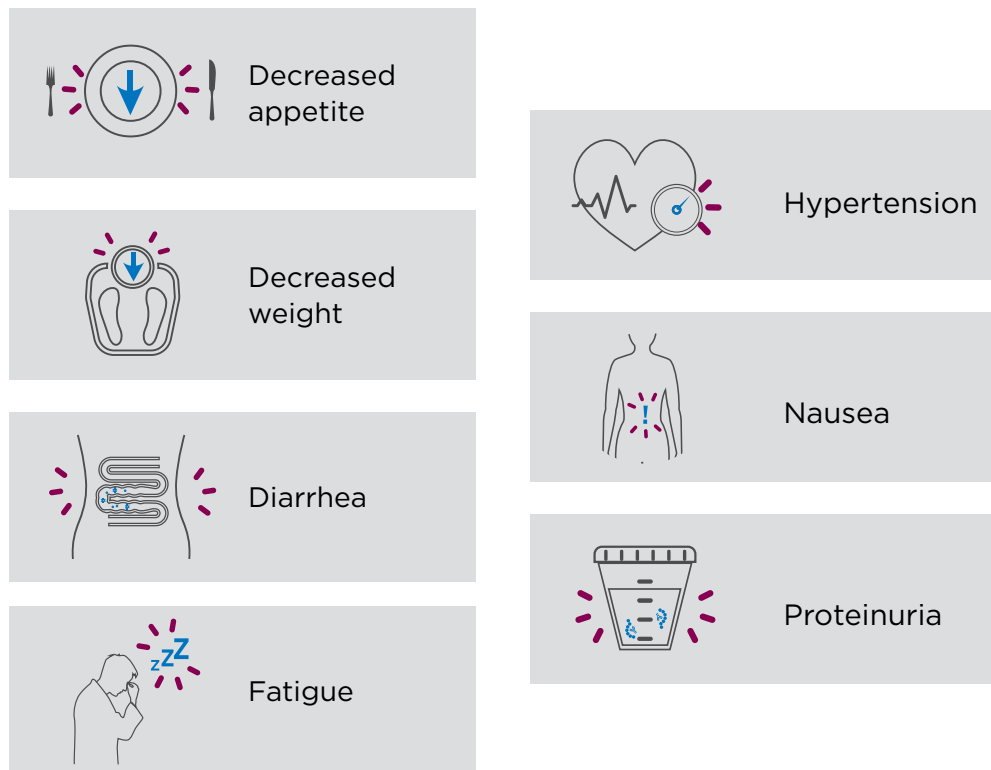
ALT=alanine aminotransferase; AST=aspartate aminotransferase.

^aWith at least 1 grade increase from baseline.

^bLaboratory 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).

Monitor Select ARs That May Occur With LENVIMA®

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



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

RAI=radioactive iodine; AR=adverse reaction.

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

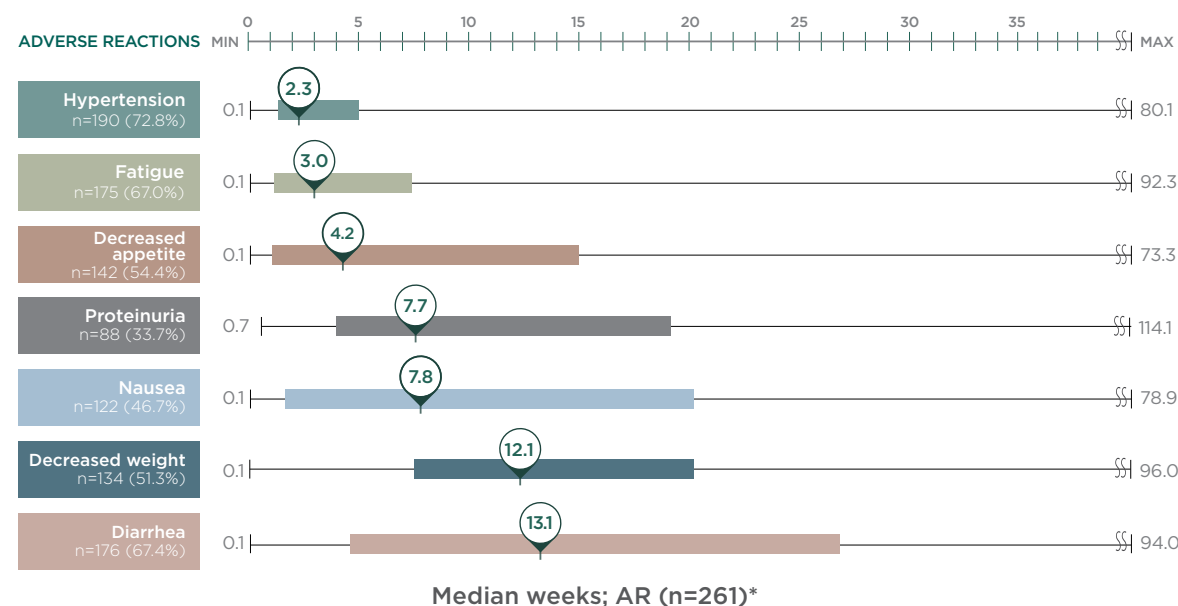
Hypocalcemia. In DTC, grade 3-4 hypocalcemia occurred in 9% of LENVIMA-treated patients. In 65% of cases, hypocalcemia improved or resolved following calcium supplementation with or without dose interruption or dose reduction. In RCC, grade 3-4 hypocalcemia occurred in 6% of LENVIMA + everolimus-treated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

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

Monitor Select ARs That May Occur With LENVIMA

Post hoc analysis of time to first onset of select ARs⁵

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



Monitor your patients for ARs throughout treatment with LENVIMA

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.

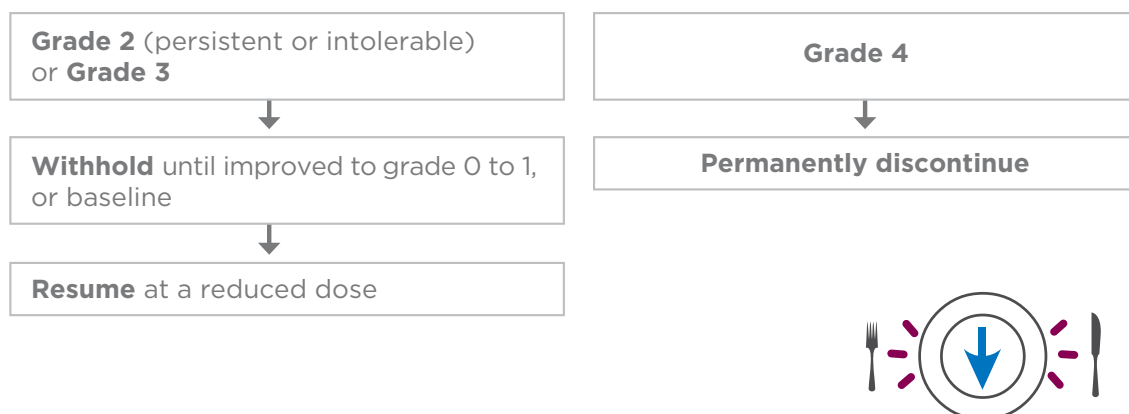
SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

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.

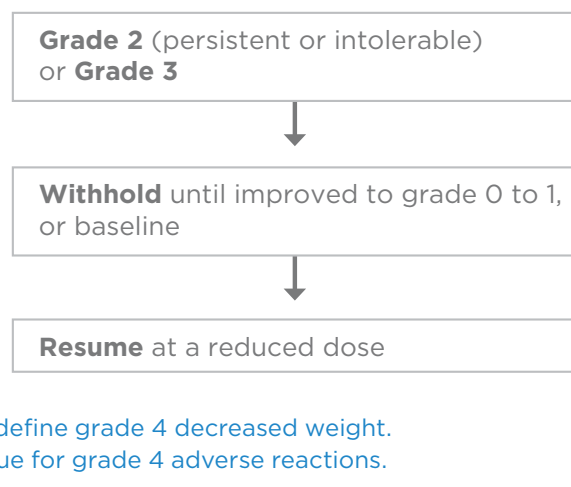
Help Manage Select ARs: **Decreased Appetite**

