LENVIMA®
(lenvatinib) capsules | 10 mg and 4 mg

MANAGING ADVERSE REACTIONS

That May Occur With LENVIMA®

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

Please see Important Safety Information on pages 28-31, and full Prescribing Information.

Recommended dosage in uHCC, RAI-R DTC, and aRCC[1]

INDICATION: uHCC

RECOMMENDED DOSE		IN PATIENTS WITH SEVERE RENAL OR MODERATE/SEVERE HEPATIC IMPAIRMENT	
Recommended Dose	Dose Formulation	Modified Dose	Dose Formulation
≥60 kg (≥132 lb) actual body weight: 12 mg LENVIMA®, QD	≥60 kg (≥132 lb): three 4-mg capsules	There is no recommended dose for patients with uHCC	
<60 kg (<132 lb) actual body weight: 8 mg LENVIMA, QD	<60 kg (<132 lb): two 4-mg capsules		

INDICATION: RAI-R DTC

RECOMMENDED DOSE		IN PATIENTS WITH SEVERE RENAL OR MODERATE/SEVERE HEPATIC IMPAIRMENT	
Recommended Dose	Dose Formulation	Modified Dose	Dose Formulation
24 mg LENVIMA, QD	two 10-mg capsules + one 4-mg capsule	14 mg, QD	one 10-mg capsule + one 4-mg capsule

INDICATION: aRCC

RECOMMENDED DOSE		IN PATIENTS WITH SEVERE RENAL OR MODERATE/SEVERE HEPATIC IMPAIRMENT	
Recommended Dose	Dose Formulation	Modified Dose	Dose Formulation
18 mg LENVIMA + 5 mg everolimus, QD	one LENVIMA 10-mg capsule + two LENVIMA 4-mg capsules + 5 mg everolimus	10 mg LENVIMA, QD	one LENVIMA 10-mg capsule

Severe renal impairment=creatinine clearance 15-29 mL/min; moderate hepatic impairment=Child-Pugh B; severe hepatic impairment=Child-Pugh C.

Recognize, monitor, and manage ARs with LENVIMA

How to recognize, monitor, and manage ARs

RECOGNIZE ARs that may occur with LENVIMA
- Understand possible ARs with LENVIMA to help you and your patients prepare for the treatment journey

MONITOR ARs that may occur with LENVIMA
- Identify points in treatment where select ARs emerged in the REFLECT Trial (uHCC), SELECT trial (RAI-R DTC), and Study 205 (aRCC) so you can provide timely management
- Monitor your patients for ARs throughout treatment with LENVIMA

MANAGE ARs that may occur with LENVIMA
- Consider ways to approach ARs to help your patients on treatment

aRCC=advanced renal cell carcinoma; RAI-R DTC=radioactive iodine-refractory differentiated thyroid cancer; uHCC=unresectable hepatocellular carcinoma; QD=once daily; 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; SELECT=**S**tudy of (**E**7080) **LE**nvatinib in Differentiated **C**ancer of the **T**hyroid.

REFLECT trial 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 (12 mg for baseline actual body weight ≥60 kg or 8 mg for baseline actual body weight <60 kg) orally once daily or sorafenib 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.

In REFLECT trial

Most common ARs (≥20%) observed in patients taking LENVIMA[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]

No grade 4 hypertension, proteinuria, decreased appetite, or diarrhea were reported in REFLECT.[2]

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; ECOG PS=Eastern Cooperative Oncology Group performance status; OS=overall survival; PFS=progression-free survival; ORR=objective response rate.

[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.

Adverse reactions occurring in ≥10% of patients in the LENVIMA arm[1]

Adverse reaction	LENVIMA 8 mg/12 mg n=476		sorafenib 800 mg n=475	
	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

- Treatment discontinuation due to an adverse reaction occurred in 20% of patients with HCC in the LENVIMA-treated group[1]
  - In HCC, the most common adverse reactions (1%) resulting in discontinuation of LENVIMA were fatigue (1%), hepatic encephalopathy (2%), hyperbilirubinemia (1%), and hepatic failure (1%)[1]

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.

SELECT trial study design[1]

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.

