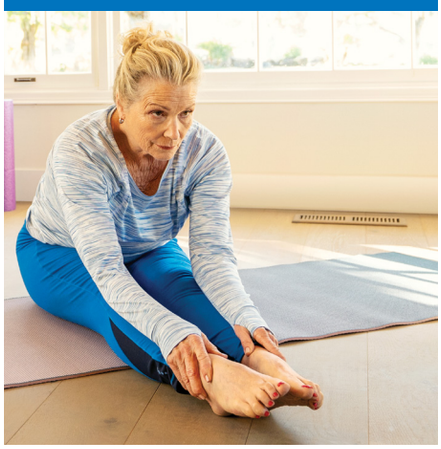
LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

For Advanced Practice Providers and Nurses

Guiding your patients on LENVIMA® with confidence

Help your patients better understand their treatment plan



Not actual patients

INDICATIONS

LENVIMA is indicated:

Differentiated Thyroid Cancer (DTC)

- For the treatment of adult patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC

Renal Cell Carcinoma (RCC)

- In combination with everolimus, for the treatment of adult patients with advanced RCC following one prior anti-angiogenic therapy

Hepatocellular Carcinoma (HCC)

- For the first-line treatment of patients with unresectable HCC

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.

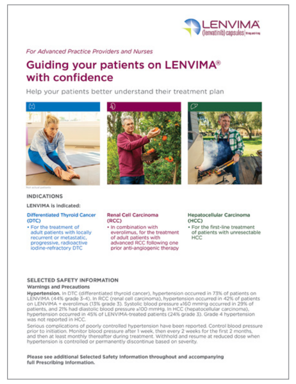
Serious complications of poorly controlled hypertension have been reported. Control blood pressure prior to initiation. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at reduced dose when hypertension is controlled or permanently discontinue based on severity.

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

Not actual patients

Help your patients better understand their treatment plan

As Advanced Practice Providers and Nurses, you play an important role in guiding patients through their treatment. Early and frequent communication is key to keeping patients informed and prepared. This resource was designed to provide you with information that can help you guide your patients to better understand their treatment plan.



This guide includes:

- A comprehensive overview across three indications
- Overviews of efficacy data to support treatment discussions
- Safety profiles, including most common ARs
- Recommended dosing and dose modifications
- PI-guided strategies for AR management
- Patient Check-In callouts throughout that highlight key points you may wish to discuss with your patients

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.

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

The confidence to treat, backed by NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

RAI-R DTC

NCCN GUIDELINES®	CATEGORY 1 PREFERRED FIRST-LINE SYSTEMIC THERAPY OPTION (NCCN)	**Lenvatinib (LENVIMA®): THE ONLY NCCN CATEGORY 1 PREFERRED FIRST-LINE SYSTEMIC THERAPY OPTION** by the 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 (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the panel) that the intervention is appropriate

*Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Thyroid Carcinoma V.1.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed March 28, 2025. 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.
†Preferred intervention=interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

2L aRCC

NCCN	RECOMMENDED OPTION	Lenvatinib (LENVIMA) + everolimus has a National Comprehensive Cancer Network® (NCCN®) category 2A other recommended regimen as a subsequent therapy option for patients with relapse or stage IV clear cell RCC‡

- **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate

‡Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V.3.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed January 10, 2025. 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.

1L uHCC

NCCN	CATEGORY 1 RECOMMENDED OPTION	Lenvatinib (LENVIMA) is a Category 1 Recommended first-line systemic treatment option for advanced HCC§

- **Category 1** recommendation is based on high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85 support of the panel) that the intervention is appropriate

§Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hepatocellular Carcinoma. V1.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed March 21, 2025. 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.

PATIENT CHECK-INS

- It may be helpful to inform patients that their doctor's decision to prescribe lenvatinib (LENVIMA) is supported by NCCN Guideline recommendations. These guidelines are developed by leading experts to provide evidence-based recommendations for cancer care

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

RAI-R DTC
2L aRCC
1L uHCC
Dosing
AR Management

Not actual patients

RAI-R DTC: Efficacy results in SELECT trial[1]

Superior PFS benefit (primary endpoint)[1]

18.3 months median PFS

18.3 months median PFS with LENVIMA® (95% CI: 15.1-NE) **vs 3.6 months with placebo** (95% CI: 2.2-3.7) (HR: 0.21 [95% CI: 0.16-0.28]); *P*<0.001

- Number of events: 107 (41%) with LENVIMA vs 113 (86%) with placebo
  - –93 patients (36%) with LENVIMA progressed vs 109 patients (83%) with placebo
  - –Death occurred in 14 patients (5%) with LENVIMA vs 4 patients (3%) with placebo

Superior response (secondary endpoint)[1,2]

65% ORR (n=169)

65% ORR* with LENVIMA (95% CI: 59%-71%) **vs 2% ORR with placebo** (95% CI: 0%-4%); *P*<0.001†

