# #1 PRESCRIBED
**first-line therapy** for
**RAI-refractory DTC** patients[1,2*]

# See a spectrum of results

Lenvatinib (LENVIMA®) is the preferred first-line treatment by the National Comprehensive Cancer Network® (NCCN®) for locally recurrent or metastatic, progressive radioactive iodine-refractory differentiated thyroid cancer[†‡]

**NCCN** **PREFERRED** FIRST-LINE THERAPY

- 18.3-month (95% CI: 15.1-NE) median PFS was observed with LENVIMA vs 3.6 months (95% CI: 2.2-3.7) with placebo (HR: 0.21 [95% CI: 0.16-0.28]; *P*<0.001; primary endpoint)[2,3]

RAI=radioactive iodine; DTC=differentiated thyroid cancer; CI=confidence interval; NE=not estimable; PFS=progression-free survival; HR=hazard ratio.
*Ipsos Healthcare US Oncology Monitor (August 2018 to July 2019, 349 physicians reporting on 1,701 Stage 4 patients, all data collected online) © Ipsos 2019, all rights reserved.
†Lenvatinib (LENVIMA)[1] has a category 2A recommendation. Category 2A recommendation is based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. All recommendations are category 2A unless otherwise indicated.
‡Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Thyroid Carcinoma V.2.2019. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed January 15, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. The National Comprehensive Cancer Network 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.

## 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.

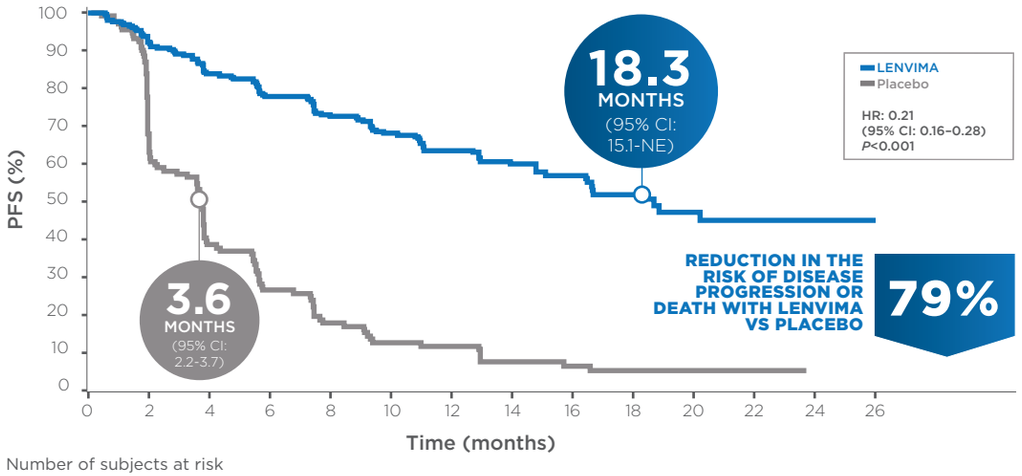
**Please see Selected Safety Information throughout and full Prescribing Information.**

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg
RESULTS THAT MATTER

# Superior PFS benefit

MAJOR EFFICACY OUTCOME

## Median PFS: 18.3 months with LENVIMA® vs 3.6 months with placebo[2,3]




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 |

SELECT study results based on a phase 3, multicenter, randomized, double-blind, placebo-controlled trial in patients with locally recurrent or metastatic RAI-refractory DTC (N=392) who have had radiographic evidence of disease progression within 12 months prior to randomization as confirmed by independent radiologic review.[2,3]

- 107 events (41%) occurred in the LENVIMA arm vs 113 events (86%) in the placebo arm[2]
  - 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

SELECT=**S**tudy of (**E**7080) **LE**nvatinib in Differentiated **C**ancer of the **T**hyroid.