In SELECT trial

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

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

Most common serious ARs (≥2%) in the LENVIMA arm[1]

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

Most common grade 3-4 ARs (≥5%) in the LENVIMA arm[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%

No grade 4 diarrhea, hand-foot skin reaction, fatigue, or proteinuria.[3]

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

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

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

	LENVIMA 24 mg (n=261)		Placebo (n=131)	
Adverse reaction	All grades (%)	Grade 3-4 (%)	All grades (%)	Grade 3-4 (%)
Vascular				
Hypertension[a]	73	44	16	4
Hypotension	9	2	2	0
Gastrointestinal				
Diarrhea	67	9	17	0
Nausea	47	2	25	1
Stomatitis[b]	41	5	8	0
Vomiting	36	2	15	0
Abdominal pain[c]	31	2	11	1
Constipation	29	0.4	15	1
Oral pain[d]	25	1	2	0
Dry mouth	17	0.4	8	0
Dyspepsia	13	0.4	4	0
General				
Fatigue[e]	67	11	35	4
Edema peripheral	21	0.4	8	0
Musculoskeletal and connective tissue				
Arthralgia/myalgia[f]	62	5	28	3
Metabolism and nutrition				
Decreased appetite	54	7	18	1
Decreased weight	51	13	15	1
Dehydration	9	2	2	1

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

Adverse reaction	LENVIMA 24 mg (n=261)		Placebo (n=131)	
	All grades (%)	Grade 3-4 (%)	All grades (%)	Grade 3-4 (%)
Nervous system				
Headache	38	3	11	1
Dysgeusia	18	0	3	0
Dizziness	15	0.4	9	0
Renal and urinary				
Proteinuria	34	11	3	0
Skin and subcutaneous tissue				
Palmar-plantar erythrodysesthesia syndrome	32	3	1	0
Rash[g]	21	0.4	3	0
Alopecia	12	0	5	0
Hyperkeratosis	7	0	2	0
Respiratory, thoracic, and mediastinal				
Dysphonia	31	1	5	0
Cough	24	0	18	0
Epistaxis	12	0	1	0
Psychiatric				
Insomnia	12	0	3	0
Infections				
Urinary tract infection	11	1	5	0
Dental and oral infections[h]	10	1	1	0
Cardiac				
Prolonged electrocardiogram QT	9	2	2	0

- Treatment discontinuation due to an adverse reaction occurred in 18% of patients with DTC[1]
  - In DTC, the most common adverse reactions (≥1%) resulting in discontinuation of LENVIMA were asthenia (1%), and hypertension (1%)[1]

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

[a]Includes hypertension, hypertensive crisis, increased blood pressure diastolic, and increased blood pressure.
[b]Includes aphthous stomatitis, stomatitis, glossitis, mouth ulceration, and mucosal inflammation.
[c]Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal pain.
[d]Includes oral pain, glossodynia, and oropharyngeal pain.
[e]Includes asthenia, fatigue, and malaise.
[f]Includes musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia.
[g]Includes macular rash, maculo-papular rash, generalized rash, and rash.
[h]Includes gingivitis, oral infection, parotitis, pericoronitis, periodontitis, sialadenitis, tooth abscess, and tooth infection.

Study 205 study design[1,2]

Study 205 randomized 153 patients with advanced or metastatic renal cell carcinoma (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 Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Other efficacy outcome measures included overall survival and objective response rate.

In Study 205

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%)[1]

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

- Renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%)[1]

Most common grade 3-4 ARs (≥5%) in the LENVIMA + everolimus arm[1]

Adverse reaction	LENVIMA 18 mg + everolimus 5 mg (n=62)	everolimus 10 mg (n=50)
Diarrhea	19%	2%
Fatigue[a]	18%	2%
Hypertension/increase 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%

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]

AR=adverse reaction.

[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.