- Complete response‡: 2% (n=4) with LENVIMA vs 0% with placebo
- Partial response§: 63% (n=165) with LENVIMA vs 2% (n=2) with placebo

Median OS (secondary endpoint) 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]

SELECT study design[1,2]

SELECT study results based on a phase 3, multicenter, randomized, double-blind, placebo-controlled trial in patients with locally recurrent or metastatic RAI-R DTC (N=392) who have had radiographic evidence of disease progression within 12 months prior to randomization as confirmed by independent radiologic review. Patients may have received 0 or 1 prior VEGF/VEGFR-targeted therapies. Patients were randomized to receive LENVIMA 24 mg once daily (n=261) or placebo (n=131) until disease progression. Patients in the placebo arm could receive lenvatinib following independent review confirmation of disease progression. The primary endpoint was PFS, as determined by blinded independent radiologic review using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Secondary endpoints included objective response rate and overall survival.

*Assessed by independent radiologic review according to RECIST v1.1; Objective response rate (ORR)=sum of CR and PR.[1-3]
†According to the Cochran-Mantel-Haenszel chi-square test.[1]
‡Complete response (CR)=disappearance of all target and non-target lesions.[3]
§Partial response (PR)=30% or greater decrease in the sum of diameters of target lesions.[3]

PATIENT CHECK-INS

- Reviewing the efficacy data from the clinical trial may help patients better understand their treatment

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.

Adverse reactions in SELECT trial[1]

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%) observed in LENVIMA-treated patients[1]

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

Most common Grade 3-4 ARs (≥5%)[1]

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%

[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.

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

PATIENT CHECK-INS

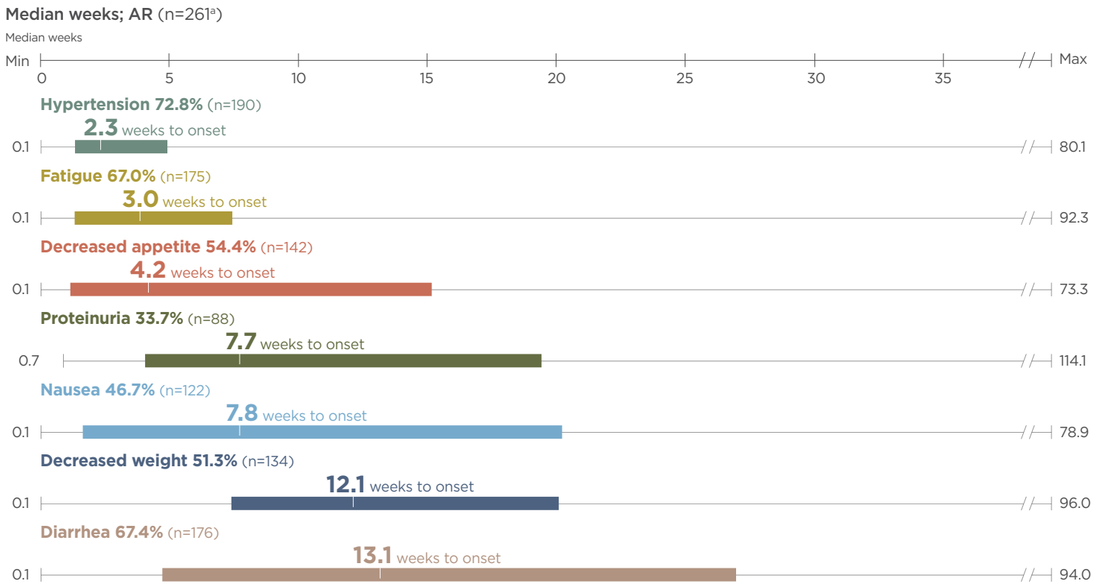
- Explain to patients that LENVIMA can affect normal, healthy cells in addition to cancer cells, and as a result causes serious side effects
- Advise patients to report any symptoms they experience right away. Early reporting allows for prompt management, including dose interruptions, reductions, and/or discontinuations
- Don't forget to remind your patients to contact their healthcare provider right away if they start to feel any new or worsening symptoms or side effects, or have any questions. Patients may use the LENVIMA Symptom Tracker to record their symptoms, which can be accessed on the website by scanning the QR code on the back cover

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

Not an actual patient

Post hoc analysis of time to first onset of certain ARs with LENVIMA® in the SELECT trial[5]

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



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

[a]This 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.

Monitor your patients for ARs throughout treatment with LENVIMA.

CLINICAL GUIDANCE

- The above chart shows the median time to first onset of select adverse reactions in patients receiving LENVIMA in the SELECT trial
- This information is descriptive only, it may not be reflective of clinical practice; it should not replace physician judgment and evaluation if a potential side effect has occurred

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

Hepatotoxicity (cont'd). 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.

Recommended dose and dose modifications[1,a]

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

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

Capsules pictured are not actual size.

Dose reductions in the SELECT trial[1]

- ARs led to dose reductions in 68% of patients receiving LENVIMA

Treatment discontinuations in the SELECT trial[1]

- Treatment discontinuation due to ARs occurred in 18% of patients

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

- 14 mg (one 10-mg capsule + one 4-mg capsule) once daily for severe renal[c] or hepatic impairment[d]
- No dose adjustment is recommended in patients with mild or moderate renal or hepatic impairment. Patients with end-stage renal disease were not studied

[a]Reduce dose in succession based on the previous dose level (20 mg, 14 mg, or 10 mg per day).
[b]Refers to the same or a different adverse reaction that requires dose modification.
[c]Severe renal impairment is defined as CrCl <30 mL/min), as calculated by the Cockcroft-Gault equation, moderate is defined as 30-59 mL/min, and mild is defined as CrCl 60-89 mL/min.
[d]Severe, moderate, and mild hepatic impairment are defined as Child-Pugh C, Child-Pugh B, and Child-Pugh A, respectively.

PATIENT CHECK-INS

- Remind patients to set a daily reminder to take LENVIMA one time each day at the same time with or without food
- It may be helpful to explain to your patients that most people taking LENVIMA in the SELECT clinical trial required some dose reduction, interruption, and/or discontinuation due to side effects
- Encourage patients to report any symptoms that arise to the care team right away

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

Not an actual patient

Second-line aRCC: Efficacy results in Study 205[1,6]

14.6 months median PFS

14.6 months median PFS (major efficacy outcome)[1*†] with LENVIMA® + everolimus (95% CI: 5.9-20.1) **vs 5.5 months with everolimus alone** (95% CI: 3.5-7.1); HR: 0.37 (95% CI: 0.22-0.62)

- Number of events: 26 events (51%) with LENVIMA + everolimus arm vs 37 events (74%) in the everolimus arm
- 21 patients (41%) who received LENVIMA + everolimus progressed vs 35 patients (70%) who received everolimus
- Number of deaths: 5 patients (10%) with LENVIMA + everolimus vs 2 patients (4%) with everolimus

The treatment effect of the combination on PFS was supported by a retrospective independent review of radiographs with an observed hazard ratio (HR) of 0.43 (95% CI: 0.24-0.75) compared with the everolimus arm.

>2 years median OS

Greater than 2 years median OS (other efficacy outcome)[1,6‡]
25.5 month median OS with LENVIMA + everolimus (95% CI: 16.4-32.1) **vs 15.4 months with everolimus alone** (95% CI: 11.8-20.6); HR: 0.67 (95% CI: 0.42-1.08)

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

37% ORR

37% ORR (other efficacy outcome)[1,6*] with LENVIMA + everolimus (95% CI: 24%-52%) **vs 6% ORR with everolimus alone** (95% CI: 1%-17%); *P*<0.001

- Complete response: 2% (n=1) with LENVIMA + everolimus vs 0% with everolimus alone
- Partial response: 35% (n=18) with LENVIMA + everolimus vs 6% (n=3) with everolimus alone

*Evaluated according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1. Objective response rate (ORR)=sum of complete response and partial response.
†Point estimates are based on Kaplan-Meier method and 95% CIs are based on the Greenwood formula using log-log transformation.
‡Based on stratified Cox model.

Study 205 study design[1,6]

Study 205 randomized 153 patients with advanced or metastatic RCC who had previously received anti-angiogenic therapy 1:1:1 to LENVIMA 18 mg + everolimus 5 mg, LENVIMA 24-mg monotherapy, or everolimus 10-mg monotherapy. All medications were administered orally once daily. Patients were required to have histological confirmation of clear cell RCC and Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were stratified by hemoglobin level (≤13 g/dL vs >13 g/dL for males and ≤11.5 g/dL vs >11.5 g/dL for females) and corrected serum calcium (≥10 mg dL vs <10 mg/dL). The major efficacy outcome measure was investigator-assessed PFS evaluated according to RECIST version 1.1. Other efficacy outcome measures included overall survival and objective response rate.

PATIENT CHECK-INS

- Reviewing the efficacy data from the clinical trial may help patients better understand their treatment

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.

Adverse reactions in Study 205[1]

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

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

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

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

Most common Grade 3-4 ARs (≥5%)[1]

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

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

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

PATIENT CHECK-INS

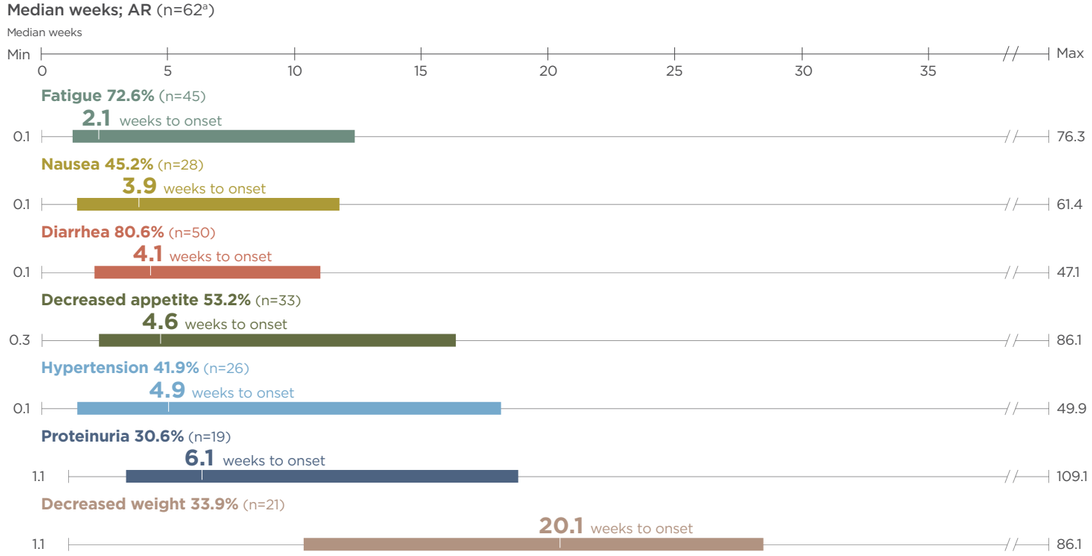
- Explain to patients that LENVIMA can affect normal, healthy cells in addition to cancer cells, and as a result causes serious side effects
- Advise patients to report any symptoms they experience right away. Early reporting allows for prompt management, including dose interruptions, reductions, and/or discontinuations
- Don't forget to remind your patients to contact their healthcare provider right away if they start to feel any new or worsening symptoms or side effects, or have any questions. Patients may use the LENVIMA Symptom Tracker to record their symptoms, which can be accessed on the website by scanning the QR code on the back cover

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

Not an actual patient

Post hoc analysis of time to first onset of certain ARs in Study 205[3]

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



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

[a]This 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.

Monitor your patients for ARs throughout treatment with LENVIMA.

CLINICAL GUIDANCE

- The above chart shows the median time to first onset of select adverse reactions in patients receiving LENVIMA in Study 205
- This information is descriptive only, it may not be reflective of clinical practice; it should not replace physician judgment and evaluation if a potential adverse reaction should occur

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.

Recommended dose and dose modifications[1,a]

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

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

Capsules pictured are not actual size.

Dose reductions in Study 205[1]

- ARs led to dose reductions and interruption in 89% of patients receiving LENVIMA + everolimus

Treatment discontinuations in Study 205[1]

- Treatment discontinuation due to ARs occurred in 29% of patients receiving LENVIMA + everolimus

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

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

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

- 10 mg (one 10-mg capsule) once daily for severe renal or hepatic impairment[e]
- No dose adjustment is recommended in patients with mild or moderate renal or hepatic impairment. Patients with end-stage renal disease were not studied

PATIENT CHECK-INS

- Educate patients on dosing for the 2 products. LENVIMA is available as 10-mg and 4-mg capsules, and everolimus is available as a 5-mg tablet. Everolimus is not included in the LENVIMA carton and requires a separate prescription
- Remind patients to set a daily reminder to take LENVIMA one time each day at the same time with or without food
- It may be helpful to explain to your patients that most people taking LENVIMA in Study 205 required some dose reduction, interruption, and/or discontinuation due to side effects
- Encourage patients to report any symptoms that arise to the care team right away

[a]Reduce dose in succession based on the previous dose level (18 mg, 14 mg, 10 mg, or 8 mg per day).
[b]Refers to the same or a different adverse reaction that requires dose modification.
[c]Refer to everolimus Prescribing Information for additional dose modification information.
[d]Severe renal impairment is defined as CrCl <30 mL/min), moderate is defined as CrCl 60-89 mL/min, and mild is defined as CrCl 30-59 mL/min. Severe, moderate, and mild hepatic impairment are defined as Child-Pugh C, Child-Pugh B, and Child-Pugh A, respectively.
[e]As calculated by the Cockcroft-Gault equation.

