国名	米国	欧州
	動物データ 授乳中の Sprague Dawley ラットに放射性ラベルしたレンバチニブの投与を行ったところ，レンバチニブ由来の放射能が母親の血漿中と比較して乳汁に約 2 倍以上（AUC 換算）検出された。	
小児への投与	小児患者における LENVIMA の安全性及び有効性は確立していない。 幼若動物データ 生後 21 日（ヒトでは約 2 歳に相当）の幼若ラットに 8 週間レンバチニブメシル酸塩を連日経口投与した結果，2 mg/kg 以上の用量（AUC 換算でヒトの推奨用量の 1.2 から 5 倍の用量）において，発育遅延（体重増加の遅延，摂食量の減少及び大腿骨並びに脛骨の横幅及び/又は長さの減少）が認められ，次に身体発育の遅延及び生殖器の未成熟が認められた。大腿骨及び脛骨の長さの減少は回復まで 4 週間を要した。全用量で認められた歯の損傷を含む毒性及び 10 mg/kg/日の用量の幼若ラットにおいて，治療早期に生じた死亡（原発の十二指腸部位による）が認められたが，概してレンバチニブの毒性プロファイルは幼若と成人のラットで同様であった。	動物実験の結果より安全性の懸念があることから，2 歳未満小児に対してレンバチニブは使用しないこと。2 歳から 18 歳までの小児に対するレンバチニブの安全性及び有効性は確立していない。利用可能なデータはない。
過量投与	LENVIMA の過量投与に対する解毒薬は知られていない。高い血漿蛋白結合率を考えるとレンバチニブは透析を要するとは考えられない。40 mg の LENVIMA の単剤投与を受けた患者の有害事象は，分化型甲状腺癌及び腎細胞癌の推奨用量における臨床試験で報告された有害事象と同様であった。	臨床試験での最高用量は 32 mg 及び 40 mg である。臨床試験で誤って 40 mg から 48 mg を単回投与したことが報告されている。これらの用量で発現した頻度の高い有害事象は高血圧，悪心，下痢，疲労，口内炎，蛋白尿，頭痛，手掌・足底発赤知覚不全症候群の悪化であった。推奨用量の 6 倍から 10 倍の量を単回投与した患者が存在したが，これらの患者で発生した有害事象は既に知られているレンバチニブの安全性プロファイル（例：腎不全や心不全）と同様であった。 症状と管理 レンバチニブの過量投与に対する特定の対処法は存在しない。過量投与が疑われる場合はレンバチニブを休薬し，必要に応じて適切な支持療法を行うこと。

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LENVIMA safely and effectively. See full prescribing information for LENVIMA.

LENVIMA® (lenvatinib) capsules, for oral use
Initial U.S. Approval: 2015

----------RECENT MAJOR CHANGES----------

Indications and Usage, Renal Cell Carcinoma (1.2)	05/2016
Dosage and Administration (2.2, 2.3, 2.4)	05/2016
Warnings and Precautions (5.1 - 5.13)	05/2016

----------INDICATIONS AND USAGE----------
LENVIMA is a kinase inhibitor that is indicated for:

- Differentiated Thyroid Cancer (DTC): single agent for patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC. (1.1)
- Renal Cell Cancer (RCC): in combination with everolimus, for patients with advanced RCC following one prior anti-angiogenic therapy. (1.2)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dose (DTC): 24 mg orally, once daily. (2.1)
- Recommended dose (RCC): 18 mg LENVIMA + 5 mg everolimus, orally, once daily. (2.2)
- Administration Instructions. (2.3)
- Dose Modifications for DTC and RCC. (2.4)
- In patients with severe renal or hepatic impairment, the dose is 14 mg once daily in DTC and 10 mg once daily in RCC. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 4 mg and 10 mg. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Hypertension: Control blood pressure prior to treatment with LENVIMA. Withhold LENVIMA for Grade 3 hypertension despite optimal anti-hypertensive therapy. Discontinue for life-threatening hypertension. (5.1)
- Cardiac Failure: Monitor for clinical symptoms or signs of cardiac decompensation. Withhold LENVIMA for Grade 3 cardiac dysfunction. Discontinue for Grade 4 cardiac dysfunction. (5.2)
- Arterial Thromboembolic Events: Discontinue LENVIMA following an arterial thromboembolic event. (5.3)
- Hepatotoxicity: Monitor liver function tests before initiation of LENVIMA and periodically throughout treatment. Withhold LENVIMA for Grade 3 or greater liver impairment. Discontinue for hepatic failure. (5.4)
- Proteinuria: Monitor for proteinuria before initiation of, and periodically throughout, treatment with LENVIMA. Withhold LENVIMA for ≥2 grams of proteinuria for 24 hours. Discontinue for nephrotic syndrome. (5.5)
- Diarrhea: May be severe and recurrent. Use standard anti-diarrheal therapy. Withhold LENVIMA for Grade 3 and discontinue for Grade 4 diarrhea. (5.6)
- Renal Failure and Impairment: Withhold LENVIMA for Grade 3 or 4 renal failure/impairment. (5.7)
- Gastrointestinal Perforation and Fistula Formation: Discontinue LENVIMA in patients who develop gastrointestinal perforation or life-threatening fistula. (5.8)
- QT Interval Prolongation: Monitor and correct electrolyte abnormalities in all patients. Withhold LENVIMA for the development of Grade 3 or greater QT interval prolongation. (5.9)
- Hypocalcemia: Monitor blood calcium levels at least monthly and replace calcium as necessary. (5.10)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Withhold LENVIMA for RPLS until fully resolved. (5.11)
- Hemorrhagic Events: Withhold LENVIMA for Grade 3 hemorrhage. Discontinue for Grade 4 hemorrhage. (5.12)
- Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction: Monitor TSH levels monthly and use thyroid replacement medication as needed. (5.13)
- Embryofetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.14, 8.1, 8.3)

----------ADVERSE REACTIONS----------
In DTC, the most common adverse reactions (incidence greater than or equal to 30%) for LENVIMA are hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, and dysphonia. (6.1)

In RCC, the most common adverse reactions (greater than 30%) for LENVIMA + everolimus are diarrhea, fatigue, arthralgia/myalgia, decreased appetite, vomiting, nausea, stomatitis/oral inflammation, hypertension, peripheral edema, cough, abdominal pain, dyspnea, rash, weight decreased, hemorrhagic events, and proteinuria. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-877-873-4724 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Discontinue breastfeeding. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 02/2017

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Differentiated Thyroid Cancer

LENVIMA is indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC.

1.2 Renal Cell Carcinoma

LENVIMA is indicated in combination with everolimus for the treatment of patients with advanced RCC following one prior anti-angiogenic therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose for DTC

The recommended daily dose of LENVIMA is 24 mg (two 10 mg capsules and one 4 mg capsule) orally taken once daily with or without food *[see Clinical Pharmacology (12.3)]*. Continue LENVIMA until disease progression or until unacceptable toxicity.

Take LENVIMA 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.

2.2 Recommended Dose for RCC

The recommended daily dose of LENVIMA is 18 mg (one 10 mg capsule and two 4 mg capsules) in combination with 5 mg everolimus orally taken once daily with or without food *[see Clinical Pharmacology (12.3)]*. Continue LENVIMA plus everolimus until disease progression or until unacceptable toxicity.

Take LENVIMA and everolimus 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.

2.3 Administration Instructions

LENVIMA capsules should be swallowed whole. Alternatively, the capsules can be dissolved in a small glass of liquid. Measure 1 tablespoon of water or apple juice and put the capsules into the liquid without breaking or crushing them. Leave the capsules in the liquid for at least 10 minutes. Stir for at least 3 minutes. Drink the mixture. After drinking, add the same amount (1 tablespoon) of water or apple juice to the glass. Swirl the contents a few times and swallow the additional liquid.

2.4 Dose Modifications for DTC and RCC

Table 1: Adverse Reactions Requiring Dose Modification of LENVIMA in DTC and RCC

Adverse Reaction	CTCAE Grade	Action	Dose Reduce and Resume LENVIMA
Hypertension	Grade 3[1]	Hold	Resolves to Grade 0, 1, or 2
	Grade 4	Discontinue	Do Not Resume
Cardiac Dysfunction	Grade 3	Hold	Resolves to Grade 0, 1, or baseline
	Grade 4	Discontinue	Do Not Resume
Arterial Thrombotic Event	Any Grade	Discontinue	Do Not Resume
Hepatotoxicity	Grade 3 or 4	Hold OR Discontinue	Consider resuming at reduced dose if resolves to Grade 0-1 or baseline
Hepatic Failure	Grade 3 or 4	Discontinue	Do Not Resume
Proteinuria	Greater than or equal to 2 gm/24 hours	Hold	Resolves to less than 2 gm/24 hours
Nephrotic Syndrome	-------	Discontinue	Do Not Resume
Nausea, Vomiting, and Diarrhea[2]	Grade 3	Hold	Resolves to Grade 0, 1, or baseline
Vomiting and Diarrhea[2]	Grade 4	Discontinue	Do Not Resume
Renal Failure or Impairment	Grade 3 or 4	Hold OR Discontinue	Consider resuming at reduced dose if resolves to Grade 0-1 or baseline
GI Perforation	Any Grade	Discontinue	Do Not Resume
Fistula	Grade 3 or 4	Discontinue	Do Not Resume
QTc Prolongation	Greater than 500 ms	Hold	Resolves to less than 480 ms or baseline
RPLS	Any Grade	Hold OR Discontinue	Consider resuming at reduced dose if resolves to Grade 0 to 1
Hemorrhage	Grade 3	Hold	Resolves to Grade 0 to 1
	Grade 4	Discontinue	Do Not Resume

[1] Grade 3 despite optimal anti-hypertensive therapy
[2] Initiate prompt medical management for nausea, vomiting or diarrhea. Permanently discontinue for Grade 4 vomiting and diarrhea despite medical management

Manage other adverse reactions according to the instructions in Table 2 for DTC or Table 3 for RCC.

Recommendations for Dose Modifications in DTC

Table 2: Dose Modifications for LENVIMA for Persistent and Intolerable Grade 2 or Grade 3 Adverse Reactions or Grade 4 Laboratory Abnormalities in DTC[a]

Adverse Reaction	Modification	Adjusted Dose[b]
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	20 mg (two 10 mg capsules) orally once daily
Second occurrence[c]	Interrupt until resolved to Grade 0-1 or baseline	14 mg (one 10 mg capsule plus one 4 mg capsule) orally once daily
Third occurrence[c]	Interrupt until resolved to Grade 0-1 or baseline	10 mg (one 10 mg capsule) orally once daily

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

Severe Renal or Hepatic Impairment in DTC

For patients with DTC, the recommended dose of LENVIMA is 14 mg taken orally once daily in patients with severe renal impairment (creatinine clearance [CLcr] less than 30 mL/min calculated by the Cockcroft-Gault equation) or severe hepatic impairment (Child-Pugh C) *[see Warnings and Precautions (5.4, 5.6), Use in Specific Populations (8.6, 8.7)]*.

Recommendations for Dose Modifications in RCC

Table 3: Dose Modifications for LENVIMA for Persistent and Intolerable Grade 2 or Grade 3 Adverse Reactions or Grade 4 Laboratory Abnormalities in RCC[a]

Adverse Reaction	Modification	Adjusted Dose[b]
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	14 mg (one 10 mg capsule plus one 4 mg capsule) orally once daily
Second occurrence[c]	Interrupt until resolved to Grade 0-1 or baseline	10 mg (one 10 mg capsule) orally once daily
Third occurrence[c]	Interrupt until resolved to Grade 0-1 or baseline	8 mg (two 4 mg capsules) orally once daily

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

Recommendations for Dose Modification of Everolimus in RCC

Review the Full Prescribing Information for everolimus for recommended dose modifications. For toxicities thought to be related to everolimus alone, discontinue, interrupt, or use alternate day dosing. For toxicities thought to be related to both LENVIMA and everolimus, first reduce LENVIMA and then everolimus.

Severe Renal or Hepatic Impairment in RCC

For patients with RCC, the recommended dose of LENVIMA is 10 mg taken orally once daily in patients with severe renal impairment (CLcr less than 30 mL/min calculated by the Cockcroft-Gault equation) or severe hepatic impairment (Child-Pugh C) *[see Warnings and Precautions (5.4, 5.6), Use in Specific Populations (8.6, 8.7)]*.

3 DOSAGE FORMS AND STRENGTHS

4 mg hard capsule: A yellowish-red body and yellowish-red cap, marked in black ink with "Є" on the cap and "LENV 4 mg" on the body.

10 mg hard capsule: A yellow body and yellowish-red cap, marked in black ink with "Є" on the cap and "LENV 10 mg" on the body.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension

In Study 1 in DTC, hypertension was reported in 73% of LENVIMA-treated patients and 16% of patients in the placebo group *[see Adverse Reactions (6.1)]*. The median time to onset of new or worsening hypertension was 16 days for LENVIMA-treated patients. The incidence of Grade 3 hypertension was 44% as compared to 4% for placebo, and the incidence of Grade 4 hypertension was less than 1% in LENVIMA-treated patients and none in the placebo group.

In Study 2 in RCC, hypertension was reported in 42% of patients in the LENVIMA + everolimus-treated group and 10% of patients in the everolimus-treated group. The median time to onset of new or worsening hypertension was 35 days for LENVIMA + everolimus-treated patients. The incidence of Grade 3 hypertension was 13% in the LENVIMA + everolimus-treated group as compared to 2% in the everolimus-treated group. Systolic blood pressure ≥ 160mmHg occurred in 29% and 21% of patients had a diastolic blood pressure ≥100 in the LENVIMA + everolimus-treated group *[see Adverse Reactions (6.1)]*.

Control blood pressure prior to treatment with LENVIMA. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment with LENVIMA. Withhold LENVIMA for Grade 3 hypertension despite optimal antihypertensive therapy; resume at a reduced dose when hypertension is controlled at less than or equal to Grade 2. Discontinue LENVIMA for life-threatening hypertension *[see Dosage and Administration (2.4)]*.

5.2 Cardiac Dysfunction

In Study 1 in DTC, cardiac dysfunction, defined as decreased left or right ventricular function, cardiac failure, or pulmonary edema, was reported in 7% of LENVIMA-treated patients (2% Grade 3 or greater) and 2% (no Grade 3 or greater) of patients in the placebo group. The majority of these cases in LENVIMA-treated patients (14 of 17 cases) were based on findings of decreased ejection fraction as assessed by echocardiography. Six of 261 (2%) LENVIMA-treated patients in Study 1 had greater than 20% reduction in ejection fraction as measured by echocardiography compared to no patients who received placebo.

In Study 2 in RCC, decreased ejection fraction and cardiac failure were reported in 10% of patients in the LENVIMA + everolimus-treated group and 6% of patients in the everolimus-treated group. Grade 3 events occurred in 3% of LENVIMA + everolimus-treated patients and 2% of everolimus-treated patients. In the LENVIMA + everolimus-treated group there were two patients with a Grade 2 to 4 decrease in LVEF as assessed by MUGA.

Monitor patients for clinical symptoms or signs of cardiac decompensation. Withhold LENVIMA for development of Grade 3 cardiac dysfunction until improved to Grade 0 or 1 or baseline. Either resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of cardiac dysfunction. Discontinue LENVIMA for Grade 4 cardiac dysfunction *[see Dosage and Administration (2.4)]*.

5.3 Arterial Thromboembolic Events

In Study 1 in DTC, arterial thromboembolic events were reported in 5% of LENVIMA-treated patients and 2% of patients in the placebo group. The incidence of arterial thromboembolic events of Grade 3 or greater was 3% in LENVIMA-treated patients and 1% in the placebo group.

In Study 2 in RCC, 2% of patients in the LENVIMA + everolimus-treated group and 6% of patients in the everolimus-treated group had arterial thromboembolic events reported. The incidence of arterial thromboembolic events of Grade 3 or greater was 2% with LENVIMA + everolimus-treated patients and 4% in the everolimus-treated group.

Discontinue LENVIMA following an arterial thrombotic event. The safety of resuming LENVIMA after an arterial thromboembolic event has not been established and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months *[see Dosage and Administration (2.4)]*.

5.4 Hepatotoxicity

Across clinical studies in which 1160 patients received LENVIMA monotherapy, hepatic failure (including fatal events) was reported in 3 patients and acute hepatitis was reported in 1 patient.

In Study 1 in DTC, 4% of LENVIMA-treated patients experienced an increase in alanine aminotransferase (ALT) and 5% experienced an increase in aspartate aminotransferase (AST) that was Grade 3 or greater. No patients in the placebo group experienced Grade 3 or greater increases in ALT or AST.

The incidence of ALT and AST elevation was similar in Study 2 in RCC. In Study 2, 3% of LENVIMA + everolimus-treated patients experienced an increase in ALT and 3% experienced an increase in AST that was Grade 3 or greater. Two percent of patients in the everolimus-treated group experienced an increase in ALT and none experienced an increase in AST that was Grade 3 or greater.

Monitor liver function before initiation of LENVIMA, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Withhold LENVIMA for the development of Grade 3 or greater liver impairment until resolved to Grade 0 to 1 or baseline. Either resume at a reduced dose or discontinue LENVIMA depending on the

severity and persistence of hepatotoxicity. Discontinue LENVIMA for hepatic failure *[see Dosage and Administration (2.4)]*.

5.5 Proteinuria

In Study 1 in DTC, proteinuria was reported in 34% of LENVIMA-treated patients and 3% of patients in the placebo group *[see Adverse Reactions (6.1)]*. The incidence of Grade 3 proteinuria in LENVIMA-treated patients was 11% compared to none in the placebo group.

In Study 2 in RCC, proteinuria was reported in 31% of patients in the LENVIMA + everolimus-treated group and 14% of patients in the everolimus-treated group. The incidence of Grade 3 proteinuria in LENVIMA + everolimus-treated patients was 8% compared to 2% in everolimus-treated patients.

Monitor for proteinuria before initiation of, and periodically throughout treatment. If urine dipstick proteinuria greater than or equal to 2+ is detected, obtain a 24 hour urine protein. Withhold LENVIMA for ≥2 grams of proteinuria/24 hours and resume at a reduced dose when proteinuria is <2 gm/24 hours. Discontinue LENVIMA for nephrotic syndrome *[see Dosage and Administration (2.4)]*.

5.6 Diarrhea

In Study 2 in RCC, diarrhea was reported in 81% of LENVIMA + everolimus-treated patients and 34% of everolimus-treated patients. Grade 3 or 4 events occurred in 19% of LENVIMA + everolimus-treated patients and 2% of everolimus-treated patients. Diarrhea was the most frequent cause of dose interruption/reduction and recurred despite dose reduction. Diarrhea resulted in discontinuation in one patient *[see Adverse Reactions (6.1)]*.

Initiate prompt medical management for the development of diarrhea. Monitor for dehydration. Interrupt LENVIMA for Grade 3 or 4 diarrhea. For Grade 3 diarrhea, resume at a reduced dose of LENVIMA when diarrhea resolves to Grade 1 or baseline. Permanently discontinue LENVIMA for Grade 4 diarrhea despite medical management.

5.7 Renal Failure and Impairment

In Study 1 in DTC, events of renal impairment were reported in 14% of LENVIMA-treated patients compared to 2% of patients in the placebo group. The incidence of Grade 3 or greater renal failure or impairment was 3% in LENVIMA-treated patients and 1% in the placebo group.

In Study 2 in RCC, renal impairment was reported in 18% of LENVIMA + everolimus-treated group and 12% in the everolimus-treated group. The incidence of Grade 3 or greater renal failure or impairment was 10% in the LENVIMA + everolimus-treated group and 2% in the everolimus-treated group.

One risk factor for severe renal impairment in LENVIMA-treated patients was dehydration/hypovolemia due to diarrhea and vomiting. Active management of diarrhea and any other gastrointestinal symptoms should be initiated for Grade 1 events.

Withhold LENVIMA for development of Grade 3 or 4 renal failure/impairment until resolved to Grade 0 to 1 or baseline. Either resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of renal impairment *[see Dosage and Administration (2.4)]*.

5.8 Gastrointestinal Perforation and Fistula Formation

In Study 1 in DTC, events of gastrointestinal perforation or fistula were reported in 2% of LENVIMA-treated patients and 0.8% of patients in the placebo group.

In Study 2 in RCC, Grade 3 or greater gastrointestinal perforation, abscess or fistula was reported in 2% of patients in the LENVIMA + everolimus-treated group and no patients in the everolimus-treated group. The events resolved in all patients.

Discontinue LENVIMA in patients who develop gastrointestinal perforation or life-threatening fistula *[see Dosage and Administration (2.4)]*.

5.9 QT Interval Prolongation

In Study 1 in DTC, QT/QTc interval prolongation was reported in 9% of LENVIMA-treated patients and 2% of patients in the placebo group. The incidence of QT interval prolongation of greater than 500 ms was 2% in LENVIMA-treated patients compared to no reports in the placebo group.

In Study 2 in RCC, QTc interval increases greater than 60 ms were reported in 11% of patients in the LENVIMA + everolimus-treated group. The incidence of QTc interval greater than 500 ms was 6% in the LENVIMA + everolimus-treated group. No reports of QTc interval prolongation greater than 500 ms or increase greater than 60 ms occurred in the everolimus-treated group.

Monitor and correct electrolyte abnormalities in all patients. 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 LENVIMA for the development of QTc interval prolongation greater than 500 ms. Resume LENVIMA at a reduced dose when QTc prolongation resolves to baseline *[see Dosage and Administration (2.4), Clinical Pharmacology (12.2)]*.

5.10 Hypocalcemia

In Study 1 in DTC, 9% of LENVIMA-treated patients experienced Grade 3 or greater hypocalcemia compared to 2% in the placebo group. In most cases hypocalcemia responded to replacement and dose interruption/dose reduction.

In Study 2 in RCC, 6% of patients in the LENVIMA + everolimus-treated group and 2% of patients in the everolimus-treated group experienced Grade 3 or greater hypocalcemia. No patients discontinued due to hypocalcemia *[see Adverse Reactions (6.1)]*.

Monitor blood calcium levels at least monthly and replace calcium as necessary during LENVIMA treatment. Interrupt and adjust LENVIMA dosing as necessary depending on severity, presence of ECG changes, and persistence of hypocalcemia *[see Dosage and Administration (2.4)]*.

5.11 Reversible Posterior Leukoencephalopathy Syndrome

Across clinical studies in which 1160 patients received LENVIMA monotherapy, there were 4 reported events of reversible posterior leukoencephalopathy syndrome (RPLS). Confirm the diagnosis of RPLS with MRI. Withhold for RPLS until fully resolved. Upon resolution, resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of neurologic symptoms *[see Dosage and Administration (2.4)]*.

5.12 Hemorrhagic Events

Across clinical studies in which 1160 patients received LENVIMA monotherapy, Grade 3 or greater hemorrhage was reported in 2% of patients.

In Study 1 in DTC, hemorrhagic events occurred in 35% of LENVIMA-treated patients and in 18% of the placebo group. However, the incidence of Grade 3 to 5 hemorrhage was similar between arms at 2% and 3%, respectively. There was 1 case of fatal intracranial hemorrhage among 16 patients who received LENVIMA and had CNS metastases at baseline. The most frequently reported hemorrhagic event was epistaxis (11% Grade 1 and 1% Grade 2). Discontinuation due to hemorrhagic events occurred in 1% of LENVIMA-treated patients.

In Study 2 in RCC, hemorrhagic events occurred in 34% of patients in the LENVIMA + everolimus-treated group and 26% of patients in the everolimus-treated group. The most frequently reported hemorrhagic event was epistaxis (LENVIMA + everolimus 23% and everolimus 24%). Grade 3 or greater events occurred in 8% of LENVIMA + everolimus-treated patients and in 2% of everolimus-treated patients. In the LENVIMA + everolimus-treated patients, this included one fatal cerebral hemorrhage. Discontinuation due to a hemorrhagic event occurred in 3% of patients in the LENVIMA + everolimus-treated group.

Serious tumor related bleeds, including fatal hemorrhagic events in LENVIMA-treated patients, have occurred in clinical trials and been reported in post-marketing experience. In post-marketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than in other tumor types. The 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/infiltration of major blood vessels (e.g. carotid artery). Withhold LENVIMA for the development of Grade 3 hemorrhage until resolved to Grade 0 to 1. Either resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of hemorrhage. Discontinue LENVIMA in patients who experience Grade 4 hemorrhage *[see Dosage and Administration (2.4)]*.

5.13 Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction

LENVIMA impairs exogenous thyroid suppression. In Study 1 in DTC, 88% of all patients had a baseline thyroid stimulating hormone (TSH) level less than or equal to 0.5 mU/L. In those patients with a normal TSH at baseline, elevation of TSH level above 0.5 mU/L was

observed post baseline in 57% of LENVIMA-treated patients as compared with 14% of patients receiving placebo.

In Study 2 in RCC, Grade 1 or 2 hypothyroidism occurred in 24% of patients in the LENVIMA + everolimus-treated group and 2% of patients in the everolimus-treated group. In those patients with a normal or low TSH at baseline, an elevation of TSH was observed post baseline in 60 % of LENVIMA + everolimus-treated patients as compared with 3% of patients receiving everolimus monotherapy.

Monitor thyroid function before initiation of, and at least monthly throughout, treatment with LENVIMA. Treat hypothyroidism according to standard medical practice to maintain a euthyroid state.

5.14 Embryofetal Toxicity

Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended human dose resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 2 weeks following completion of therapy *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the label:

- Hypertension *[see Warnings and Precautions (5.1)]*
- Cardiac Dysfunction *[see Warnings and Precautions (5.2)]*
- Arterial Thromboembolic Events *[see Warnings and Precautions (5.3)]*
- Hepatotoxicity *[see Warnings and Precautions (5.4)]*
- Proteinuria *[see Warnings and Precautions (5.5)]*
- Diarrhea *[see Warnings and Precautions (5.6)]*
- Renal Failure and Impairment *[see Warnings and Precautions (5.7)]*
- Gastrointestinal Perforation and Fistula Formation *[see Warnings and Precautions (5.8)]*
- QT Interval Prolongation *[see Warnings and Precautions (5.9)]*
- Hypocalcemia *[see Warnings and Precautions (5.10)]*
- Reversible Posterior Leukoencephalopathy Syndrome *[see Warnings and Precautions (5.11)]*
- Hemorrhagic Events *[see Warnings and Precautions (5.12)]*
- Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction *[see Warnings and Precautions (5.13)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the Warnings and Precautions section reflect exposure to LENVIMA as a single agent in 261 DTC patients (Study 1) and LENVIMA + everolimus in 62 RCC patients (Study 2). Safety data obtained in 1160 patients with advanced solid tumors who received LENVIMA as a single agent across multiple clinical studies was used to further characterize the risks of serious adverse reactions *[see Warnings and Precautions (5.4, 5.10, 5.11)]*. In the entire single agent population, the median age was 60 years (range 21-89 years), the dose range was 0.2 mg to 32 mg, and the median duration of exposure was 5.5 months.

Differentiated Thyroid Cancer

The safety data described below are derived from Study 1 which randomized (2:1) patients with radioactive iodine-refractory differentiated thyroid cancer (RAI-refractory DTC) to LENVIMA (n=261) or placebo (n=131) *[see Clinical Studies (14.1)]*. The median treatment duration was 16.1 months for LENVIMA and 3.9 months for placebo. Among 261 patients who received LENVIMA in Study 1, median age was 64 years, 52% were women, 80% were White, 18% were Asian, and 2% were Black; 4% identified themselves as having Hispanic or Latino ethnicity.

In Study 1, the most common adverse reactions observed in LENVIMA-treated patients (greater than or equal to 30%) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia (PPE) syndrome, abdominal pain, and dysphonia. The most common serious adverse reactions (at least 2%) were pneumonia (4%), hypertension (3%), and dehydration (3%).

Adverse reactions led to dose reductions in 68% of patients receiving LENVIMA and 5% of patients receiving placebo; 18% of patients discontinued LENVIMA and 5% discontinued placebo for adverse reactions. The most common adverse reactions (at least 10%) resulting in dose reductions of LENVIMA were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions (at least 1%) resulting in discontinuation of LENVIMA were hypertension (1%) and asthenia (1%).

Table 4 presents the percentage of patients in Study 1 experiencing adverse reactions at a higher rate in LENVIMA-treated patients than patients receiving placebo in the double-blind phase of the DTC study.

Table 4: Adverse Reactions Occurring in Patients with a Between-Group Difference of Greater than or Equal to 5% in All Grades or Greater than or Equal to 2% in Grades 3 and 4

Adverse Reaction	LENVIMA 24 mg N=261		Placebo N=131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Vascular Disorders				
Hypertension[a]	73	44	16	4
Hypotension	9	2	2	0
Gastrointestinal Disorders				
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 Disorders and Administration Site Conditions				
Fatigue[e]	67	11	35	4
Edema peripheral	21	0.4	8	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/Myalgia[f]	62	5	28	3
Metabolism and Nutrition Disorders				
Weight decreased	51	13	15	1
Decreased appetite	54	7	18	1
Dehydration	9	2	2	1
Nervous System Disorders				
Headache	38	3	11	1
Dysgeusia	18	0	3	0
Dizziness	15	0.4	9	0
Renal and Urinary Disorders				
Proteinuria	34	11	3	0
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia	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 Disorders				
Dysphonia	31	1	5	0
Cough	24	0	18	0
Epistaxis	12	0	1	0
Psychiatric Disorders				
Insomnia	12	0	3	0

Table 4: Adverse Reactions Occurring in Patients with a Between-Group Difference of Greater than or Equal to 5% in All Grades or Greater than or Equal to 2% in Grades 3 and 4

Adverse Reaction	LENVIMA 24 mg N=261		Placebo N=131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Infections and Infestations				
Dental and oral infections[h]	10	1	1	0
Urinary tract infection	11	1	5	0
Cardiac Disorders				
Electrocardiogram QT prolonged	9	2	2	0

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, sialoadenitis, tooth abscess, and tooth infection

A clinically important adverse reaction occurring more frequently in LENVIMA-treated patients than patients receiving placebo, but with an incidence of less than 5% was pulmonary embolism (3%, including fatal reports vs 2%, respectively).

Table 5: Laboratory Abnormalities with a Difference of at Least ≥2% in Grade 3 - 4 Events and at a Higher Incidence in LENVIMA-Treated Patients[a]

Laboratory Abnormality	LENVIMA 24 mg N=258[b]	Placebo N=131[b]
	Grades 3-4 (%)	Grades 3-4 (%)
Chemistry		
Creatinine increased	3	0
Alanine aminotransferase (ALT) increased	4	0
Aspartate aminotransferase (AST) increased	5	0
Hypocalcemia	9	2
Hypokalemia	6	1
Lipase increased	4	1
Hematology		
Platelet count decreased	2	0

a With at least 1 grade increase from baseline
b Subject with at least 1 post baseline laboratory value

In addition the following laboratory abnormalities (all Grades) occurred in greater than 5% of LENVIMA-treated patients and at a rate that was two-fold or higher than in patients who

received placebo: hypoalbuminemia, increased alkaline phosphatase, hypomagnesemia, hypoglycemia, hyperbilirubinemia, hypercalcemia, hypercholesterolemia, increased serum amylase, and hyperkalemia.

Renal Cell Carcinoma

The data described below are derived from Study 2 which randomized (1:1:1) patients with unresectable advanced or metastatic renal cell carcinoma (RCC) to LENVIMA 18 mg + everolimus 5 mg (n=51), LENVIMA 24 mg (n=52), or everolimus 10 mg (n=50) once daily *[see Clinical Studies (14.2)]*. This data also includes patients on the dose escalation portion of the study who received LENVIMA 18 mg + everolimus 5 mg (n=11). The median treatment duration was 8.1 months for LENVIMA + everolimus and 4.1 months for everolimus. Among 62 patients who received LENVIMA + everolimus in Study 2, the median age was 61 years, 71% were men, and 98% were White.