Recognize ARs that may occur with LENVIMA® + everolimus in the Study 205

Adverse reactions occurring in >15% of patients in the LENVIMA with everolimus arm[1]*

	LENVIMA 18 mg + everolimus 5 mg n=62		everolimus 10 mg n=50	
Adverse reaction	**Grade 1-4 (%)**	**Grade 3-4 (%)**	**Grade 1-4 (%)**	**Grade 3-4 (%)**
Endocrine				
Hypothyroidism	24	0	2	0
Gastrointestinal				
Constipation	16	0	18	0
Diarrhea	81	19	34	2
Dyspepsia/gastroesophageal reflux	21	0	12	0
Abdominal pain[a]	37	3	8	0
Nausea	45	5	16	0
Oral pain[b]	23	2	4	0
Stomatitis/oral inflammation[c]	44	2	50	4
Vomiting	48	7	12	0
General				
Fatigue[d]	73	18	40	2
Peripheral edema	42	2	20	0
Pyrexia/increased body temperature	21	2	10	2
Metabolism and nutrition				
Decreased appetite	53	5	18	0
Decreased weight	34	3	8	0

*The safety data are derived from Study 205 and an additional 11 patients in the dose escalation portion of the study who received LENVIMA 18 mg + everolimus 5 mg.

[a]Includes abdominal discomfort, gastrointestinal pain, lower abdominal pain, and upper abdominal pain.
[b]Includes gingival pain, glossodynia, and oropharyngeal pain.
[c]Includes aphthous stomatitis, gingival inflammation, glossitis, and mouth ulceration.
[d]Includes asthenia, fatigue, lethargy, and malaise.

Advanced Renal Cell Carcinoma (aRCC)

Recognize ARs that may occur with LENVIMA + everolimus in the Study 205 (cont'd)

Adverse reactions occurring in >15% of patients in the LENVIMA with everolimus arm[1]*

	LENVIMA 18 mg + everolimus 5 mg n=62		everolimus 10 mg n=50	
Adverse reaction	**Grade 1-4 (%)**	**Grade 3-4 (%)**	**Grade 1-4 (%)**	**Grade 3-4 (%)**
Musculoskeletal and connective tissue				
Arthralgia/myalgia[e]	55	5	32	0
Musculoskeletal chest pain	18	2	4	0
Nervous system				
Headache	19	2	10	2
Psychiatric				
Insomnia	16	2	2	0
Renal and urinary				
Proteinuria/urine protein present	31	8	14	2
Renal failure event[f]	18	10	12	2
Respiratory, thoracic, and mediastinal				
Cough	37	0	30	0
Dyspnea/exertional dyspnea	35	5	28	8
Dysphonia	18	0	4	0
Skin and subcutaneous tissue				
Rash[g]	35	0	40	0
Vascular				
Hemorrhagic events[h]	32	6	26	2
Hypertension/increased blood pressure	42	13	10	2

- Treatment discontinuation due to an adverse reaction occurred in 29% of patients with RCC[1]
  - In RCC, the most common adverse reactions (≥1%) resulting in discontinuation of LENVIMA were thrombocytopenia (4%), alanine aminotransferase increased (2%), arthralgia (2%), aspartate aminotransferase increased (2%), cerebral hemorrhage (2%), confusional state (2%), convulsion (2%), diarrhea (2%), dyspnea (2%), gastric hemorrhage (2%), hepatic pain (2%), hypokalemia (2%), penile edema (2%), proteinuria (2%), and weight decreased (2%)[1]

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]

AR=adverse reaction.

*The safety data are derived from Study 205 and an additional 11 patients in the dose escalation portion of the study who received LENVIMA 18 mg + everolimus 5 mg.

[e]Includes arthralgia, back pain, extremity pain, musculoskeletal pain, and myalgia.
[f]Includes blood creatinine increased, blood urea increased, creatinine renal clearance decreased, nephropathy toxic, renal failure, renal failure acute, and renal impairment.
[g]Includes erythema, erythematous rash, genital rash, macular rash, maculopapular rash, papular rash, pruritic rash, pustular rash, and septic rash.
[h]Includes hemorrhagic diarrhea, epistaxis, gastric hemorrhage, hemarthrosis, hematoma, hematuria, hemoptysis, lip hemorrhage, renal hematoma, and scrotal hematocele.

Recommended plan for AR management[1]

Managing ARs with interruptions, reductions, and/or discontinuations

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

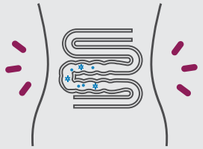
[a]National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Monitor ARs that may occur with LENVIMA®

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

Hypertension

Fatigue



Diarrhea

Decreased weight

Nausea

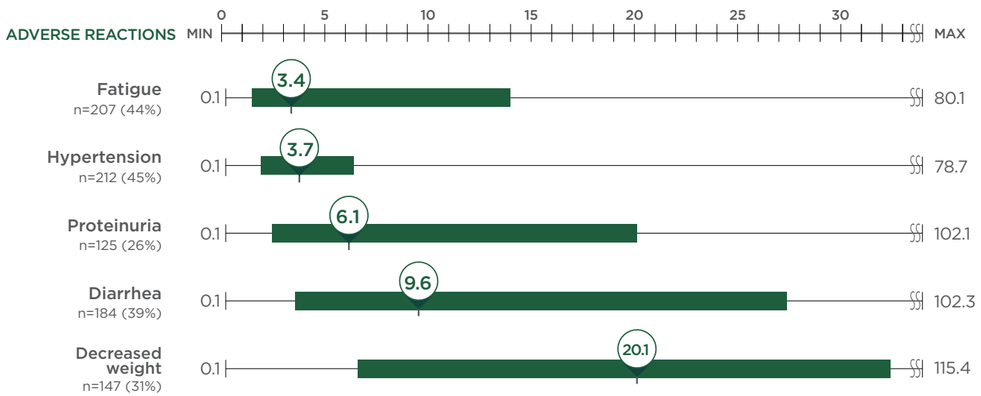
Proteinuria

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

AR=adverse reaction.

Post hoc analysis of time to onset for select ARs for uHCC in REFLECT

Post hoc analysis of REFLECT data of time to first onset of select ARs (all grades)[2] median weeks; AR (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.

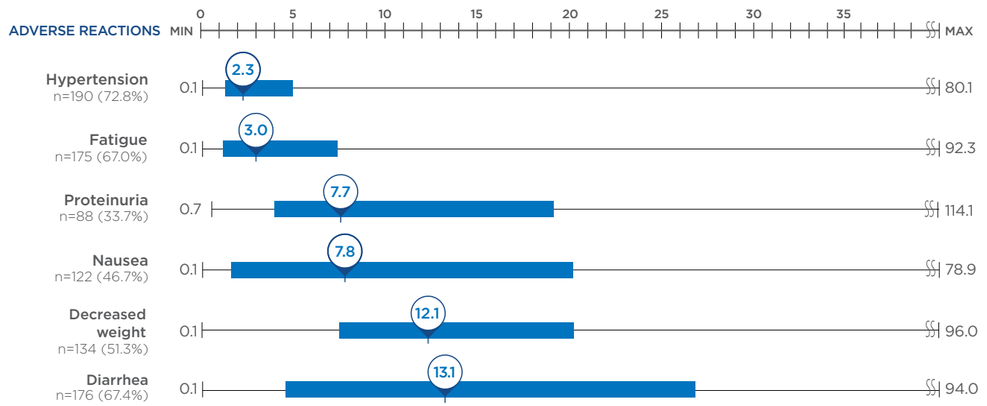
*The bar represents the time to first onset of select ARs for the middle 50% of the patients who experienced that AR from quartile 1 to 3.

AR=adverse reaction; uHCC=unresectable hepatocellular carcinoma.

Please see Important Safety Information on pages 28-31, and full Prescribing Information.

Post hoc analysis of time to onset for select ARs for RAI-R DTC in SELECT

Post hoc analysis of SELECT data of time to first onset of select ARs (all grades) median weeks; AR (n=261)[2]*



