Not an actual patient

LENVIMA®: Efficacy that drives results

- LENVIMA achieved its noninferiority primary endpoint vs sorafenib in OS in REFLECT; 13.6- vs 12.3-month median OS (HR: 0.92 [95% CI: 0.79-1.06]).* LENVIMA did not demonstrate a statistically significant improvement in OS vs sorafenib[1]
  - Number of events: 351 (73%) with LENVIMA and 350 (74%) with sorafenib

Offering more time without disease progression[1]

- 7.3-month median PFS vs 3.6 months with sorafenib (HR: 0.64 [95% CI: 0.55-0.75]; *P*<0.001) (mRECIST)[1]
  - Number of events: 311 (65%) with LENVIMA and 323 (68%) with sorafenib

OS=overall survival; 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; HR=hazard ratio; CI=confidence interval; PFS=progression-free survival; mRECIST=modified Response Evaluation Criteria in Solid Tumors.

*Based on a stratified Cox-model. The noninferiority margin for the HR of LENVIMA vs sorafenib is 1.08.

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.

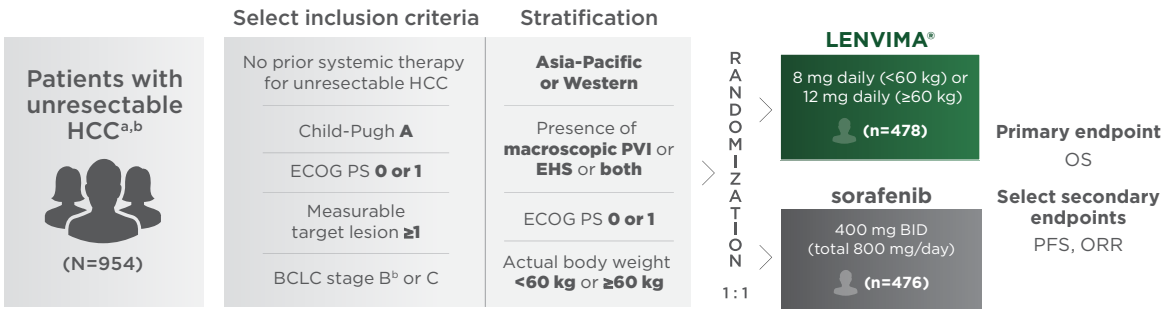
Serious complications of poorly controlled hypertension have been reported. Control blood pressure prior to initiation. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at reduced dose when hypertension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

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.

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 its 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
- 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*

OS=overall survival; 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; CI=confidence interval; PFS=progression-free survival; ORR=objective response rate; HR=hazard ratio; mRECIST=modified Response Evaluation Criteria In Solid Tumors.

[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]

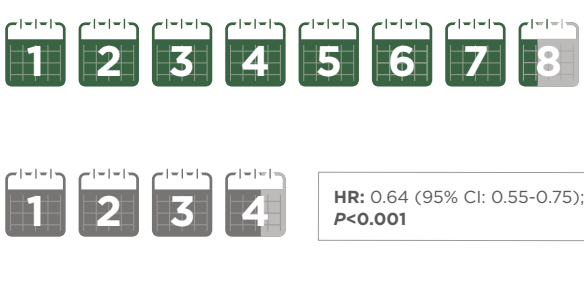
SELECTED SAFETY INFORMATION
Warnings and Precautions (cont'd)
Arterial Thromboembolic Events. Among patients receiving LENVIMA or LENVIMA + everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in RCC and HCC and 5% in DTC. Grade 3-5 arterial thromboembolic events ranged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

DOUBLE THE MEDIAN PFS:
More time without progression

LENVIMA® demonstrated statistically superior PFS per independent radiology review (mRECIST)[1]



Patients who received LENVIMA had more time without their disease progressing

- Number of events: 311 (65%) with LENVIMA vs 323 (68%) with sorafenib[1]
- An independent assessment using RECIST 1.1 criteria demonstrated a median PFS of 7.3 months with LENVIMA and 3.6 months with sorafenib (HR: 0.65 [95% CI: 0.56-0.77])[1]
  - Number of events: 307 (64%) with LENVIMA vs 320 (67%) with sorafenib[1]

PFS=progression-free survival; mRECIST=modified Response Evaluation Criteria In Solid Tumors; CI=confidence interval; HR=hazard ratio; RECIST=Response Evaluation Criteria In Solid Tumors.

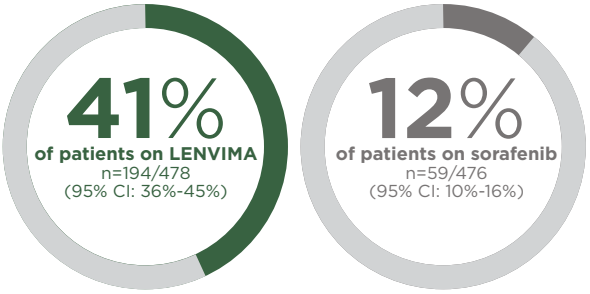
SELECTED SAFETY INFORMATION
Warnings and Precautions (cont'd)
Arterial Thromboembolic Events (cont'd). Permanently discontinue following an arterial thrombotic event. The safety of resuming after an arterial thromboembolic event has not been established, and LENVIMA has not been studied in patients who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

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

MORE THAN TRIPLE THE ORR:
More patients with a response

LENVIMA® demonstrated statistically superior ORR per independent radiology review (mRECIST)[1]