The most common adverse reactions observed in the LENVIMA + everolimus-treated group (> 30%) were, in order of decreasing frequency, diarrhea, fatigue, arthralgia/myalgia, decreased appetite, vomiting, nausea, stomatitis/oral inflammation, hypertension, peripheral edema, cough, abdominal pain, dyspnea, rash, weight decreased, hemorrhagic events, and proteinuria. 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 receiving LENVIMA + everolimus and 54% in patients receiving everolimus. The most common adverse reactions (≥ 5%) resulting in dose reductions in the LENVIMA + everolimus-treated group 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 the LENVIMA + everolimus-treated group and 12% of patients in the everolimus-treated group.

Table 6 presents the adverse reactions in > 15% of patients in the LENVIMA + Everolimus arm.

Table 6: Grades 1-4 Adverse Reactions in > 15% of Patients in the LENVIMA + Everolimus Arm

	LENVIMA 18 mg + Everolimus 5 mg (N=62)		Everolimus 10 mg (N=50)	
System Organ Class Preferred Term	**Grade 1-4 (%)**	**Grade 3-4 (%)**	**Grade 1-4 (%)**	**Grade 3-4 (%)**
Endocrine Disorders				
Hypothyroidism	24	0	2	0
Gastrointestinal Disorders				
Constipation	16	0	18	0
Diarrhea	81	19	34	2
Dyspepsia/Gastro-esophageal 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 Disorders and Administration Site Conditions				
Fatigue[d]	73	18	40	2
Peripheral edema	42	2	20	0
Pyrexia/Increased body temperature	21	2	10	2
Investigations				
Weight decreased	34	3	8	0
Metabolism and Nutrition Disorders				
Decreased appetite	53	5	18	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/Myalgia[e]	55	5	32	0
Musculoskeletal chest pain	18	2	4	0
Nervous System Disorders				
Headache	19	2	10	2
Psychiatric Disorders				
Insomnia	16	2	2	0
Renal and Urinary Disorders				
Proteinuria/Urine protein present	31	8	14	2
Renal failure event[f]	18	10	12	2
Respiratory, Thoracic and Mediastinal Disorders				
Cough	37	0	30	0
Dysphonia	18	0	4	0
Dyspnea/Exertional dyspnea	35	5	28	8
Skin and Subcutaneous Tissue Disorders				
Rash[g]	35	0	40	0
Vascular Disorders				
Hemorrhagic events[h]	32	6	26	2

	LENVIMA 18 mg + Everolimus 5 mg (N=62)		Everolimus 10 mg (N=50)	
System Organ Class Preferred Term	**Grade 1-4 (%)**	**Grade 3-4 (%)**	**Grade 1-4 (%)**	**Grade 3-4 (%)**
Hypertension/Increased blood pressure	42	13	10	2

[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

[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, maculo-papular 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

Table 7: Grade 3-4 Laboratory Abnormalities in ≥ 3% of Patients in the LENVIMA + Everolimus Arm[a,b]

Laboratory Abnormality	LENVIMA 18 mg + Everolimus 5 mg N=62	Everolimus 10 mg N=50
	Grades 3-4 (%)	Grades 3-4 (%)
Chemistry		
Aspartate aminotransferase (AST) increased	3	0
Alanine aminotransferase (ALT) increased	3	2
Alkaline phosphatase increased	3	0
Hyperkalemia	6	2
Hypokalemia	6	2
Hyponatremia	11	6
Hypocalcemia	6	2
Hypophosphatemia	11	6
Hyperglycemia	3	16
Hypertriglyceridemia	18	18
Elevated cholesterol	11	0
Creatine kinase increased	3	4
Lipase increased	13	12
Hematology		
Hemoglobin decreased	8	16
Platelet count decreased	5	0
Lymphocyte count decreased	10	20

[a] With at least 1 grade increase from baseline
[b] Subject with at least 1 post baseline laboratory value

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of LENVIMA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: amylase increased, pancreatitis
Hepatobiliary Disorders: cholecystitis

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Lenvatinib

No dose adjustment of LENVIMA is recommended when co-administered with CYP3A, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP) inhibitors and CYP3A and P-gp inducers *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended human dose resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits *[see Data]*. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Data

Animal Data

In an embryofetal development study, daily oral administration of lenvatinib mesylate at doses greater than or equal to 0.3 mg/kg [approximately 0.14 times the recommended human dose based on body surface area (BSA)] to pregnant rats during organogenesis resulted in dose-related decreases in mean fetal body weight, delayed fetal ossifications, and dose-related increases in fetal external (parietal edema and tail abnormalities), visceral, and skeletal anomalies. Greater than 80% postimplantation loss was observed at 1.0 mg/kg/day (approximately 0.5 times the recommended human dose based on BSA).

Daily oral administration of lenvatinib mesylate to pregnant rabbits during organogenesis resulted in fetal external (short tail), visceral (retroesophageal subclavian artery), and skeletal anomalies at doses greater than or equal to 0.03 mg/kg (approximately 0.03 times the human dose of 24 mg based on body surface area). At the 0.03 mg/kg dose, increased post-implantation loss, including 1 fetal death, was also observed. Lenvatinib was abortifacient in rabbits, resulting in late abortions in approximately one-third of the rabbits treated at a dose level of 0.5 mg/kg/day (approximately 0.5 times the recommended clinical dose of 24 mg based on BSA).

8.2 Lactation

Risk Summary

It is not known whether LENVIMA is present in human milk. However, lenvatinib and its metabolites are excreted in rat milk at concentrations higher than in maternal plasma *[see*

Data]. Because of the potential for serious adverse reactions in nursing infants from LENVIMA, advise women to discontinue breastfeeding during treatment with LENVIMA.

Data
Animal Data
Following administration of radiolabeled lenvatinib to lactating Sprague Dawley rats, lenvatinib-related radioactivity was approximately 2 times higher (based on AUC) in milk compared to maternal plasma.

8.3 Females and Males of Reproductive Potential

Contraception
Based on its mechanism of action, LENVIMA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 2 weeks following completion of therapy.

Infertility
Females
LENVIMA may result in reduced fertility in females of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

Males
LENVIMA may result in damage to male reproductive tissues leading to reduced fertility of unknown duration *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use
The safety and effectiveness of LENVIMA in pediatric patients have not been established.

Juvenile Animal Data
Daily oral administration of lenvatinib mesylate to juvenile rats for 8 weeks starting on postnatal day 21 (approximately equal to a human pediatric age of 2 years) resulted in growth retardation (decreased body weight gain, decreased food consumption, and decreases in the width and/or length of the femur and tibia) and secondary delays in physical development and reproductive organ immaturity at doses greater than or equal to 2 mg/kg (approximately 1.2 to 5 times the clinical exposure by AUC at the recommended human dose). Decreased length of the femur and tibia persisted following 4 weeks of recovery. In general, the toxicologic profile of lenvatinib was similar between juvenile and adult rats, though toxicities including broken teeth at all dose levels and mortality at the 10 mg/kg/day dose level (attributed to primary duodenal lesions) occurred at earlier treatment time-points in juvenile rats.

8.5 Geriatric Use
Of 261 patients who received LENVIMA in Study 1, 118 (45.2%) were greater than or equal to 65 years of age and 29 (11.1%) were greater than or equal to 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Of the 62 patients who received LENVIMA + everolimus in Study 2, 22 (35.5%) were greater than or equal to 65 years of age. Conclusions are limited due to the small

sample size, but there appeared to be no overall differences in safety or effectiveness between these subjects and younger subjects.

8.6 Renal Impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended dose is 14 mg in the treatment of DTC and 10 mg in the treatment of RCC, either taken orally once daily. Patients with end stage renal disease were not studied *[see Dosage and Administration (2.4), Warnings and Precautions (5.6), and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

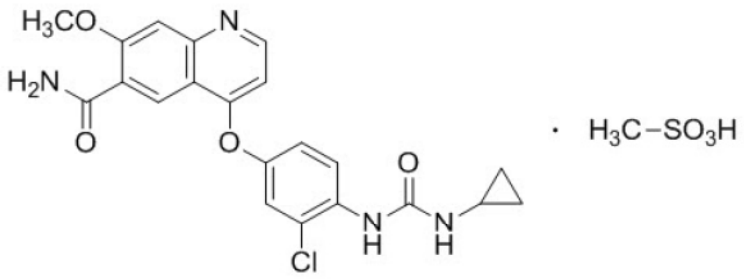
No dose adjustment is recommended in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, the recommended dose is 14 mg in the treatment of DTC and 10 mg in the treatment of RCC, either taken orally once daily *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no specific antidote for overdose with LENVIMA. Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable *[see Clinical Pharmacology (12.3)]*. Adverse reactions in patients receiving single doses of LENVIMA as high as 40 mg were similar to the adverse events reported in the clinical studies at the recommended dose for DTC and RCC.

11 DESCRIPTION

LENVIMA, a kinase inhibitor, is the mesylate salt of lenvatinib. Its chemical name is 4-[3-chloro-4-(*N*'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate. The molecular formula is $C_{21}H_{19}ClN_4O_4 \cdot CH_4O_3S$, and the molecular weight of the mesylate salt is 522.96. The chemical structure of lenvatinib mesylate is:



Lenvatinib mesylate is a white to pale reddish yellow powder. It is slightly soluble in water and practically insoluble in ethanol (dehydrated). The dissociation constant (pKa value) of lenvatinib mesylate is 5.05 at 25°C. The partition coefficient (log P value) is 3.30.

Each 4 mg or 10 mg capsule of lenvatinib is equivalent to 4.90 mg or 12.25 mg of lenvatinib mesylate. Following are inactive ingredients: Calcium Carbonate, USP; Mannitol, USP;

Microcrystalline Cellulose, NF; Hydroxypropyl Cellulose, NF; Hydroxypropyl Cellulose (type H), NF; and Talc, USP. The hypromellose capsule shell contains titanium dioxide, ferric oxide yellow, and ferric oxide red. The printing ink contains shellac, black iron oxide, potassium hydroxide, and propylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib also inhibits other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET. The combination of lenvatinib and everolimus showed increased antiangiogenic and antitumor activity as demonstrated by decreased human endothelial cell proliferation, tube formation, and VEGF signaling in vitro and tumor volume in mouse xenograft models of human renal cell cancer greater than each drug alone.

12.2 Pharmacodynamics

Cardiac Electrophysiology

A single 32 mg dose (1.3 times the recommended daily dose) of lenvatinib did not prolong the QT/QTc interval in a thorough QT study in healthy subjects. However, QT prolongation was observed in clinical studies *[see Warnings and Precautions (5.9)]*.

12.3 Pharmacokinetics

Absorption: After oral administration of LENVIMA, time to peak plasma concentration (T_{max}) typically occurred from 1 to 4 hours post-dose. Administration with food did not affect the extent of absorption, but decreased the rate of absorption and delayed the median T_{max} from 2 hours to 4 hours.

In patients with solid tumors administered single and multiple doses of LENVIMA once daily, the maximum lenvatinib plasma concentration (C_{max}) and the area under the concentration-time curve (AUC) increased proportionally over the dose range of 3.2 to 32 mg with a median accumulation index of 0.96 (20 mg) to 1.54 (6.4 mg).

Distribution: In vitro binding of lenvatinib to human plasma proteins ranged from 98% to 99% (0.3 – 30 µg/mL). In vitro, the lenvatinib blood-to-plasma concentration ratio ranged from 0.589 to 0.608 (0.1 – 10 µg/mL).

Based on in vitro data, lenvatinib is a substrate of P-gp and BCRP but not a substrate for organic anion transporter (OAT) 1, OAT3, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, or the bile salt export pump (BSEP).

Elimination: Plasma concentrations declined bi-exponentially following C_{max}. The terminal elimination half-life of lenvatinib was approximately 28 hours.

Metabolism: CYP3A is one of the main metabolic enzymes of lenvatinib. The main metabolic pathways for lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes.

Excretion: Ten days after a single administration of radiolabeled lenvatinib to 6 patients with solid tumors, approximately 64% and 25% of the radiolabel were eliminated in the feces and urine, respectively.

Specific Populations:

Renal Impairment
The pharmacokinetics of lenvatinib following a single 24 mg dose were evaluated in subjects with mild (CLcr 60-89 mL/min), moderate (CLcr 30-59 mL/min), and severe (CLcr <30 mL/min) renal impairment, and compared to healthy subjects. Subjects with end stage renal disease were not studied. After a single 24 mg oral dose of LENVIMA, the $AUC_{0\text{-}inf}$ for subjects with renal impairment were similar compared to those for healthy subjects *[see Dosage and Administration (2.4), Warnings and Precautions (5.6), Use in Specific Populations (8.6)]*.

Hepatic Impairment
The pharmacokinetics of lenvatinib following a single 10 mg dose of LENVIMA were evaluated in subjects with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment. The pharmacokinetics of a single 5 mg dose were evaluated in subjects with severe (Child-Pugh C) hepatic impairment. Compared to subjects with normal hepatic function, the dose-adjusted $AUC_{0\text{-}inf}$ of lenvatinib for subjects with mild, moderate, and severe hepatic impairment were 119%, 107%, and 180%, respectively *[see Dosage and Administration (2.4), Use in Specific Populations (8.7)]*.

Effects of Age, Sex, and Race

Based on a population PK analysis, weight, age, sex, and race did not have a significant effect on apparent clearance (Cl/F) of lenvatinib.

Drug Interaction Studies

Effect of Other Drugs on Lenvatinib

CYP3A, P-gp, and BCRP Inhibitors: Ketoconazole (400 mg for 18 days) increased lenvatinib (administered as a single dose on Day 5) AUC by 15% and C_{max} by 19% in a dedicated clinical trial.

P-gp Inhibitors: Rifampicin (600 mg as a single dose) increased lenvatinib (24 mg as a single dose) AUC by 31% and C_{max} by 33% in a dedicated clinical trial.

CYP3A and P-gp Inducers: Rifampicin (600 mg administered daily for 21 days) decreased lenvatinib (a single 24 mg administered on Day 15) AUC by 18% in a dedicated clinical trial. The C_{max} was unchanged.

Effect of Lenvatinib on Other Drugs

CYP3A4 or CYP2C8 Substrates: There is no projected significant drug-drug interaction risk between lenvatinib and midazolam (a CYP3A4 substrate) or repaglinide (a CYP2C8 substrate).

In Vitro Studies with CYP or UDP-glucuronosyltransferase (UGT) Substrates: Lenvatinib inhibits CYP2C8, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A, but an increase in lenvatinib exposure that impacts safety is unlikely. Lenvatinib does not inhibit CYP2A6 and CYP2E1.

Lenvatinib induces CYP3A, but a decrease in lenvatinib exposure that impacts efficacy is unlikely. Lenvatinib does not induce CYP1A1, CYP1A2, CYP2B6, and CYP2C9. Lenvatinib directly inhibits UGT1A1 and UGT1A4. The clinical implication of this finding is unknown. Lenvatinib shows little or no inhibition on UGT1A6, UGT1A9, UGT2B7, or aldehyde oxidase.

Lenvatinib does not induce UGT1A1, UGT1A4, UGT1A6, UGT1A9, or UGT2B7.

In Vitro Studies with Drug Transporter System Substrates: Lenvatinib inhibits OAT1, OAT3, OCT1, OCT2, OATP1B1, and BSEP. The clinical implication of this finding is unknown. Lenvatinib shows little or no inhibition on OATP1B3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with lenvatinib. Lenvatinib mesylate was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay. Lenvatinib was not clastogenic in the in vitro mouse lymphoma thymidine kinase assay or the in vivo rat micronucleus assay.

No specific studies with lenvatinib have been conducted in animals to evaluate the effect on fertility; however, results from general toxicology studies in rats, monkeys, and dogs suggest there is a potential for lenvatinib to impair fertility. Male dogs exhibited testicular hypocellularity of the seminiferous epithelium and desquamated seminiferous epithelial cells in the epididymides at lenvatinib exposures approximately 0.02 to 0.09 times the clinical exposure by AUC at the recommended human dose. Follicular atresia of the ovaries was observed in monkeys and rats at exposures 0.2 to 0.8 times and 10 to 44 times the clinical exposure by AUC at the 24 mg clinical dose, respectively. In addition, in monkeys, a decreased incidence of menstruation was reported at lenvatinib exposures lower than those in humans at the 24 mg clinical dose.

14 CLINICAL STUDIES

14.1 Differentiated Thyroid Cancer

A multicenter, randomized (2:1), double-blind, placebo-controlled trial was conducted in 392 patients with locally recurrent or metastatic radioactive iodine-refractory differentiated thyroid cancer and radiographic evidence of disease progression within 12 months prior to randomization, confirmed by independent radiologic review. Radioactive iodine-refractory was defined as 1 or more measurable lesions with no iodine uptake on RAI scan, iodine uptake with progression within 12 months of RAI therapy, or having received cumulative RAI activity of >600 mCi (22 GBq) with the last dose administered at least 6 months prior to study entry. Patients were randomized to receive LENVIMA 24 mg once daily (n=261) or placebo (n=131) until disease progression. Randomization was stratified by geographic region, prior VEGF/VEGFR-targeted therapy, and age. The major efficacy outcome measure was progression-free survival as determined by blinded independent radiologic review using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Independent review confirmation of disease progression was required prior to discontinuing patients from the randomization phase of the study. Other efficacy outcome measures included objective response rate and overall survival. Patients in the placebo arm could receive lenvatinib following independent review confirmation of disease progression.

Of the 392 patients randomized, 51% were male, the median age was 63 years, 40% were older than 65 years, 79% were White, 54% had an ECOG performance status of 0, and 24% had received 1 prior VEGF/VEGFR-targeted therapy. Metastases were present in 99% of the patients: lungs in 89%, lymph nodes in 52%, bone in 39%, liver in 18%, and brain in 4%. The histological diagnoses were papillary thyroid cancer (66%) and follicular thyroid cancer (34%); of those with follicular histology, 44% had Hürthle cell and 11% had clear cell subtypes. In the LENVIMA arm, 67% of patients did not demonstrate iodine uptake on any radioiodine scan compared to 77% in the placebo arm. Additionally, 59% of patients on the LENVIMA arm and 61% of patients on placebo arm progressed, according to RECIST 1.1, within 12 months of prior ^{131}I therapy; 19.2% of patients on the LENVIMA arm and 17.6% of patients on placebo arm received prior cumulative activity of >600 mCi or 22 gigabecquerels (GBq) ^{131}I, with the last dose administered at least 6 months prior to study entry. The median cumulative RAI activity administered prior to study entry was 350 mCi (12.95 GBq).

A statistically significant prolongation in PFS was demonstrated in LENVIMA-treated patients compared to those receiving placebo (see Table 8 and Figure 1). Upon confirmation of progression, 109 (83%) patients randomly assigned to placebo crossed over to receive open-label LENVIMA.

Table 8: Efficacy Results for Study 1

	LENVIMA N=261	Placebo N=131
Progression-free Survival[a]		
Number of events (%)	107 (41)	113 (86)
Progressive disease	93 (36)	109 (83)
Death	14 (5)	4 (3)
Median PFS in months (95% CI)	18.3 (15.1, NE)	3.6 (2.2, 3.7)
Hazard ratio (95% CI)[b]	0.21 (0.16, 0.28)	
P-value[c]	<0.001	
Objective Response Rate[a]		
Objective response rate	65%	2%
(95% CI)	(59%, 71%)	(0%, 4%)
Complete response	2%	0%
Partial response	63%	2%
P-value[d]	<0.001	
Overall Survival[e]		
Number of deaths (%)	71 (27)	47 (36)
Median OS in months (95% CI)	NE (22.1, NE)	NE (20.3, NE)
Hazard ratio (95% CI)[b]	0.73 (0.50, 1.07)	
P-value[b]	0.10	

[a] Independent radiologic review

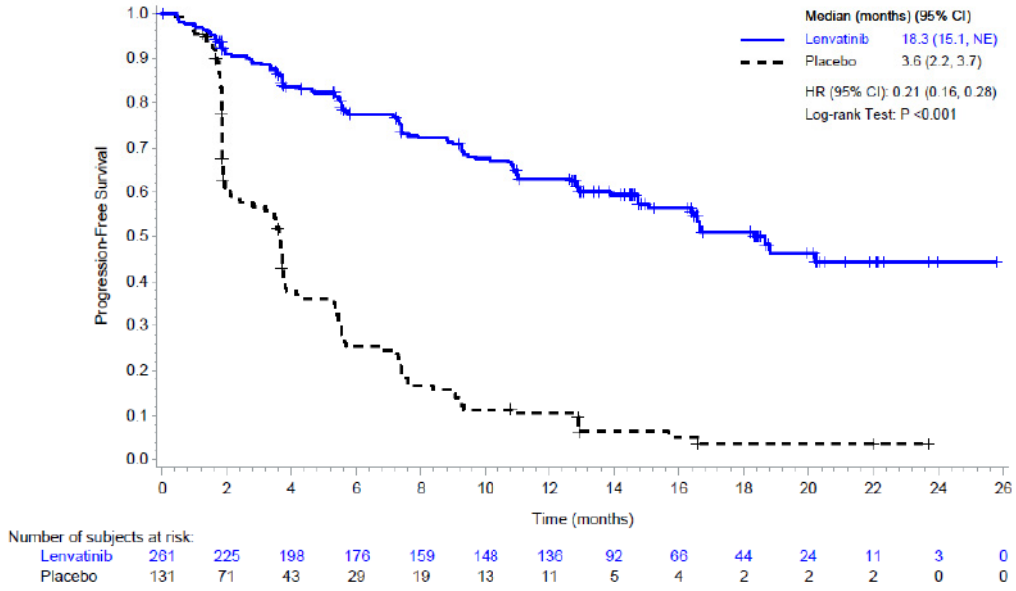
[b] Estimated with Cox proportional hazard model stratified by region (Europe vs North America vs other), age group (≤65 years vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs 1)

[c] Log-rank test stratified by region (Europe vs North America vs other), age group (≤65 years vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs 1)

[d] Cochran-Mantel-Haenszel chi-square test

[e] NE = Not estimable

Figure 1: Kaplan-Meier Plot of Progression-Free Survival (Study 1)



14.2 Renal Cell Carcinoma

A multicenter study (Study 2) randomized 153 patients with advanced or metastatic renal cell carcinoma who have previously received anti-angiogenic therapy 1:1:1 to LENVIMA 18 mg plus 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 ECOG Performance Status of 0 or 1. Patients were stratified by hemoglobin level (≤ or > 13 g/dL for males and ≤ or > 11.5 g/dL for females) and corrected serum calcium (≥10 mg/dL vs. <10 mg/dL).

Of the 101 patients randomly allocated to the LENVIMA + everolimus arm and everolimus monotherapy arm, 72% were male, the median age was 60 years, 31% were older than 65 years, 96% were White. Metastases were present in 95% of the patients and unresectable advanced disease was present in 5%. All patients had a baseline ECOG PS of either 0 (54%) or 1 (46%) with similar distribution across the 2 treatment arms. Memorial Sloan Kettering Cancer Center (MSKCC) favorable, intermediate, and poor risk categories were observed respectively, in 24%, 37%, and 39% of patients in the LENVIMA + everolimus arm, and 24%, 38%, and 38% of patients in the everolimus arm.

The major efficacy outcome measure was investigator-assessed PFS evaluated according to RECIST 1.1. Efficacy results from Study 2 are summarized in Table 9 and Figures 2 and 3. The treatment effect of the combination on PFS was supported by a retrospective independent review of radiographs with an observed hazard ratio (HR) of 0.43 (95% CI: 0.24, 0.75) compared with the everolimus arm.

Table 9: Efficacy Results in Renal Cell Carcinoma Per Investigator Assessment (Study 2)

	LENVIMA 18 mg + Everolimus 5 mg (N=51)	Everolimus 10 mg (N=50)
Progression-Free Survival (PFS)[a]		
Number of events, n (%)	26 (51)	37 (74)
Progressive disease	21 (41)	35 (70)
Death	5 (10)	2 (4)
Median PFS in months (95% CI)	14.6 (5.9, 20.1)	5.5 (3.5, 7.1)
Hazard Ratio (95% CI)[b] LENVIMA + Everolimus vs Everolimus	0.37 (0.22, 0.62)	-
Overall Survival[c]		
Number of deaths, n (%)	32 (63)	37 (74)
Median OS in months (95% CI)	25.5 (16.4, 32.1)	15.4 (11.8, 20.6)
Hazard Ratio (95% CI)[b] LENVIMA + Everolimus vs Everolimus	0.67 (0.42, 1.08)	-
Objective Response Rate (Confirmed)		
Objective response rate, n (%)	19 (37)	3 (6)
(95% CI)	(24, 52)	(1, 17)
Number of complete responses, n (%)	1 (2)	0
Number of partial responses (%)	18 (35)	3 (6)

Tumor assessments were based on RECIST v1.1 criteria for progression but only confirmed responses are included for ORR. Data cutoff date = 13 Jun 2014

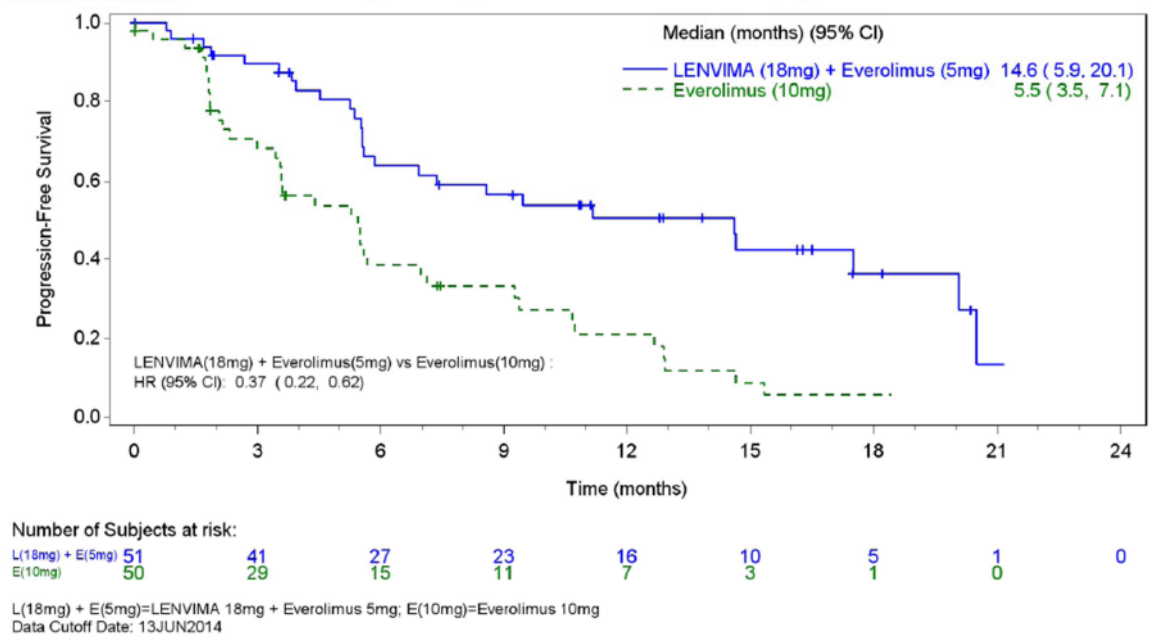
CI = confidence interval

a Point estimates are based on Kaplan-Meier method and 95% CIs are based on the Greenwood formula using log-log transformation.

b Hazard ratio is based on a stratified Cox regression model including treatment as a covariate factor and hemoglobin and corrected serum calcium as strata.

c Data cutoff date = 31 Jul 2015

Figure 2: Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment-Study 2)

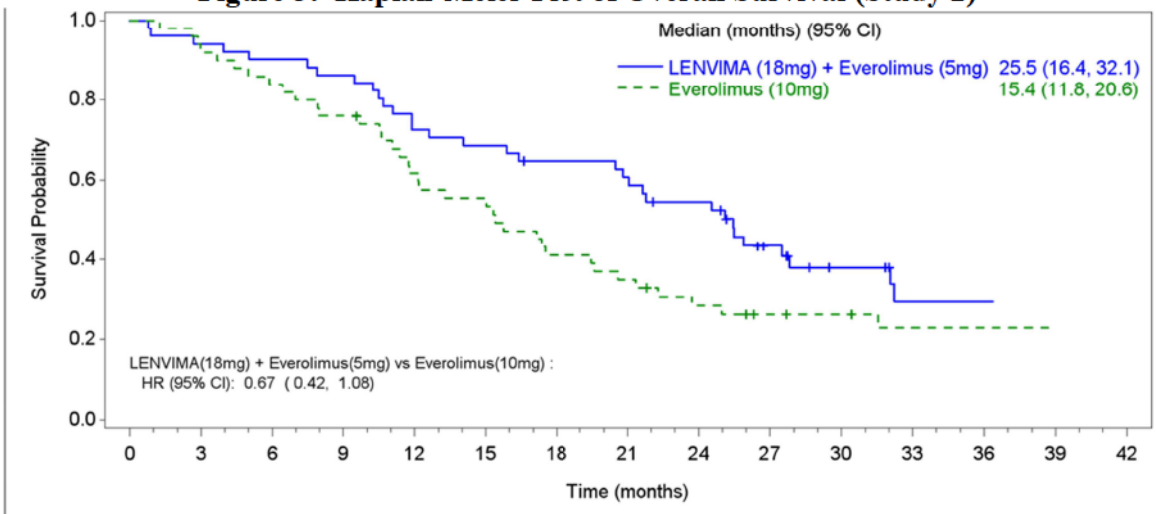


Number of Subjects at risk:

L(18mg) + E(5mg)	51	41	27	23	16	10	5	1	0
E(10mg)	50	29	15	11	7	3	1	0	

L(18mg) + E(5mg)=LENVIMA 18mg + Everolimus 5mg; E(10mg)=Everolimus 10mg
Data Cutoff Date: 13JUN2014

Figure 3: Kaplan-Meier Plot of Overall Survival (Study 2)



Number of Subjects at risk:

L(18mg) + E(5mg)	51	48	46	44	37	35	32	30	26	17	11	7	2	0	0
E(10mg)	50	46	42	38	30	27	20	17	13	10	9	5	1	0	0

L(18mg) + E(5mg)=LENVIMA 18mg + Everolimus 5mg; E(10mg)=Everolimus 10mg
Data Cutoff Date: 31JUL2015

16 HOW SUPPLIED/STORAGE AND HANDLING

LENVIMA 4 mg capsules are supplied as hard hypromellose capsules with yellowish-red body and yellowish-red cap, marked in black ink with "Є" on the cap and "LENV 4 mg" on the body.

LENVIMA 10 mg capsules are supplied as hard hypromellose capsules with yellow body and yellowish-red cap, marked in black ink with "Є" on the cap and "LENV 10 mg" on the body.

LENVIMA capsules are supplied in cartons of 6 cards. Each card is a 5-day blister card as follows:

- NDC 62856-724-30: 24 mg, carton with 6 cards NDC 62856-724-05 (ten 10 mg capsules and five 4 mg capsules per card).
- NDC 62856-720-30: 20 mg, carton with 6 cards NDC 62856-720-05 (ten 10 mg capsules per card).
- NDC 62856-718-30: 18 mg, carton with 6 cards NDC 62856-718-05 (five 10 mg capsules and ten 4 mg capsules per card).
- NDC 62856-714-30: 14 mg, carton with 6 cards NDC 62856-714-05 (five 10 mg capsules and five 4 mg capsules per card).
- NDC 62856-710-30: 10 mg, carton with 6 cards NDC 62856-710-05 (five 10 mg capsules per card).
- NDC 62856-708-30: 8 mg, carton with 6 cards NDC 62856-708-05 (ten 4 mg capsules per card).

Store at 25°C (77°F); excursions permitted to 15 – 30°C (59 – 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypertension:
Advise patients to undergo regular blood pressure monitoring and to contact their health care provider if blood pressure is elevated *[see Warnings and Precautions (5.1)]*.

Cardiac Dysfunction:
Advise patients that LENVIMA can cause cardiac dysfunction and to immediately contact their healthcare provider if they experience any clinical symptoms of cardiac dysfunction such as shortness of breath or swelling of ankles *[see Warnings and Precautions (5.2)]*.

Arterial Thrombotic Events:
Advise patients to seek immediate medical attention for new onset chest pain or acute neurologic symptoms consistent with myocardial infarction or stroke *[see Warnings and Precautions (5.3)]*.