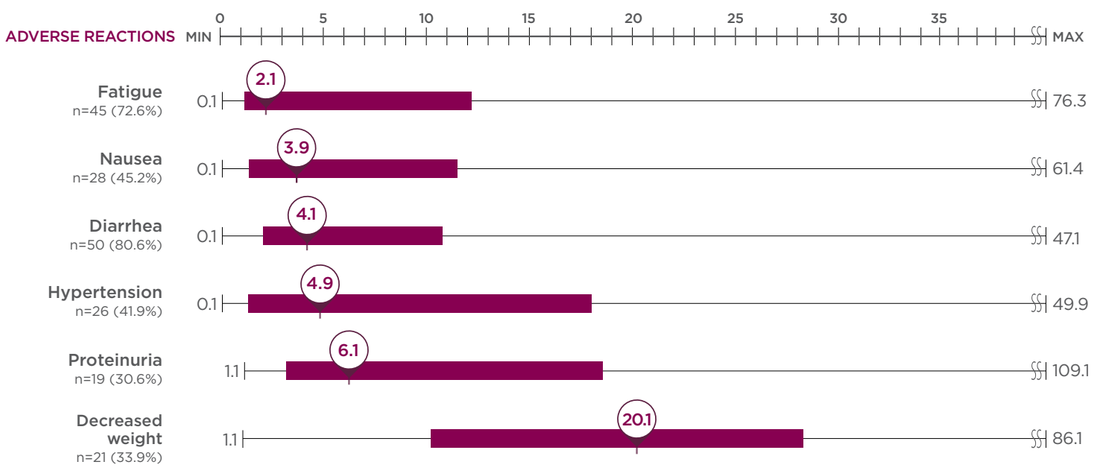
- Monitor your patients for ARs throughout treatment with LENVIMA

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

RAI-R DTC=radioactive iodine-refractory differentiated thyroid cancer.

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Post hoc analysis of Study 205 data of time to first onset of select ARs (all grades) median weeks; AR (n=62)[2]*



- Monitor your patients for ARs throughout treatment with LENVIMA® + everolimus

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.

AR=adverse reaction; aRCC=advanced renal cell carcinoma.

PI-guided strategies to help manage hypertension[1]

Control blood pressure prior to initiating treatment

Monitor
Educate patients on importance of self-monitoring in addition to regular in-office monitoring

After 1 week of treatment → Every 2 weeks for first 2 months → At least monthly during treatment

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

Hypertension

- Based on the REFLECT, SELECT, and Study 205 study protocols, 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[2]
  - 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

AR=adverse reaction; BP=blood pressure.

Help manage ARs: **Fatigue**

PI-guided strategies to help manage fatigue[1]

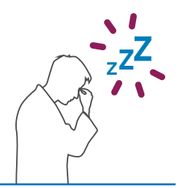
Grade 2 (persistent or intolerable) or **Grade 3**

↓

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.

Please see Important Safety Information on pages 28-31, and full Prescribing Information.

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

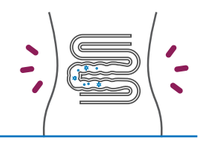
↓

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® (lenvatinib) based on severity.

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

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.

Help manage ARs: **Nausea**

PI-guided strategies to help manage nausea[1]

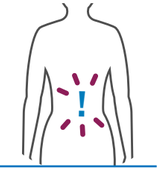
Grade 2 (persistent or intolerable)
or **Grade 3**

↓

Withhold until improved to grade 0 to 1, or baseline

↓

Resume at a reduced dose



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

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

PI-guided strategies to help manage proteinuria[1]

Monitor
For proteinuria prior to starting treatment and periodically during treatment

If ≥2+ g/hr on urine dipstick

↓

Obtain 24-hour urine protein sample

↓

Withhold for >2 g/24 hr

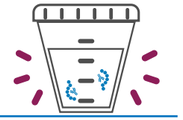
↓

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

For nephrotic syndrome
Disorder characterized by symptoms that include severe edema, proteinuria, and hypoalbuminemia; it is indicative of renal dysfunction[4]

↓

Permanently discontinue



AR=adverse reaction; PI=prescribing information; QD=once daily.

Managing ARs with reductions and/or discontinuations. Recommended dose modifications for certain persistent or intolerable grade 2 or grade 3 adverse reactions or grade 4 laboratory abnormalities[a-c]

	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.

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

[a]Initiate medical management for nausea, vomiting, or diarrhea prior to interruption or dose reduction of LENVIMA®.
[b]Refers to the occurrence of the same or a different adverse reaction that requires dose modification.
[c]Reduce dose in succession based on the previous dose level (<60 kg: 8 mg per day, 4 mg per day, 4 mg every other day, or discontinue therapy/≥60 kg: 12 mg per day, 8 mg per day, 4 mg per day, or 4 mg every other day).

Dose modifications for RAI-R DTC recommended dose

Managing ARs with reductions and/or discontinuations. Recommended dose modifications for certain persistent or intolerable grade 2 or grade 3 adverse reactions or grade 4 laboratory abnormalities[a-c]

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

Capsules pictured are not actual size.

[a]Initiate medical management for nausea, vomiting, or diarrhea prior to interruption or dose reduction of LENVIMA®.
[b]Refers to the occurrence of the same or a different adverse reaction that requires dose modification.
[c]Reduce dose in succession based on previous dose level (24 mg, 20 mg, 14 mg, or 10 mg per day).

Please see Important Safety Information on pages 28-31, and full Prescribing Information.

Dose modifications for aRCC recommended dose

Managing ARs with reductions and/or discontinuations. Recommended dose modifications for certain persistent or intolerable grade 2 or grade 3 adverse reactions or grade 4 laboratory abnormalities[a-c]

How to dose modify with 2 oral therapies[1,a,b]

Recommended dose: 18 mg LENVIMA (one 10-mg capsule and two 4-mg capsules) + one 5-mg tablet of everolimus[1]

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

Capsules pictured are not actual size.

For toxicities thought to be related to		
	Everolimus alone	Modify the everolimus dose in accordance with the everolimus package insert[5]
	OR	
	LENVIMA + everolimus	First reduce LENVIMA and then everolimus[1]

Review the full prescribing information for everolimus for recommended dose modifications.

RAI-R DTC=radioactive iodine-refractory differentiated thyroid cancer; QD=once daily; AR=adverse reaction; aRCC=advanced renal cell carcinoma.

[a]Initiate medical management for nausea, vomiting, or diarrhea prior to interruption or dose reduction of LENVIMA.
[b]Refers to the occurrence of the same or a different adverse reaction that requires dose modification.
[c]Reduce dose in succession based on the previous dose level (18 mg, 14 mg, 10 mg, or 8 mg per day).

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

Unresectable Hepatocellular Carcinoma (uHCC)

Dosing

<60 kg (<132 lb): 4 4 — ≥60 kg (≥132 lb): 4 4 4

Once daily at the same time each day based on actual body weight

Administration

With or without food

<60 kg (<132 lb): 4 4 — ≥60 kg (≥132 lb): 4 4 4

Swallow LENVIMA capsules whole. Do not crush or chew

OR

Prepare oral suspension with water or apple juice
Note: *See preparation on opposite page*

OR

Prepare suspension for feeding tube administration with water
Note: *See preparation on opposite page*

Capsules pictured are not actual size.

The recommended daily dose of LENVIMA® for uHCC is 8 mg for patients with <60 kg of actual body weight (two 4-mg capsules) or 12 mg for patient with ≥60 kg of actual body weight (three 4-mg capsules).

Locally recurrent or metastatic, progressive, RAI-refractory Differentiated Thyroid Cancer (RAI-R DTC)

Dosing

10 10 4

Once daily at the same time each day

Administration

With or without food

10 10 4

Swallow LENVIMA capsules whole. Do not crush or chew

OR

Prepare oral suspension with water or apple juice
Note: *See preparation on opposite page*

OR

Prepare suspension for feeding tube administration with water
Note: *See preparation on opposite page*

Capsules pictured are not actual size.

The recommended daily dose of LENVIMA for locally recurrent or metastatic, progressive, RAI-refractory DTC is 24 mg (two 10-mg capsules and one 4-mg capsule).

Advanced Renal Cell Carcinoma (aRCC)

Dosing

10 4 4 + 5

Once daily at the same time each day (LENVIMA and everolimus dose)

LENVIMA Administration

With or without food

10 4 4

Swallow LENVIMA capsules whole. Do not crush or chew

OR

Prepare oral suspension with water or apple juice
Note: *See preparation on opposite page*

OR

Prepare suspension for feeding tube administration with water
Note: *See preparation on opposite page*

Capsules pictured are not actual size. Refer to the everolimus prescribing information for recommended everolimus dosing information.

Two separate prescriptions are required for the combination. The recommended daily dose is 18 mg LENVIMA (one 10-mg capsule and two 4-mg capsules) + one 5-mg tablet of everolimus.

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

DTC=differentiated thyroid cancer; HCC=hepatocellular carcinoma; RAI=radioactive iodine.
Everolimus is distributed by Novartis Pharmaceuticals Corporation.

Doses available in convenient blister packs

aRCC and RAI-R DTC

uHCC

Every pack of LENVIMA includes a 30-day treatment supply consisting of 6 individual blister cards. Each blister card contains a 5-day supply. Patients will receive a pack specific to their prescribed dose.

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

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).

Indications and Important Safety Information

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

IMPORTANT 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.

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.

Hepatotoxicity. Across clinical studies enrolling 1327 LENVIMA-treated patients with malignancies other than HCC, serious hepatic adverse reactions occurred in 1.4% of patients. Fatal events, including hepatic failure, acute hepatitis and hepatorenal syndrome, occurred in 0.5% of patients. In HCC, hepatic encephalopathy occurred in 8% of LENVIMA-treated patients (5% grade 3-5). Grade 3-5 hepatic failure occurred in 3% of LENVIMA-treated patients; 2% of patients discontinued LENVIMA due to hepatic encephalopathy and 1% discontinued due to hepatic failure.

Monitor liver function prior to initiation, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Monitor patients with HCC closely for signs of hepatic failure, including hepatic encephalopathy. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Renal Failure or Impairment. Serious including fatal renal failure or impairment can occur with LENVIMA. Renal impairment was reported in 14% and 7% of LENVIMA-treated patients in DTC and HCC, respectively. Grade 3-5 renal failure or impairment occurred in 3% of patients with DTC and 2% of patients with HCC, including 1 fatal event in each study. In RCC, renal impairment or renal failure was reported in 18% of LENVIMA + everolimus–treated patients (10% grade 3).

Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at reduced dose upon recovery or permanently discontinue for renal failure or impairment based on severity.

Important Safety Information

IMPORTANT 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.

Fistula Formation and Gastrointestinal Perforation. Of the 799 patients treated with LENVIMA or LENVIMA + everolimus in DTC, RCC, and HCC, fistula or gastrointestinal perforation occurred in 2%. Permanently discontinue in patients who develop gastrointestinal perforation of any severity or grade 3-4 fistula.

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

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

Hypocalcemia. In DTC, grade 3-4 hypocalcemia occurred in 9% of LENVIMA-treated patients. In 65% of cases, hypocalcemia improved or resolved following calcium supplementation with or without dose interruption or dose reduction. In RCC, grade 3-4 hypocalcemia occurred in 6% of LENVIMA + everolimus–treated patients. In HCC, grade 3 hypocalcemia occurred in 0.8% of LENVIMA-treated patients. Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity.

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

Hemorrhagic Events. Serious including fatal hemorrhagic events can occur with LENVIMA. In DTC, RCC, and HCC clinical trials, hemorrhagic events, of any grade, occurred in 29% of the 799 patients treated with LENVIMA as a single agent or in combination with everolimus. The most frequently reported hemorrhagic events (all grades and occurring in at least 5% of patients) were epistaxis and hematuria. In DTC, grade 3-5 hemorrhage occurred in 2% of LENVIMA-treated patients, including 1 fatal intracranial hemorrhage among 16 patients who received LENVIMA and had CNS metastases at baseline. In RCC, grade 3-5 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.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont'd)

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

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

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.

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%).

IMPORTANT SAFETY INFORMATION

Adverse Reactions (cont'd)

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.

Please see Important Safety Information on pages 28-31, and full Prescribing Information.

References: 1. LENVIMA [package insert]. Nutley, NJ: Eisai Inc. **2.** Data on file. Eisai Inc. **3.** Haddad RI, Schulmberger 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. **4.** Kodner C. Diagnosis and management of nephrotic syndrome in adults. *Am Fam Physician*. 2016;93(6):479-485. **5.** Afinitor [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2020.

LENVIMA®
(lenvatinib) capsules 10 mg and 4 mg