***P*<0.001**
Responses: LENVIMA vs sorafenib
CR: 2.1% (n=10) vs 0.8% (n=4)
PR: 38.5% (n=184) vs 11.6% (n=55)

41% of patients with a response to LENVIMA vs 12% with a response to sorafenib[1]

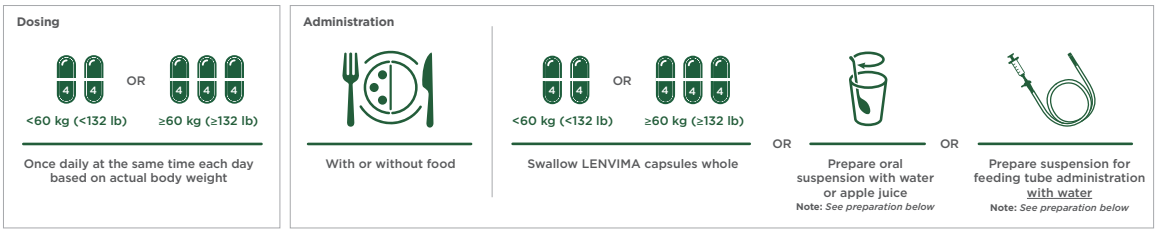
- An independent assessment using RECIST 1.1 criteria demonstrated 19% ORR with LENVIMA (95% CI: 15%-22%) and 7% with sorafenib (95% CI: 4%-9%)[1]
  - CR: 0.4% (n=2) with LENVIMA vs 0.2% (n=1) with sorafenib
  - PR: 18.4% (n=88) with LENVIMA vs 6.3% (n=30) with sorafenib

ORR=objective response rate; mRECIST=modified Response Evaluation Criteria In Solid Tumors; CI=confidence interval; CR=complete response; PR=partial response; RECIST=Response Evaluation Criteria In Solid Tumors.

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

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

Take LENVIMA® 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)
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.

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Take LENVIMA® 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.

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

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

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

Adverse reactions (ARs) with LENVIMA®

- The most common ARs (≥20%) observed in patients taking LENVIMA 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%)[1]
- The most common serious ARs (≥2%) observed in the LENVIMA arm were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%)[1]

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

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

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

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

Dose modifications with LENVIMA®

Interrupt, reduce, and/or discontinue LENVIMA based on the type and/or severity (grade) of the adverse reaction[1]

	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 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 palmar-plantar erythrodysesthesia syndrome (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 conclusions can be drawn

For additional management strategies, please visit **www.LENVIMAHCP.com**

AR=adverse reaction.

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).

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg

Doses available in blister packs

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

12-mg daily dose

8-mg daily dose

- 12-mg and 8-mg blister packs facilitate initial prescriptions
- 8-mg and 4-mg blister packs help you and your 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

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

SELECTED SAFETY INFORMATION
Warnings and Precautions (cont'd)

Proteinuria (cont'd). 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.

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

SELECTED SAFETY INFORMATION
Warnings and Precautions (cont'd)

Hemorrhagic Events (cont'd). Serious tumor-related bleeds, including fatal hemorrhagic events, occurred in LENVIMA®-treated patients in clinical trials and in the postmarketing setting. In postmarketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than other tumors. Safety and effectiveness of LENVIMA in patients with ATC have not been demonstrated in clinical trials.

Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (eg, carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

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

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

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

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

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

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

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

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

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.

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.

LENVIMA®: Efficacy that drives results

Not an actual patient

LENVIMA achieved its noninferiority primary endpoint vs sorafenib in OS in REFLECT[1]

13.6-MONTH MEDIAN OS vs sorafenib (12.3 months)[1] HR: 0.92 (95% CI: 0.79-1.06)*

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

Statistical superiority vs sorafenib in select secondary efficacy endpoints in REFLECT[1,2]

Offering more time without disease progression[1]

DOUBLE THE MEDIAN PFS (mRECIST), 7.3 months vs 3.6 months with sorafenib[1†]

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 with LENVIMA and 3.6 months with sorafenib (HR: 0.65 [95% CI: 0.56-0.77])[1]
  - Number of events: 307 (64%) with LENVIMA vs 320 (67%) with sorafenib[1]

MORE THAN TRIPLE THE ORR (mRECIST), 41% vs 12% with sorafenib[1†]

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%)[1]
  - 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

SUMMARY OF WARNINGS AND PRECAUTIONS

Adverse reactions, some of which can be serious or fatal, may occur with LENVIMA, including hypertension, cardiac dysfunction, arterial thromboembolic events, hepatotoxicity, renal failure or impairment, proteinuria, diarrhea, fistula formation and gastrointestinal perforation, QT interval prolongation, hypocalcemia, reversible posterior leukoencephalopathy syndrome, hemorrhagic events, impairment of thyroid stimulating hormone suppression/thyroid dysfunction, impaired wound healing, osteonecrosis of the jaw, and embryo-fetal toxicity. Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should be advised to use effective contraception. Based on the severity of the adverse reaction, LENVIMA should be interrupted, reduced, and/or discontinued.

Visit **www.LENVIMAHCP.com** to learn more

HCC=hepatocellular carcinoma; 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; OS=overall survival; HR=hazard ratio; CI=confidence interval; PFS=progression-free survival; ORR=objective response rate; mRECIST=modified Response Evaluation Criteria In Solid Tumors; RECIST=Response Evaluation Criteria In Solid Tumors.

*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]

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

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg