MANAGING ADVERSE REACTIONS

That May Occur With LENVIMA®

For First-line Treatment of Unresectable Hepatocellular Carcinoma

RECOGNIZE ARs

Understand possible ARs to help prepare your patients for the treatment journey

MONITOR ARs

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

MANAGE ARs

Consider ways to approach ARs to help your patients on treatment

AR=adverse reaction.

INDICATION

LENVIMA is indicated for the first-line treatment of patients with unresectable hepatocellular carcinoma (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.

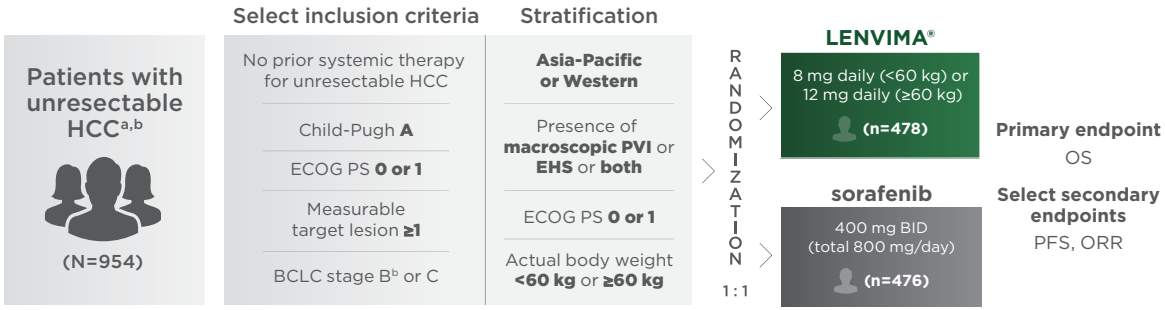
Serious complications of poorly controlled hypertension have been reported. Control blood pressure prior to initiation. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at reduced dose when hypertension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

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

REFLECT is a positive, head-to-head phase 3 trial against sorafenib in first-line unresectable HCC[1,2]

A large, phase 3, multicenter, randomized, open-label noninferiority trial[1-3]



[a]Eligible patients had unresectable HCC, with diagnoses confirmed histologically or cytologically, or confirmed clinically in accordance with American Association for the Study of Liver Diseases criteria.
[b]Ineligible for local liver-directed therapy.

- The REFLECT trial included 217 patients (23%) with hepatitis C and 479 patients (50%) with hepatitis B[2]
- Patients with ≥50% liver occupation, obvious bile duct invasion, or main portal vein invasion were excluded from the trial[2]
- The primary endpoint, OS, was tested for noninferiority[1]
- mRECIST and RECIST version 1.1 were used for independent assessment of PFS and ORR. Secondary endpoints were tested for superiority[2]
  - 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[4,5]
- REFLECT excluded patients who had a gastrointestinal bleeding event or active hemoptysis within 28 days prior to randomization[3]

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.

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Median OS of 13.6 months[1]

LENVIMA achieved noninferiority primary endpoint vs sorafenib in the REFLECT trial[1]

Overall survival	LENVIMA n=478	sorafenib n=476
Median OS in months (95% CI)	**13.6 (12.1-14.9)**	12.3 (10.4-13.9)
Hazard ratio (95% CI)[a]	0.92 (0.79-1.06)[a]	

- Number of events: 351 (73%) with LENVIMA vs 350 (74%) with sorafenib[1]
- LENVIMA did not demonstrate a statistically significant improvement in OS vs sorafenib[1]

LENVIMA achieved statistical superiority in secondary endpoints PFS and ORR[1,2]

- 7.3 months median PFS vs 3.6 months with sorafenib (HR: 0.64 [95% CI: 0.55-0.75]; *P*<0.001)*
  - Number of events: 311 (65%) with LENVIMA vs 323 (68%) with sorafenib
  - An independent assessment using 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
- 41% ORR vs 12% with sorafenib (95% CI: 36%-45% vs 95% CI: 10%-16%; *P*<0.001)*
  - 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*
  - An independent assessment using 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

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; HCC=hepatocellular carcinoma; ECOG PS=Eastern Cooperative Oncology Group performance status; BCLC=Barcelona Clinic Liver Cancer; PVI=portal vein invasion; EHS=extrahepatic spread; BID=twice daily; OS=overall survival; PFS=progression-free survival; ORR=objective response rate; mRECIST=modified Response Evaluation Criteria In Solid Tumors; RECIST=Response Evaluation Criteria In Solid Tumors; CI=confidence interval; HR=hazard ratio.

[a]Based on stratified Cox-model. The noninferiority margin for the HR of LENVIMA vs sorafenib is 1.08.
*Based on a masked independent imaging review according to mRECIST.[2]

SELECTED SAFETY INFORMATION
Warnings and Precautions (cont'd)
Arterial Thromboembolic Events. Among patients receiving LENVIMA or LENVIMA + everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in RCC and HCC and 5% in DTC. Grade 3-5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials.

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%).

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Recognize ARs That May Occur With LENVIMA®

Most common ARs (≥20%) observed in patients taking LENVIMA in the REFLECT trial[1]

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

Serious ARs (≥2%) in LENVIMA-treated patients[1]

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

Most common grade 3-4 (≥5%) ARs 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%
Hand-foot skin reaction	3%	11%

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

AR=adverse reaction; 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.

[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, and protein urine present.

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Recognize ARs That May Occur With LENVIMA®

ARs occurring in ≥10% of patients in the LENVIMA arm in REFLECT[1]

	LENVIMA 8 mg/12 mg n=476		sorafenib 800 mg n=475	
Adverse reaction	**Grade 1-4 (%)**	**Grade 3-4 (%)**	**Grade 1-4 (%)**	**Grade 3-4 (%)**
Endocrine				
Hypothyroidism[a]	21	0	3	0
Gastrointestinal				
Diarrhea	39	4	46	4
Abdominal pain[b]	30	3	28	4
Nausea	20	1	14	1
Vomiting	16	1	8	1
Constipation	16	1	11	0
Ascites[c]	15	4	11	3
Stomatitis[d]	11	0.4	14	1
General				
Fatigue[e]	44	7	36	6
Pyrexia[f]	15	0	14	0.2
Peripheral edema	14	1	7	0.2
Metabolism and nutrition				
Decreased appetite	34	5	27	1
Decreased weight	31	8	22	3
Musculoskeletal and connective tissue				
Arthralgia/myalgia[g]	31	1	20	2
Nervous system				
Headache	10	1	8	0
Renal and urinary				
Proteinuria[h]	26	6	12	2
Respiratory, thoracic, and mediastinal				
Dysphonia	24	0.2	12	0
Skin and subcutaneous tissue				
Hand-foot skin reaction	27	3	52	11
Rash[i]	14	0	24	2
Vascular				
Hypertension[j]	45	24	31	15
Hemorrhagic events[k]	23	4	15	4

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

[a]Includes hypothyroidism and blood thyroid stimulating hormone increased.
[b]Includes abdominal discomfort, abdominal pain, abdominal tenderness, epigastric discomfort, gastrointestinal pain, lower abdominal pain, and upper abdominal pain.
[c]Includes ascites and malignant ascites.
[d]Includes aphthous ulcer, gingival erosion, gingival ulceration, glossitis, mouth ulceration, oral mucosal blistering, and stomatitis.
[e]Includes asthenia, fatigue, lethargy, and malaise.
[f]Includes increased body temperature and pyrexia.
[g]Includes arthralgia, back pain, extremity pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, and myalgia.
[h]Includes proteinuria, increased urine protein, and protein urine present.
[i]Includes erythema, erythematous rash, exfoliative rash, genital rash, macular rash, maculo-papular rash, papular rash, pruritic rash, pustular rash, and rash.
[j]Includes increased diastolic blood pressure, increased blood pressure, hypertension, and orthostatic hypertension.
[k]Includes all hemorrhage terms. Hemorrhage terms that occurred in 5 or more subjects in either treatment group include epistaxis, hematuria, gingival bleeding, hemoptysis, esophageal varices hemorrhage, hemorrhoidal hemorrhage, mouth hemorrhage, rectal hemorrhage, and upper gastrointestinal hemorrhage.