### SELECTED SAFETY INFORMATION

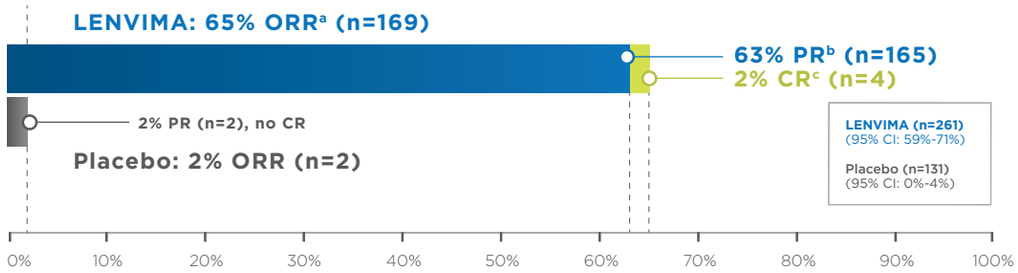
**Warnings and Precautions (cont'd)**

**Hypertension (cont'd).** 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.

# Superior response

OTHER EFFICACY OUTCOME

## 65% ORR[a] with LENVIMA® (including 2% CR) vs 2% ORR with placebo[2-4]




**LENVIMA IS THE FIRST TKI TO DEMONSTRATE A COMPLETE RESPONSE IN A PHASE 3 TRIAL FOR LOCALLY RECURRENT OR METASTATIC, PROGRESSIVE RAI-REFRACTORY DTC[2,3,5]**

- **Median OS was not estimable** due to crossover from placebo at disease progression (HR: 0.73 [95% CI: 0.50-1.07]; *P*=0.10)[2]

TKI=tyrosine kinase inhibitor; OS=overall survival; RECIST=Response Evaluation Criteria In Solid Tumors.
Responses evaluated using RECIST 1.1.[2,3]
*P*<0.001, according to the Cochran–Mantel–Haenszel chi-square test.[2]
[a]Objective response rate (ORR)=sum of CR and PR.[2,4]
[b]Partial response (PR)=30% or greater decrease in the sum of diameters of target lesions.[4]
[c]Complete response (CR)=disappearance of all target and nontarget lesions.[4]

### 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.

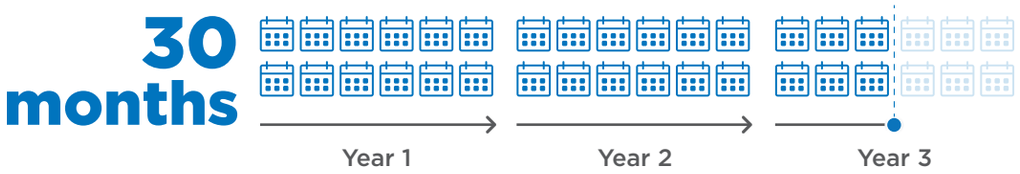
**Arterial Thromboembolic Events.** Among patients receiving LENVIMA or LENVIMA + everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in RCC and HCC and 5% in DTC. Grade 3-5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials.

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%).

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.

# Duration of response analysis

**30-month (95% CI: 18.4-36.7) median duration of response among patients who responded to LENVIMA®[6]**




- Post hoc analysis (n=261) was conducted based on investigator-assessed response; 157 patients (60.2%) in the LENVIMA arm responded per investigator assessment[6]

**Limitations:** the post hoc exploratory subgroup analysis (data cutoff: September 1, 2016) was not a prespecified study endpoint. Patients who did not respond were not evaluated. No conclusions can be drawn.

## 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.

# Selected Safety Information

**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.

**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.

**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.

**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.

**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

# Selected Safety Information

**Warnings and Precautions (cont'd)**

**Hemorrhagic Events (cont'd).** 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 at least 30 days after the last dose.

**Adverse Reactions**

In DTC, the most common adverse reactions (≥30%) observed in LENVIMA-treated patients were hypertension (73%), fatigue (67%), diarrhea (67%), arthralgia/myalgia (62%), decreased appetite (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 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 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.

**References: 1.** Data on file. Eisai Inc. **2.** LENVIMA [package insert]. Woodcliff Lake, NJ: Eisai Inc. **3.** 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. **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.** NEXAVAR [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2018. **6.** Gianoukakis AG, Dutcus CE, Batty N, Guo M, Baig M. Prolonged duration of response in lenvatinib responders with thyroid cancer. *Endocr Relat Cancer*. 2018;25(6):699-704.