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

Not an actual patient

First-line uHCC: Efficacy results in REFLECT[1]

LENVIMA® achieved its noninferiority primary endpoint vs sorafenib[1]

13.6 months median OS

13.6 months median OS with LENVIMA (95% CI: 12.1-14.9) **vs 12.3 months with sorafenib** (95% CI: 10.4-13.9); HR: 0.92 (95% CI: 0.79-1.06)*

- Number of events: 351 (73%) with LENVIMA vs 350 (74%) with sorafenib
- LENVIMA did not demonstrate a statistically significant improvement in OS vs sorafenib

DOUBLE the median PFS (secondary endpoint)[1†]

2x median PFS

7.3 months median PFS with LENVIMA (95% CI: 5.6-7.5) **vs 3.6 months with sorafenib** (95% CI: 3.6-3.7) (HR: 0.64 [95%CI: 0.55-0.75]; *P*<0.001) (mRECIST)‡

- Number of events: 311 (65%) with LENVIMA vs 323 (68%) with sorafenib
- RECIST 1.1 criteria demonstrated a median PFS of 7.3 months (95% CI: 5.6-7.5) with LENVIMA and 3.6 months (95% CI: 3.6-3.9) with sorafenib (HR: 0.65 [95% CI: 0.56-0.77])‡
- Number of events: 307 (64%) with LENVIMA vs 320 (67%) with sorafenib

TRIPLE the ORR (secondary endpoint)[1†]

3x ORR

41% ORR with LENVIMA (95% CI: 36%-45%) **vs 12% ORR with sorafenib** (95% CI: 10%-16%); *P*<0.001 (mRECIST)†‡

- Complete response: 2.1% (n=10) with LENVIMA vs 0.8% (n=4) with sorafenib
- Partial response: 38.5% (n=184) with LENVIMA vs 11.6% (n=55) with sorafenib
- RECIST 1.1 criteria demonstrated 19% ORR with LENVIMA (95% CI: 15%-22%) and 7% with sorafenib (95% CI: 4%-9%)‡
- Complete response: 0.4% (n=2) with LENVIMA vs 0.2% (n=1) with sorafenib
- Partial response: 18.4% (n=88) with LENVIMA vs 6.3% (n=30) with sorafenib

*Based on a stratified Cox-model. The noninferiority margin for the HR of LENVIMA vs sorafenib is 1.08.
†mRECIST for HCC criteria measure the sum of viable (enhancement in the arterial phase) tumor diameters and may more accurately measure response in HCC liver lesions than RECIST 1.1.
‡Per independent radiology review.

REFLECT study design[1]

The efficacy and safety of LENVIMA was evaluated in a randomized, open-label, multicenter, international study conducted in patients with previously untreated unresectable hepatocellular carcinoma (HCC). The study enrolled adults with Child-Pugh A and Barcelona Clinic Liver Cancer (BCLC) Stage C or B HCC who were ineligible for local liver-directed therapy; had an ECOG PS of 0 or 1; had received no prior systemic therapy for HCC; and had at least one measurable target lesion according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) for HCC. Patients were randomized (1:1) to receive LENVIMA (n=478) (12 mg for baseline actual body weight ≥60 kg or 8 mg for baseline actual body weight <60 kg) orally once daily or sorafenib (n=476) 400 mg orally twice daily until radiological disease progression or unacceptable toxicity. The major efficacy outcome measure was OS. REFLECT was designed to show the noninferiority of LENVIMA to sorafenib for OS. Additional efficacy outcome measures were PFS and ORR according to mRECIST for HCC.

PATIENT CHECK-INS

- Reviewing the efficacy data from the clinical trial may help patients better understand their treatment

Adverse reactions in the REFLECT trial[1]

Most common ARs (≥20%) observed in LENVIMA-treated patients[1]

- Hypertension (45%), fatigue (44%), diarrhea (39%), decreased appetite (34%), arthralgia/myalgia (31%), decreased weight (31%), abdominal pain (30%), palmar-plantar erythrodysesthesia syndrome (27%), proteinuria (26%), dysphonia (24%), hemorrhagic events (23%), hypothyroidism (21%), and nausea (20%)

Most common serious ARs (≥2%) observed in LENVIMA-treated patients[1]

- Hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%)

Most common Grade 3-4 ARs (≥5%) in either arm[1]

Adverse reaction	LENVIMA (n=476)	Sorafenib (n=475)
Hypertension[a]	24%	15%
Decreased weight	8%	3%
Fatigue[b]	7%	6%
Proteinuria[c]	6%	2%
Decreased appetite	5%	1%
Palmar-plantar erythrodysesthesia syndrome	3%	11%

[a]Includes increased diastolic blood pressure, increased blood pressure, hypertension and orthostatic hypertension.
[b]Includes asthenia, fatigue, lethargy and malaise.
[c]Includes proteinuria, increased urine protein, protein urine present.

REFLECT was not designed to demonstrate a statistically significant reduction in AR rates for LENVIMA vs sorafenib.[1]

PATIENT CHECK-INS

- Explain to patients that LENVIMA can affect normal, healthy cells in addition to cancer cells, and as a result causes serious side effects
- Advise patients to report any symptoms they experience right away. Early reporting allows for prompt management, including dose interruptions, reductions, and/or discontinuations
- Don't forget to remind your patients to contact their healthcare provider right away if they start to feel any new or worsening symptoms or side effects, or have any questions. Patients may use the LENVIMA Symptom Tracker to record their symptoms, which can be accessed on the website by scanning the QR code on the back cover

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.