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Recognize ARs That May Occur With LENVIMA®

Grade 3-4 lab abnormalities in ≥2% of patients in the LENVIMA arm[1,a,b]

Laboratory abnormality	LENVIMA %	sorafenib %
Chemistry		
Increased GGT	17	20
Hyponatremia	15	9
Hyperbilirubinemia	13	10
Increased aspartate aminotransferase (AST)	12	18
Increased alanine aminotransferase (ALT)	8	9
Increased alkaline phosphatase	7	5
Increased lipase	6	17
Hypokalemia	3	4
Hyperkalemia	3	2
Decreased albumin	3	1
Increased creatinine	2	2
Hematology		
Thrombocytopenia	10	8
Lymphopenia	8	9
Neutropenia	7	3
Anemia	4	5

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

AR=adverse reaction; GGT=gamma glutamyl transpeptidase; 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.

[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=278 to 470) and sorafenib (n=260 to 473).

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

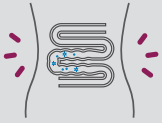
Monitor ARs That May Occur With LENVIMA

Understand possible ARs with LENVIMA to help you and your patients prepare for their treatment journey[1]


Hypertension


Decreased weight


Hypothyroidism


Diarrhea


Hand-foot skin reaction

Fatigue


Decreased appetite

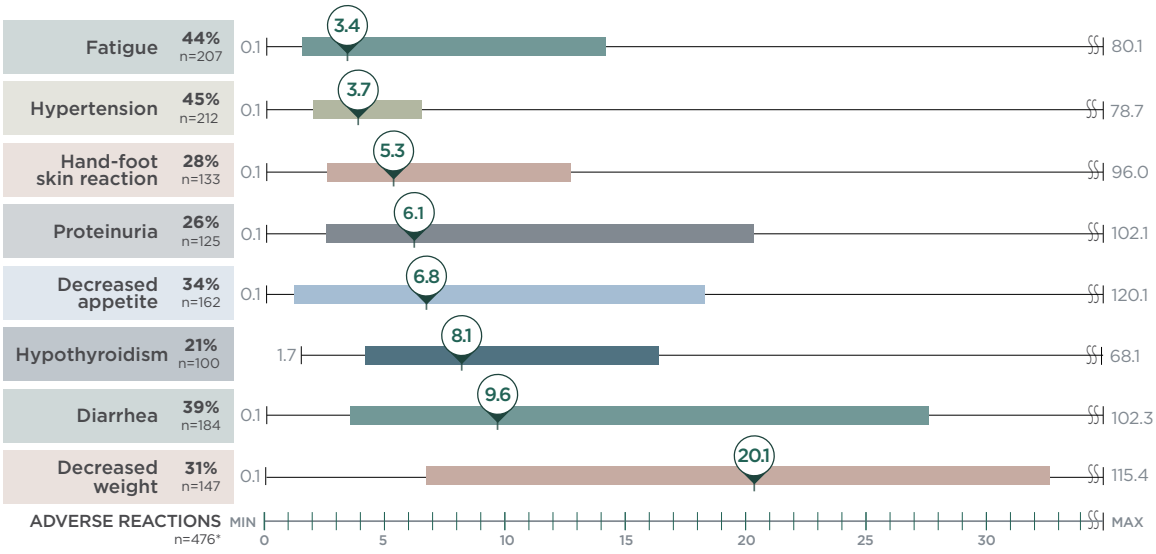

Proteinuria

The list of ARs above is not the full list mentioned in the PI. For the complete list of ARs, please see available full Prescribing Information.

Monitor ARs That May Occur With LENVIMA®

Post hoc analysis of time to first onset of select ARs[3]

Identify points in treatment when ARs emerged in the REFLECT trial



Median weeks; n=476*

Monitor your patients for ARs throughout treatment with LENVIMA

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

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

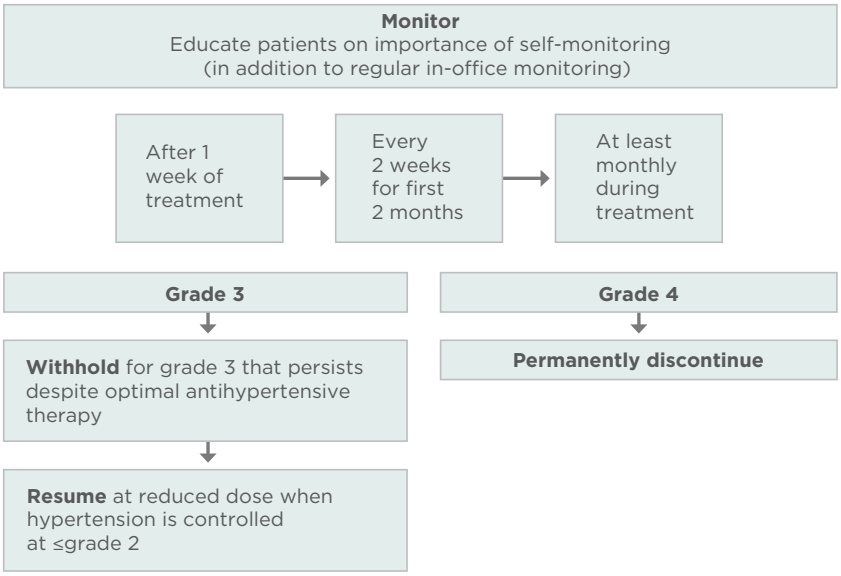
Please see additional Selected Safety Information throughout and accompanying full Prescribing Information.

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Help Manage ARs: **Hypertension**

PI-guided strategies to help manage hypertension[1]

Control blood pressure prior to initiating treatment



Hypertension in REFLECT protocol

- REFLECT's inclusion criteria included adequately controlled BP, with up to 3 antihypertensive agents[1]
- Based on the study protocol, the following guidelines were used for the management of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg confirmed on repeat measurements after 1 hour[3]
  - LENVIMA was continued and antihypertensive therapy was instituted for patients not already receiving antihypertensive medication
  - For patients already on antihypertensive medication, dose or medication choice was modified as per the investigator

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LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

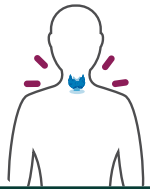
Help Manage ARs: **Hypothyroidism**

PI-guided strategies to help manage hypothyroidism[1]

Monitor thyroid function prior to initiating LENVIMA® and at least monthly during treatment

↓

Treat hypothyroidism according to standard medical practice



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

Help Manage ARs: **Hand-Foot Skin Reaction**

PI-guided strategies to help manage hand-foot skin reaction[1]

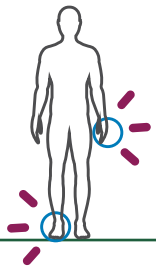
Grade 2 (persistent or intolerable)
or **Grade 3**

↓

Withhold until improved to grade 0 to 1, or baseline

↓

Resume at a reduced dose



CTCAE v4.0 does not define grade 4 hand-foot skin reaction.
Permanently discontinue for grade 4 adverse reactions.

SELECTED SAFETY INFORMATION
Warnings and Precautions (cont'd)
Arterial Thromboembolic Events (cont'd). Permanently discontinue following an arterial thrombotic event. The safety of resuming after an arterial thromboembolic event has not been established, and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

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.

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Help Manage ARs: **Decreased Appetite**

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

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

↓

Withhold until improved to grade 0 to 1, or baseline

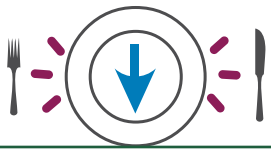
↓

Resume at a reduced dose

Grade 4

↓

Permanently discontinue



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

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.

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.

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Help Manage 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.

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.

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Help Manage ARs: **Diarrhea**

PI-guided strategies to help manage diarrhea[1]

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

↓

Withhold until improved to grade 0 to 1, or baseline

↓

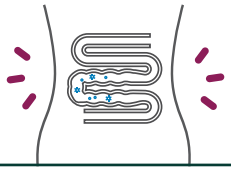
Resume at a reduced dose

Grade 4

↓

Permanently discontinue

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



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

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%.

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Help Manage ARs: **Fatigue**

PI-guided strategies to help manage fatigue[1]

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

↓

Withhold until improved to grade 0 to 1, or baseline

↓

Resume at a reduced dose

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

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

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.

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Help Manage ARs: **Proteinuria**

PI-guided strategies to help manage proteinuria[1]

Monitor
For proteinuria prior to starting treatment and periodically during treatment

If ≥2+ on urine dipstick

↓

Obtain 24-hour urine protein sample

↓

Proteinuria ≥2 g/24 hr:
Withhold LENVIMA until ≤2 g/24 hr

↓

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

For nephrotic syndrome
Disorder characterized by symptoms that include severe edema, proteinuria, and hypoalbuminemia; it is indicative of renal dysfunction[6]

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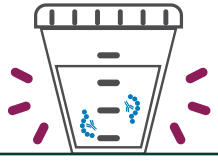
Permanently discontinue



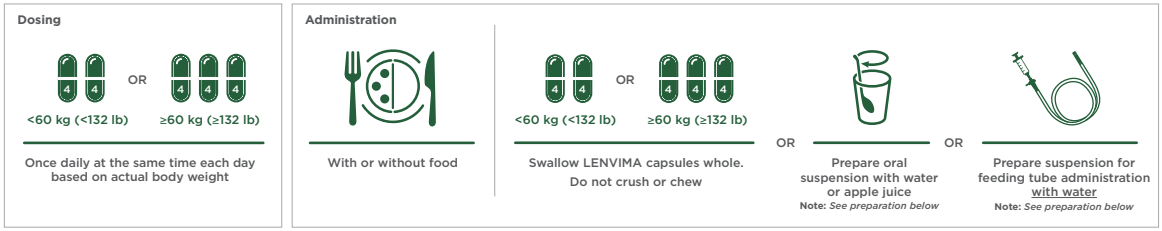
AR=adverse reaction; HCC=hepatocellular carcinoma.

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

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

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



Capsules pictured are not actual size.

Recommended LENVIMA® dose: **8 mg (two 4-mg capsules) for a patient weighing less than 132 lb (<60 kg), and 12 mg (three 4-mg capsules) for a patient weighing 132 lb or more (≥60 kg).**

Preparation of suspension:

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

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

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

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.

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

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

Continue LENVIMA until disease progression or unacceptable toxicity.[1]

Hepatic impairment[1]

- 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

Renal impairment[1]

- No dose adjustment is recommended for patients with mild (creatinine clearance 60-89 mL/min) or moderate (creatinine clearance 30-59 mL/min) renal impairment
- There is no recommended dose of LENVIMA for patients with HCC and severe renal impairment
- LENVIMA has not been studied in patients with end-stage renal disease

Missed doses of LENVIMA[1]

- LENVIMA should be taken at the same time each day
- If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration

HCC=hepatocellular carcinoma; AR=adverse reaction.

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LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Dose Modifications With LENVIMA®[1]

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	3rd dosage reduction to
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.

- Treatment discontinuation due to ARs occurred in 20% of patients taking LENVIMA[1]
- The most common ARs (≥5%) resulting in dose reduction or interruption of LENVIMA were fatigue (9%), decreased appetite (8%), diarrhea (8%), proteinuria (7%), hypertension (6%), and hand-foot skin reaction (5%)[1]
- The median time to first dose reduction was 10 weeks with LENVIMA and 3.7 weeks with sorafenib[3]
  - **Limitation:** this is a post hoc exploratory analysis for descriptive purposes only; no conclusion can be drawn

SELECTED SAFETY INFORMATION
Warnings and Precautions (cont'd)
Hemorrhagic Events (cont'd). 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.

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LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Doses Available in Blister Packs

- 12-mg and 8-mg blister packs facilitate initial prescriptions
- 8-mg and 4-mg blister packs help you and patients implement dose modifications
- For instance, if reducing from 12 mg to 8 mg, instruct your patient to take two 4-mg capsules instead of three until current prescription runs out, then prescribe your patient the 8-mg pack

12-mg daily dose

8-mg daily dose

Each blister card contains a 5-day supply of LENVIMA® capsules

Prescribing LENVIMA (recommended doses and/or modified doses)

12-mg dose: Three 4-mg capsules (12 mg total) PO once daily x 30 days (90 capsules)

8-mg dose: Two 4-mg capsules (8 mg total) PO once daily x 30 days (60 capsules)

4-mg dose: One 4-mg capsule PO once daily x 30 days (30 capsules)

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

SELECTED SAFETY INFORMATION
Warnings and Precautions (cont'd)
Hemorrhagic Events (cont'd). Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (eg, carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction. LENVIMA impairs exogenous thyroid suppression. In DTC, 88% of patients had baseline thyroid stimulating hormone (TSH) level ≤0.5 mU/L. In patients with normal TSH at baseline, elevation of TSH level >0.5 mU/L was observed post baseline in 57% of LENVIMA-treated patients. In RCC and HCC, grade 1 or 2 hypothyroidism occurred in 24% of LENVIMA + everolimus–treated patients and 21% of LENVIMA-treated patients, respectively. In patients with normal or low TSH at baseline, elevation of TSH was observed post baseline in 70% of LENVIMA-treated patients in HCC and 60% of LENVIMA + everolimus–treated patients in RCC.

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

Impaired Wound Healing. Impaired wound healing has been reported in patients who received LENVIMA. Withhold LENVIMA for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of LENVIMA after resolution of wound healing complications has not been established.

Osteonecrosis of the Jaw (ONJ). ONJ has been reported in patients receiving LENVIMA. Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease, or invasive dental procedures, may increase the risk of ONJ.

Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA treatment. Advise patients regarding good oral hygiene practices and to consider having preventive dentistry performed prior to treatment with LENVIMA and throughout treatment with LENVIMA.

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

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

Embryo-Fetal Toxicity. Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to pregnant women. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended clinical doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for 30 days after the last dose.

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LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

SELECTED SAFETY INFORMATION

Adverse Reactions

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.

ACCESS AND SUPPORT INFORMATION

For Patients Prescribed LENVIMA®

- With the LENVIMA Co-Pay Program, eligible commercially insured patients may pay as little as $0 per month.* Annual limits apply. Depending on the insurance plan, patients could have additional financial responsibility. See **www.LENVIMAREIMBURSEMENT.com/hcp** for complete terms and conditions. For assistance, **call 1-855-347-2448** or visit **www.LENVIMACopay.com** to enroll eligible patients
- Eisai Patient Support provides support for eligible patients. By contacting Eisai Patient Support, patients can get help understanding their coverage for LENVIMA through a benefits investigation. They can also request a patient welcome kit. The Patient Assistance Program also provides LENVIMA at no cost to eligible patients with financial need

Please call Eisai Patient Support at
1-866-EISAI (1-866-613-4724) for more information.

Please visit **www.LENVIMAREIMBURSEMENT.com**
for more information about **access and reimbursement.**

*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.** Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non inferiority trial. *Lancet.* 2018;391(10126):1163-1173. **3.** Data on file. Eisai Inc. **4.** Takada J, Hidaka H, Nakazawa T, et al. Modified response evaluation criteria in solid tumors is superior to response evaluation criteria in solid tumors for assessment of responses to sorafenib in patients with advanced hepatocellular carcinoma. *BMC Res Notes.* 2015;8:609. **5.** Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis.* 2010;30(1):52-60. **6.** Kodner C. Diagnosis and management of nephrotic syndrome in adults. *Am Fam Physician.* 2016;93(6):479-485.

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.

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