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

# #1 PRESCRIBED

**first-line therapy** for **RAI-refractory DTC** patients[1,2*]

Lenvatinib (LENVIMA®) is the preferred first-line treatment by the National Comprehensive Cancer Network® (NCCN®) for locally recurrent or metastatic, progressive radioactive iodine-refractory differentiated thyroid cancer[†‡]

**NCCN** **PREFERRED** FIRST-LINE THERAPY

## Superior PFS benefit

**18.3-month (95% CI: 15.1-NE)** median PFS was observed with LENVIMA vs 3.6 months (95% CI: 2.2-3.7) with placebo[2]

## Superior response

**65% ORR[a]** with LENVIMA (including 2% CR[b]) vs 2% ORR with placebo (no CR)[2,4]

Visit **www.LENVIMA.com/hcp** to learn more

[a]ORR=sum of CR and PR.[2,4]
[b]CR=disappearance of all target and nontarget lesions.[4]
*Ipsos Healthcare US Oncology Monitor (August 2018 to July 2019, 349 physicians reporting on 1,701 Stage 4 patients, all data collected online) © Ipsos 2019, all rights reserved.
†Lenvatinib (LENVIMA) has a category 2A recommendation. Category 2A recommendation is based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. All recommendations are category 2A unless otherwise indicated.
‡Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Thyroid Carcinoma V.2.2019. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed January 15, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. The National Comprehensive Cancer Network 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.

Price disclosure information for prescribers available here: https://us.eisai.com/RequiredPriceDisclosures

## 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.

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

Eisai


September 2021 LENV-US6635

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg
RESULTS THAT MATTER

# MANAGING ADVERSE REACTIONS

## That May Occur With LENVIMA®

***For First-line Treatment of***
***RAI-Refractory Differentiated Thyroid Cancer***

RAI=radioactive iodine.

### 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.**

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

# **Recognize, Monitor, and Manage ARs** With LENVIMA®

## **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=**S**tudy of (**E**7080) **LE**nvatinib in Differentiated **C**ancer of the **T**hyroid.

### 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%).

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.



# **Recognize ARs** With LENVIMA

## In SELECT trial

**Most common ARs (≥30%) observed in LENVIMA-treated patients[1]**

- 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[1]**

- 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% |

**SELECT was not designed to demonstrate a statistically significant reduction in AR rates for LENVIMA vs placebo.**

**No grade 4 diarrhea, hand-foot skin reaction, fatigue, or proteinuria.[2]**

AR=adverse reaction; 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 |
| **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[g] | 21 | 0.4 | 3 | 0 |
| Alopecia | 12 | 0 | 5 | 0 |
| Hyperkeratosis | 7 | 0 | 2 | 0 |
| **Respiratory, thoracic, and mediastinal** | | | | |
| Dysphonia | 31 | 1 | 5 | 0 |
| Cough | 24 | 0 | 18 | 0 |
| Epistaxis | 12 | 0 | 1 | 0 |
| **Psychiatric** | | | | |
| Insomnia | 12 | 0 | 3 | 0 |
| **Infections** | | | | |
| Urinary tract infection | 11 | 1 | 5 | 0 |
| Dental and oral infections[h] | 10 | 1 | 1 | 0 |
| **Cardiac** | | | | |
| Prolonged electrocardiogram QT | 9 | 2 | 2 | 0 |

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

## Grade 3-4 laboratory abnormalities

With a difference ≥2% in grade 3-4 events and at a higher incidence in patients treated with LENVIMA® in SELECT[1,a,b]

| | LENVIMA 24 mg (n=258) | Placebo (n=131) |
|---|---|---|
| **Laboratory abnormality** | **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

AR=adverse reaction; ALT=alanine aminotransferase; AST=aspartate aminotransferase; SELECT=**S**tudy of (**E**7080) **LE**nvatinib in Differentiated **C**ancer of the **T**hyroid.
[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)**
**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.