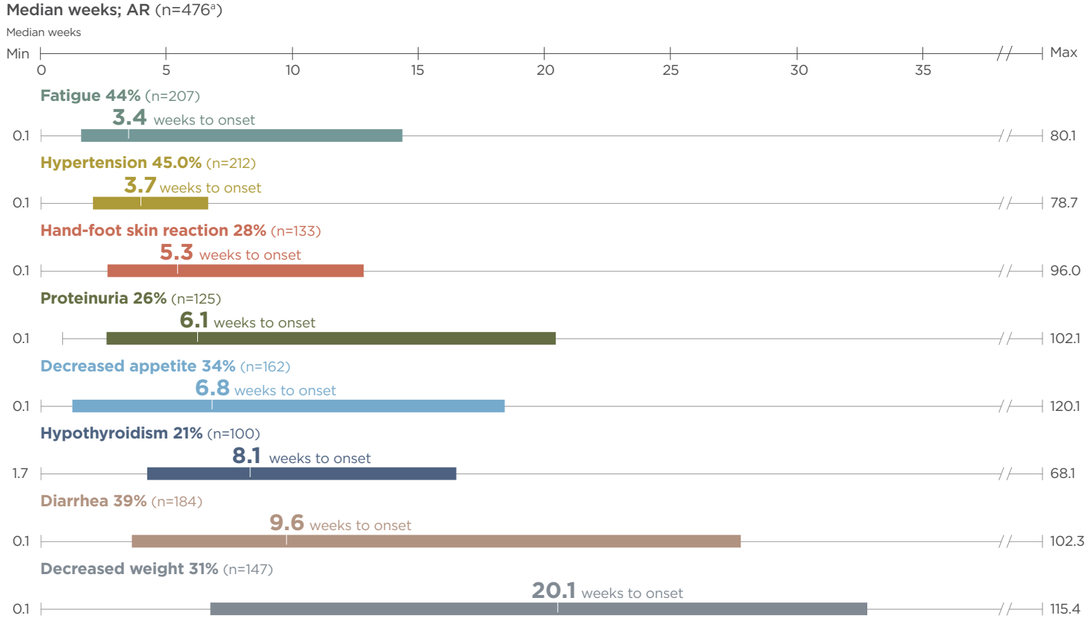
Please see additional Selected Safety Information throughout and accompanying full Prescribing Information.

Not an actual patient

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Post hoc analysis of time to first onset of certain ARs in the REFLECT trial[3]

Median weeks; AR (n=476[a])



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.

Monitor your patients for ARs throughout treatment with LENVIMA.

CLINICAL GUIDANCE

- The above chart shows the median time to first onset of select adverse reactions in patients receiving LENVIMA in the REFLECT trial
- This information is descriptive only, it may not be reflective of clinical practice; it should not replace physician judgment and evaluation if a potential adverse reaction should occur

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.

Recommended dose and dose modifications[1,a]

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

	Recommended dose	1st dosage reduction to	2nd dosage reduction to[b]	3rd dosage reduction to[b]
Patients <60 kg (<132 lb)	8 mg Once daily (two 4-mg capsules)	4 mg Once daily (one 4-mg capsule)	4 mg Once ***every other*** day (one 4-mg capsule)	Discontinue therapy
Patients ≥60 kg (≥132 lb)	12 mg Once daily (three 4-mg capsules)	8 mg Once daily (two 4-mg capsules)	4 mg Once daily (one 4-mg capsule)	4 mg Once ***every other*** day (one 4-mg capsule)

Capsules pictured are not actual size.

Dose reductions in the REFLECT trial[1]

- ARs led to dose reduction or interruption in 62% of patients receiving LENVIMA

Treatment discontinuations in the REFLECT trial[1]

- Treatment discontinuation due to ARs occurred in 20% of patients taking LENVIMA

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

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

PATIENT CHECK-INS

- Remind patients to set a daily reminder to take LENVIMA one time each day at the same time with or without food
- It may be helpful to explain to your patients that most people taking LENVIMA in the REFLECT clinical trial required some dose reduction, interruption, and/or discontinuation due to side effects
- Encourage patients to report any symptoms that arise to the care team right away

[a]Reduce dose in succession based on the previous dose level (12 mg, 8 mg, or 4 mg per day).
[b]Refers to the same or a different adverse reaction that requires dose modification.
[c]Severe renal impairment is defined as CrCl <30 mL/min), moderate is defined as CrCl 60-89 and mild is defined as CrCl 30-59 mL/min. Severe, moderate, and mild hepatic impairment are defined as Child-Pugh C, Child-Pugh B, and Child-Pugh A, respectively.
[d]As calculated by the Cockcroft-Gault equation.

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

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

Dosing and administration

Dosing

Once daily at the same time each day

Administration

With or without food

Swallow LENVIMA capsules whole. Do not crush or chew

OR

Prepare oral suspension with water or apple juice

Note: *See preparation below*

OR

Prepare suspension for feeding tube administration with water

Note: *See preparation below*

Capsules pictured are not actual size. Number of capsules may vary by indication.

- 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

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).

SELECTED SAFETY INFORMATION

Warnings and Precautions (cont'd)

QT Interval Prolongation. In DTC, QT/QTc interval prolongation occurred in 9% of LENVIMA-treated patients and QT interval prolongation of >500 ms occurred in 2%. In RCC, QTc interval increases of >60 ms occurred in 11% of patients receiving LENVIMA + everolimus and QTc interval >500 ms occurred in 6%. In HCC, QTc interval increases of >60 ms occurred in 8% of LENVIMA-treated patients and QTc interval >500 ms occurred in 2%.

Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Withhold and resume at reduced dose upon recovery based on severity.

Every pack of LENVIMA® includes a 30-day treatment supply consisting of 6 individual blister cards[1]

RAI-R DTC and **2L aRCC**

uHCC

Each blister card contains a 5-day supply. Patients will receive a pack specific to their prescribed dose.[1]

PATIENT CHECK-INS

- Advise patients to take LENVIMA once daily, at the same time of day, with or without food
- If the 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
- Instruct patients who are able to swallow to take LENVIMA capsules whole, do not crush or chew
- Remind patients that the number of LENVIMA capsules they will take each day may change if a dose modification is advised
- To see if your patient qualifies for the LENVIMA Dose Exchange Program, scan the QR code on the back cover

Everolimus is distributed by Novartis Pharmaceuticals Corporation.
Everolimus is not included in the LENVIMA carton and requires a separate prescription.

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

LENVIMA® Recommendations for Management of Adverse Reactions[1]

Adverse Reaction	Monitoring	Severity	Dose Modifications
Hypertension [see Warnings and Precautions]	• 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.	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.
Cardiac Dysfunction [see Warnings and Precautions]	• Monitor for clinical symptoms or signs of cardiac dysfunction.	Grade 3	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at a reduced dose or discontinue depending on the severity and persistence of adverse reaction.
		Grade 4	• Permanently discontinue.
Arterial Thromboembolic Events [see Warnings and Precautions]	• The safety of resuming LENVIMA 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.	Any Grade	• Permanently discontinue.
Hepatotoxicity [see Warnings and Precautions]	• 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.	Grade 3 or 4	• Withhold until improves to Grade 0 to 1 or baseline. • Either resume at a reduced dose or discontinue depending on severity and persistence of hepatotoxicity. • Permanently discontinue for hepatic failure.
Renal Failure or Impairment [see Warnings and Precautions]	• Initiate prompt management of diarrhea or dehydration/ hypovolemia.	Grade 3 or 4	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at a reduced dose or discontinue depending on severity and persistence of renal impairment.

Adverse Reaction	Monitoring	Severity	Dose Modifications
Proteinuria [see Warnings and Precautions]	• Monitor for proteinuria prior to initiation and periodically during treatment. —If urine dipstick proteinuria ≥2+ is detected, obtain a 24-hour urine protein.	2 g or greater proteinuria in 24 hours	• Withhold until less than or equal to 2 g of proteinuria per 24 hours. • Resume at a reduced dose. • Permanently discontinue for nephrotic syndrome.
Diarrhea [see Warnings and Precautions]	• Promptly initiate management of diarrhea.	Persistent or intolerable Grade 2 or 3 adverse reaction	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at reduced dose.
		Grade 4 adverse reaction	• Permanently discontinue.
Gastrointestinal Perforation [see Warnings and Precautions]		Any Grade	• Permanently discontinue.
Fistula Formation [see Warnings and Precautions]		Grade 3 or 4	• Permanently discontinue.
QT Interval Prolongation [see Warnings and Precautions]	• 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.	>500 ms or >60 ms increase from baseline	• Withhold until improves to less than or equal to 480 ms or baseline. • Resume at a reduced dose.
Hypocalcemia [see Warnings and Precautions]	• Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment.	Persistent or intolerable Grade 2 or 3 adverse reaction Grade 4 laboratory abnormality	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at a reduced dose.
		Grade 4 adverse reaction	• Permanently discontinue.