PI-guided strategies to help manage decreased appetite¹



Help Manage Select ARs: **Decreased Weight**

PI-guided strategies to help manage decreased weight¹

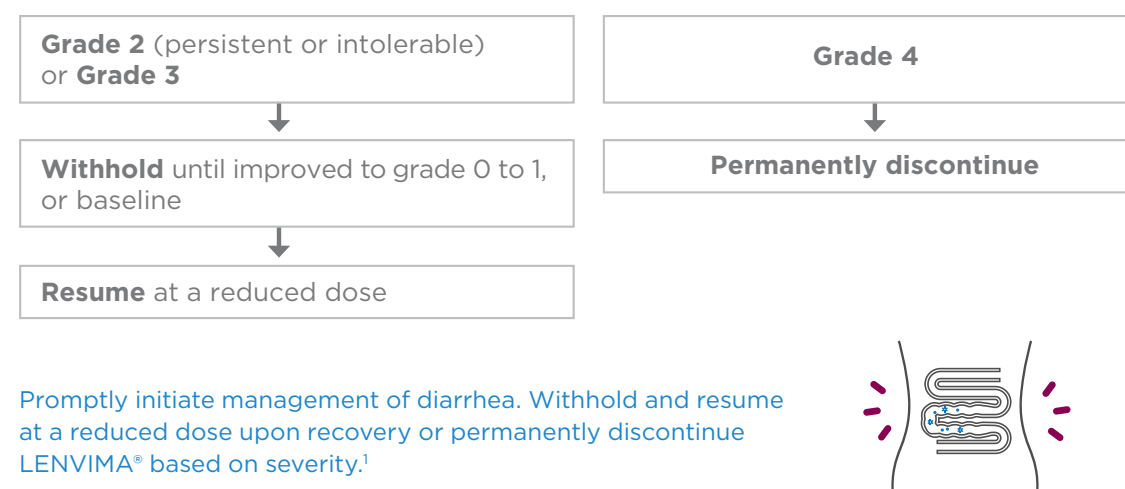


CTCAE v4.0 does not define grade 4 decreased weight. Permanently discontinue for grade 4 adverse reactions.

RAI=radioactive iodine; AR=adverse reaction; CTCAE=Common Terminology Criteria for Adverse Events.

Help Manage Select ARs: **Diarrhea**

PI-guided strategies to help manage diarrhea¹



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

SELECTED SAFETY INFORMATION

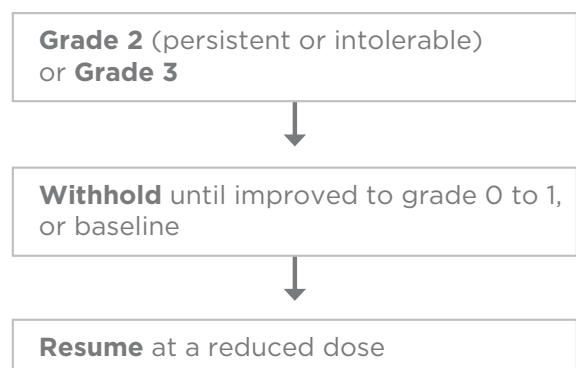
Warnings and Precautions (cont'd)

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 fatigue¹



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

RAI=radioactive iodine; AR=adverse reaction; 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.

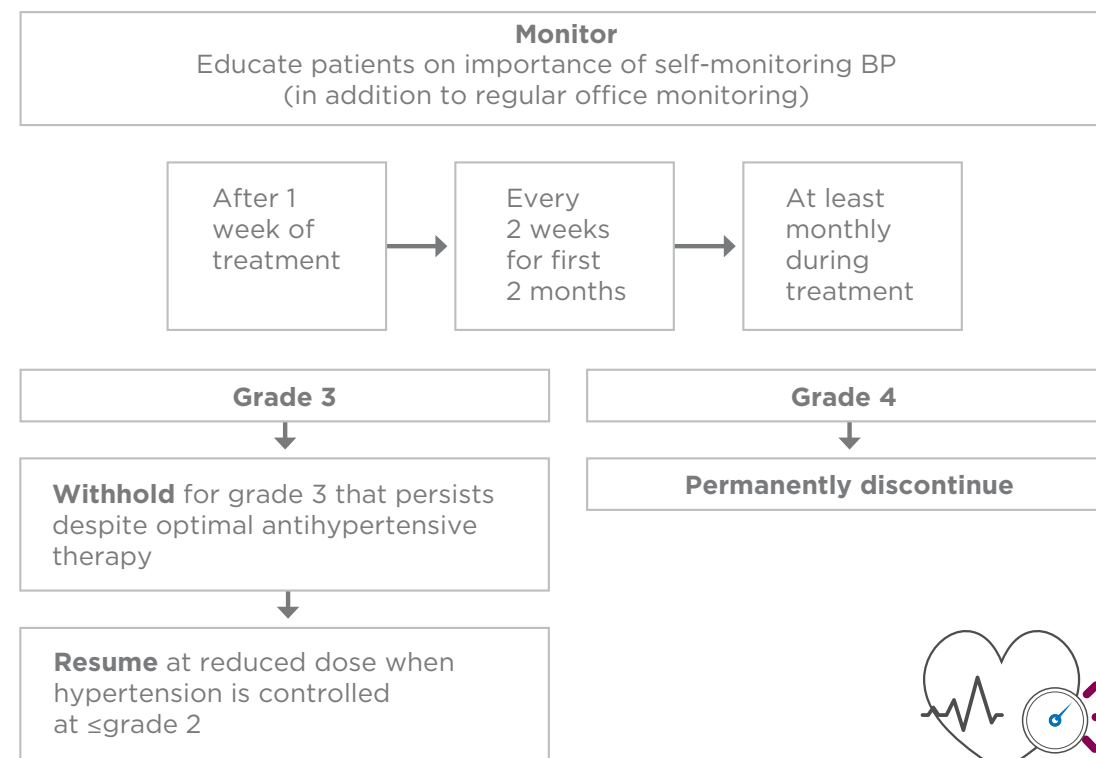
Monitor thyroid function prior to initiation and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

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

Help Manage Select ARs: **Hypertension**

Control BP prior to initiating treatment with LENVIMA[®]

PI-guided strategies to help manage hypertension¹



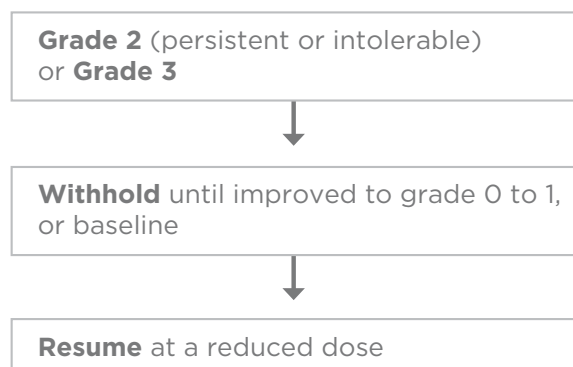
SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

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: **Nausea**

PI-guided strategies to help manage nausea¹



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

RAI=radioactive iodine; AR=adverse reaction; 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.

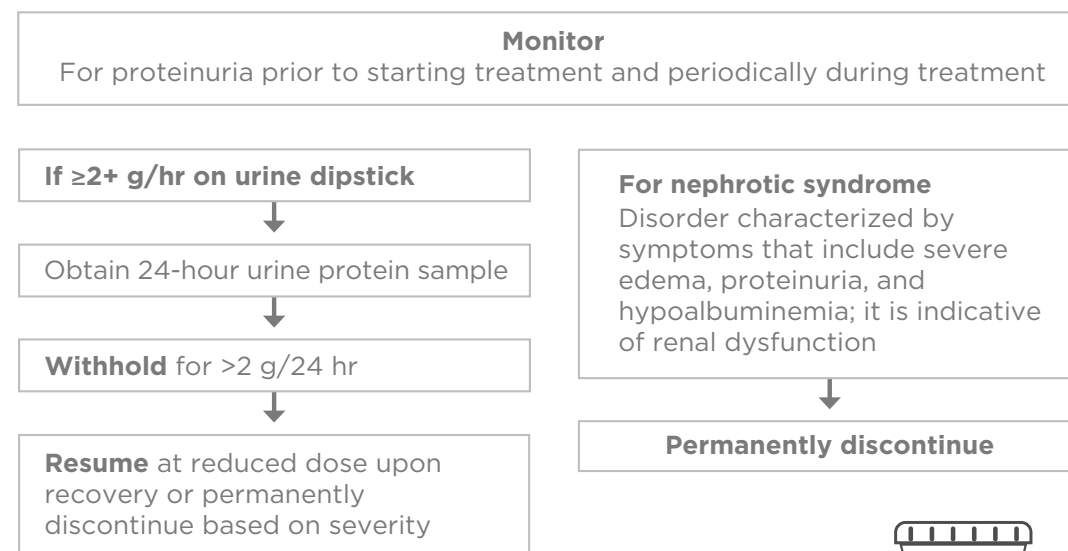
Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk. Withhold LENVIMA for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ.

Withhold LENVIMA if ONJ develops and restart based on clinical judgement of adequate resolution.

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.

Help Manage Select ARs: **Proteinuria**

PI-guided strategies to help manage proteinuria¹



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%).

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

- A clinically important AR that occurred more frequently in patients who received LENVIMA than in patients who received placebo, but with an incidence of <5%, was pulmonary embolism (3%, including fatal reports, vs 2%, respectively)¹
- No overall differences in safety or effectiveness were observed between older patients (≥65 years) and younger patients¹

Dose reductions or interruptions with LENVIMA in the SELECT trial

- ARs led to dose reductions in 68% of patients receiving LENVIMA¹
- The most common ARs (≥10%) resulting in dose reductions of LENVIMA were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%)¹

Treatment discontinuations with LENVIMA in the SELECT trial

- Treatment discontinuations due to ARs occurred in 18% of patients taking LENVIMA¹
- The most common ARs that led to discontinuation in the LENVIMA-treated group were asthenia (1%) and hypertension (1%)¹

SELECTED SAFETY INFORMATION

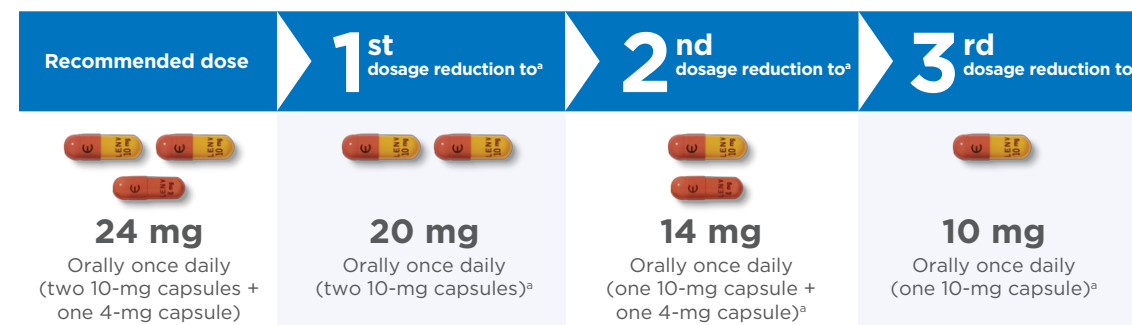
Use in Specific Populations

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 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.

Recommended Dose and Dose Modifications¹

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



Capsules pictured are not actual size

^aReduce dose in succession based on the previous dose level (20 mg, 14 mg, or 10 mg per day).

- In SELECT, ARs led to dose reductions in 68% of patients receiving LENVIMA
- Treatment discontinuation due to ARs occurred in 18% of patients

Dose adjustments for renal or hepatic impairment

Recommended dose of LENVIMA® for severe renal or hepatic impairment

In patients with:	Recommended dose:	No dose adjustment is recommended in patients with mild or moderate renal or hepatic impairment.* Patients with end-stage renal disease were not studied.
Severe renal impairment (CrCl <30 mL/min) ^b	14 mg (one 10-mg capsule + one 4-mg capsule) orally once daily	
Severe hepatic impairment (Child-Pugh C)	14 mg (one 10-mg capsule + one 4-mg capsule) orally once daily	

RAI=radioactive iodine; 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.

^bAs calculated by the Cockcroft-Gault equation.

SELECTED SAFETY INFORMATION

Use in Specific Populations (cont'd)

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 Assistance Program

The Eisai Assistance Program provides support for patients. By contacting the Eisai Assistance Program, 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.



Financial assistance

With the LENVIMA \$0 Co-Pay Program, eligible commercially insured patients will pay as little as \$0 out-of-pocket for each prescription. Eisai will pay up to a maximum of \$40,000 per year to assist with the out-of-pocket costs for LENVIMA.* For assistance with the LENVIMA \$0 Co-Pay Program, call 1-855-347-2448.

*Maximum benefit and eligibility: Depending on the insurance plan, patients could have additional financial responsibility for any amounts over Eisai's maximum liability. Not available to patients enrolled in state or federal health care programs, including Medicare, Medicaid, Medigap, VA, DoD, or TRICARE. Offer only available to patients with private, commercial insurance. See www.LENVIMAREIMBURSEMENT.com for complete terms and conditions.

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.** 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.



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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