# An established plan for AR management[1]

## Managing ARs with interruptions, reductions, and/or discontinuations

| AR | Severity[a] | Dose modifications for LENVIMA® |
|---|---|---|
| Hypertension | Grade 3 | • Withhold for grade 3 that persists despite optimal antihypertensive therapy<br>• Resume at reduced dose when hypertension is controlled at less than or equal to grade 2 |
| | Grade 4 | • Permanently discontinue |
| Cardiac dysfunction | Grade 3 | • Withhold until improves to grade 0 to 1, or baseline<br>• Resume at a reduced dose or discontinue depending on the severity and persistence of AR |
| | Grade 4 | • Permanently discontinue |
| Arterial thromboembolic event | Any grade | • Permanently discontinue |
| Hepatotoxicity | Grade 3 or 4 | • Withhold until improves to grade 0 to 1, or baseline<br>• Either resume at a reduced dose or discontinue depending on severity and persistence of hepatotoxicity<br>• Permanently discontinue for hepatic failure |
| Renal failure or impairment | Grade 3 or 4 | • Withhold until improves to grade 0 to 1, or baseline<br>• Resume at a reduced dose or discontinue depending on severity and persistence of renal impairment |
| Proteinuria | 2 g or greater proteinuria in 24 hours | • Withhold until less than or equal to 2 grams of proteinuria per 24 hours<br>• Resume at a reduced dose<br>• Permanently discontinue for nephrotic syndrome |
| Gastrointestinal perforation | Any grade | • Permanently discontinue |
| Fistula formation | Grade 3 or 4 | • Permanently discontinue |
| QT prolongation | Greater than 500 ms or greater than 60 ms increase from baseline | • Withhold until improves to less than or equal to 480 ms or baseline<br>• Resume at a reduced dose |
| Reversible posterior leukoencephalopathy syndrome | Any grade | • Withhold until fully resolved<br>• Resume at a reduced dose or discontinue depending on severity and persistence of neurologic symptoms |
| Other ARs | Grade 2 (persistent or intolerable) or grade 3 AR<br>Grade 4 laboratory abnormality | • Withhold until improves to grade 0 to 1 or baseline<br>• Resume at reduced dose |
| | Grade 4 AR | • Permanently discontinue |

AR=adverse reaction.
[a]National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

# **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

- 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.**

RAI=radioactive iodine; AR=adverse reaction.

## SELECTED SAFETY INFORMATION

**Warnings and Precautions (cont'd)**

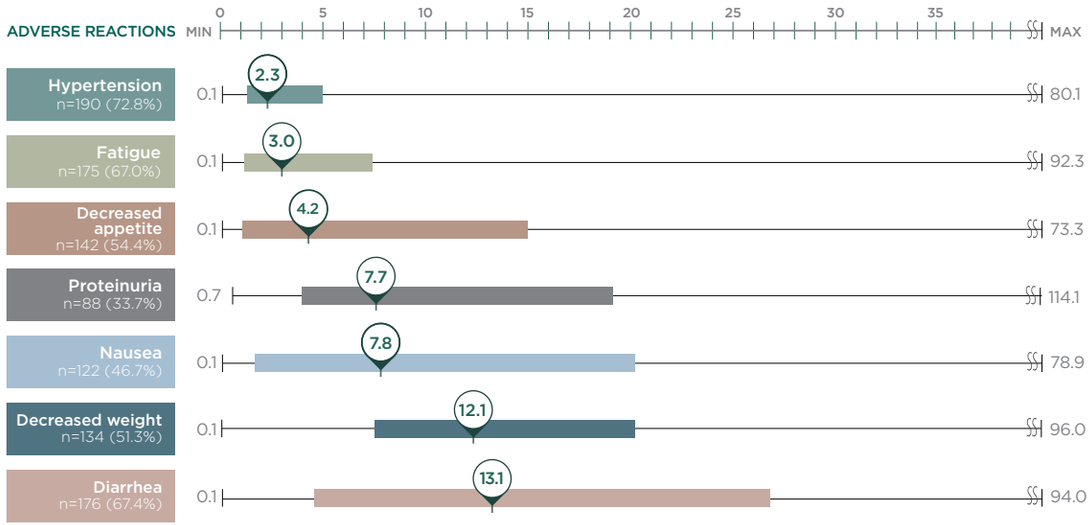
**Renal Failure or Impairment.** Serious including fatal renal failure or impairment can occur with LENVIMA. Renal impairment was reported in 14% and 7% of LENVIMA-treated patients in DTC and HCC, respectively. Grade 3-5 renal failure or impairment occurred in 3% of patients with DTC and 2% of patients 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.

## Post hoc analysis of time to first onset of select ARs in SELECT trial[3]

- Monitor your patients for ARs throughout treatment with LENVIMA

### Median weeks; AR (n=261)*




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

AR=adverse reaction.
*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.

# 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**

RAI=radioactive iodine; AR=adverse reaction.

# 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.

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

### 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.



### 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.

**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.

# 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

↓

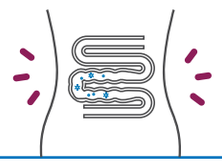
**Resume** at a reduced dose

**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]



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.

**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: **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 decreased fatigue. Permanently discontinue for grade 4 adverse reactions.


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

## 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: **Hypertension**

Control BP prior to initiating treatment with LENVIMA®

## PI-guided strategies to help manage hypertension[1]

**Monitor**
Educate patients on importance of self-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**

RAI=radioactive iodine; AR=adverse reaction.

### 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.



# Help Manage Select ARs: **Nausea**

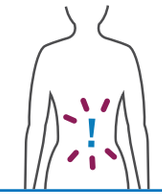
## PI-guided strategies to help manage nausea[1]

**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.



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

### 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: **Proteinuria**

## PI-guided strategies to help manage proteinuria[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

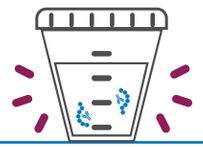
↓

**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

↓

**Permanently discontinue**



RAI=radioactive iodine; AR=adverse reaction.

### 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.



# 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 patients[1]

**Dose reductions or interruptions with LENVIMA**

- ARs led to dose reductions in 68% of patients receiving LENVIMA[1]
- 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**

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

### 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 at least 30 days after the last dose.

**Adverse Reactions**
In DTC, the most common adverse reactions (≥30%) observed in LENVIMA-treated patients were hypertension (73%), fatigue (67%), diarrhea (67%), arthralgia/myalgia (62%), decreased appetite (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%).

# Recommended Starting Dose and Dose Modifications[1]

## Managing ARs with interruptions, reductions, and/or discontinuations

| Recommended Starting dose | 1st dosage reduction to | 2nd dosage reduction to | 3rd dosage reduction to |
|---|---|---|---|
|  |  |  |  |
| **24 mg** Orally once daily (two 10-mg capsules + one 4-mg capsule) | **20 mg** Orally once daily (two 10-mg capsules) | **14 mg** Orally once daily (one 10-mg capsule + one 4-mg capsule) | **10 mg** Orally once daily (one 10-mg capsule) |

Capsules pictured are not actual size.

**For the management of specific adverse reactions, please see the Adverse Reaction Management section of this presentation.**

## Dose adjustments for renal or hepatic impairment

**Recommended dose of LENVIMA® for severe renal or hepatic impairment**

| In patients with: | Recommended dose: |
|---|---|
| Severe renal impairment (CrCl <30 mL/min)[a] | 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 |

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

AR=adverse reaction; CrCl=creatinine clearance.
*Mild renal impairment is defined as CLcr 60-89 mL/min and moderate renal impairment is defined as CLcr 30-59 mL/min.
[a]As calculated by the Cockcroft-Gault equation.

### 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 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.



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

Orally, once daily, at the same time each day

With or without food

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

The recommended daily starting dose of LENVIMA for RAI-refractory DTC is **24 mg (two 10-mg capsules and one 4-mg capsule)** taken orally 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

**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

RAI=radioactive iodine; DTC=differentiated thyroid cancer.


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

### 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®

- 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**
- 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 starter kit. The Patient Assistance Program also provides LENVIMA at no cost to eligible patients with financial need

Please visit **www.LENVIMAREIMBURSEMENT.com/hcp** for more information about access and reimbursement
Please visit **https://us.eisai.com/RequiredPriceDisclosures** for price disclosure information

*__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.

**References: 1.** LENVIMA [package insert]. Woodcliff Lake, NJ: Eisai Inc. **2.** 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. **3.** Data on file, Eisai Inc.

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



LENVIMA® (lenvatinib) capsules 10 mg and 4 mg