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

LENVIMA® Recommendations for Management of Adverse Reactions (cont'd)[1]

Adverse Reaction	Monitoring	Severity	Dose Modifications
Reversible Posterior Leukoencephalopathy Syndrome (RPLS) [see Warnings and Precautions]	• Confirm diagnosis of RPLS with magnetic resonance imaging (MRI).	Any Grade	• Withhold until fully resolved. • Resume at a reduced dose or discontinue depending on severity and persistence of neurologic symptoms.
Hemorrhagic Events [see Warnings and Precautions]	• Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (eg, carotid artery).	Persistent or intolerable Grade 2 or 3 adverse reaction	• Withhold until improves to Grade 0 to 1 or baseline.
		Grade 4 adverse reaction	• Permanently discontinue.
Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction [see Warnings and Precautions]	• Monitor thyroid function prior to initiation and at least monthly during treatment. • Treat hypothyroidism according to standard medical practice.		
Impaired Wound Healing [see Warnings and Precautions]	• The safety of resumption of LENVIMA after resolution of wound healing complications has not been established.		• 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.
Osteonecrosis of the Jaw (ONJ) [see Warnings and Precautions]	• Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA treatment. • Advise patients regarding good oral hygiene practices. • Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk. • For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ.		• Withhold LENVIMA for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. • Withhold LENVIMA if ONJ develops and restart based on clinical judgement of adequate resolution.
Other Adverse Reactions [see Warnings and Precautions for Diarrhea, Hypocalcemia, and Hemorrhagic Events]		Persistent or intolerable Grade 2 or 3 adverse reaction Grade 4 laboratory abnormality	• Withhold until improves to Grade 0 to 1 or baseline. • Resume at reduced dose.
		Grade 4 adverse reaction	• Permanently discontinue.

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.

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.

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

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 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%).

In RCC, the most common adverse reactions (≥30%) observed in LENVIMA + everolimus–treated patients were diarrhea (81%), fatigue (73%), arthralgia/myalgia (55%), decreased appetite (53%), vomiting (48%), nausea (45%), stomatitis (44%), hypertension (42%), peripheral edema (42%), cough (37%), abdominal pain (37%), dyspnea (35%), rash (35%), decreased weight (34%), hemorrhagic events (32%), and proteinuria (31%). The most common serious adverse reactions (≥5%) were renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%). Adverse reactions led to dose reductions or interruption in 89% of patients. The most common adverse reactions (≥5%) resulting in dose reductions were diarrhea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%). Treatment discontinuation due to an adverse reaction occurred in 29% of patients.

In HCC, the most common adverse reactions (≥20%) observed in LENVIMA-treated patients were hypertension (45%), fatigue (44%), diarrhea (39%), decreased appetite (34%), arthralgia/myalgia (31%), decreased weight (31%), abdominal pain (30%), palmar-plantar erythrodysesthesia syndrome (27%), proteinuria (26%), dysphonia (24%), hemorrhagic events (23%), hypothyroidism (21%), and nausea (20%). The most common serious adverse reactions (≥2%) were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%). Adverse reactions led to dose reductions or interruption in 62% of patients. The most common adverse reactions (≥5%) resulting in dose reductions were fatigue (9%), decreased appetite (8%), diarrhea (8%), proteinuria (7%), hypertension (6%), and palmar-plantar erythrodysesthesia syndrome (5%). Treatment discontinuation due to an adverse reaction occurred in 20% of patients. The most common adverse reactions (≥1%) resulting in discontinuation of LENVIMA were fatigue (1%), hepatic encephalopathy (2%), hyperbilirubinemia (1%), and hepatic failure (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.

Glossary

1L=first-line; 2L=second line; AR=adverse reaction; aRCC=advanced renal cell carcinoma; CI=confidence interval; CrCl=creatinine clearance; DTC=differentiated thyroid cancer; ECOG=Eastern Cooperative Oncology Group; HCC=hepatocellular carcinoma; HR=hazard ratio; mRECIST=modified Response Evaluation Criteria in Solid Tumors; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PI=prescribing information; PS=performance status; SELECT=**S**tudy of (**E**7080) **LE**nvatinib in Differentiated **C**ancer of the **T**hyroid; RAI-R=radioactive iodine-refractory; RECIST=Response Evaluation Criteria in Solid Tumors; REFLECT=A Multicenter, **R**andomized, Open-Label, Phase 3 Trial to Compare the **EF**ficacy and Safety of **LE**nvatinib (E7080) Versus Sorafenib in First-Line Treatment of Subjects With Unrese**C**table Hepa**T**ocellular Carcinoma; VEGF=vascular endothelial growth factor; VEGFR=vascular endothelial growth factor receptor.

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

Access and Support Information

For Patients Prescribed LENVIMA®

Eisai Patient Support

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 LENVIMA Patient Assistance Program also provides LENVIMA at no cost to eligible patients with financial need. For assistance, call the Eisai Patient Support at 1-866-61-EISAI (1-866-613-4724) for more information.

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.

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 www.eisaipatientsupport.com/hcp/lenvima.

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 www.LENVIMA.com for additional resources for patients and caregivers, including the LENVIMA Symptom Tracker.

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

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.

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

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.** Motzer RJ, Hutson TE, Glen H. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. *Lancet Oncol.* 2015;16(15):1473-1482.

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg