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Lenvatinib

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Pronunciation

(len VA ti nib)

Index Terms

- E7080
- Lenvatinib Mesylate

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule Therapy Pack, Oral:

Lenvima (10 MG Daily Dose): 10 mg (30 ea)

Lenvima (12 MG Daily Dose): 3x4 mg (15 ea, 90 ea)

Lenvima (14 MG Daily Dose): 10 mg & 4 mg (60 ea)

Lenvima (18 MG Daily Dose): 10 mg & 2x4 mg (15 ea, 90 ea)

Lenvima (20 MG Daily Dose): 2x10 mg (60 ea)

Lenvima (24 MG Daily Dose): 2x10 mg & 4 mg (90 ea)

Lenvima (4 MG Daily Dose): 4 mg (5 ea, 30 ea)

Lenvima (8 MG Daily Dose): 2x4 mg (10 ea, 60 ea)

Brand Names: U.S.

- Lenvima (10 MG Daily Dose)
- Lenvima (12 MG Daily Dose)
- Lenvima (14 MG Daily Dose)
- Lenvima (18 MG Daily Dose)
- Lenvima (20 MG Daily Dose)
- Lenvima (24 MG Daily Dose)
- Lenvima (4 MG Daily Dose)
- Lenvima (8 MG Daily Dose)

Pharmacologic Category

- Antineoplastic Agent, Tyrosine Kinase Inhibitor
- Antineoplastic Agent, Vascular Endothelial Growth Factor (VEGF) Inhibitor

Pharmacology

Lenvatinib is a multitargeted tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), VEGFR3 (FLT4), fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET. Inhibition of these receptor tyrosine kinases leads to decreased tumor growth and slowing of cancer progression. In hepatocellular carcinoma cell lines dependent on activated FGFR signaling (with a concurrent inhibition of FGF-receptor substrate 2α phosphorylation), lenvatinib exhibited antiproliferative activity. Combining lenvatinib with everolimus has demonstrated increased antiangiogenic and antitumor activity by decreasing human endothelial cell proliferation, tube formation, and VEGF signaling (in vitro) compared to either drug alone.

Absorption

Administration with a high fat meal (~900 calories; ~55% from fat, ~15% from protein, and ~30% from carbohydrates) decreased the rate of absorption and delayed the median T_{max} from 2 hours to 4 hours, but did not affect the extent of absorption.

Metabolism

Primarily enzymatic through CYP3A and aldehyde oxidase; nonenzymatic metabolism also occurs

Excretion

Feces (~64%); urine (~25%)

Time to Peak

1 to 4 hours

Half-Life Elimination

~28 hours

Protein Binding

98% to 99%

Special Populations: Renal Function Impairment

Lenvatinib concentrations may increase in some patients with CrCl 15 to 29 mL/minute.

Special Populations: Hepatic Function Impairment

In a single 10 mg dose study of lenvatinib in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, or a single 5 mg dose in patients with severe (Child-Pugh class C) hepatic impairment (excluding patients with hepatocellular cancer), the dose-adjusted AUC of lenvatinib was 119%, 107%, and 180%, respectively, as compared to patients with normal hepatic function.

Special Populations Note

Tumor type: Patients with hepatocellular cancer had a 13% lower clearance (compared to other cancer types).

Use: Labeled Indications

Endometrial carcinoma, advanced: Treatment of advanced endometrial carcinoma (in combination with pembrolizumab) that is not microsatellite instability-high or mismatch repair deficient, in patients who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.

Hepatocellular carcinoma, unresectable: First-line treatment of unresectable hepatocellular carcinoma.

Renal cell carcinoma, advanced: Treatment of advanced renal cell carcinoma (in combination with everolimus) following one prior anti-angiogenic therapy.

Thyroid cancer, differentiated: Treatment of locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer.

Contraindications

There are no contraindications listed in the manufacturer's US labeling.

Canadian labeling: Hypersensitivity to lenvatinib or any component of the formulation.

Dosing: Adult

Note: Lenvatinib is associated with a moderate emetic potential; antiemetics are recommended to prevent nausea and vomiting (Hesketh 2017).

Endometrial carcinoma, advanced: Oral: 20 mg once daily (in combination with pembrolizumab), continue until disease progression or unacceptable toxicity (Makker 2019).

Hepatocellular carcinoma, unresectable: Oral: 12 mg once daily (patients ≥60 kg [actual body weight]) or 8 mg once daily (patients <60 kg [actual body weight]) (Kudo 2018); continue until disease progression or unacceptable toxicity.

Renal cell carcinoma, advanced: Oral: 18 mg once daily (in combination with everolimus), continue until disease progression or unacceptable toxicity (Motzer 2015).

Thyroid cancer, differentiated: Oral: 24 mg once daily until disease progression or unacceptable toxicity (Schlumberger 2015).

Missed doses: Do not take a missed dose within 12 hours of the next dose (if within 12 hours, skip the missed dose and return to regular administration time).

Dosage adjustment for surgery: Temporarily interrupt lenvatinib for at least 6 days prior to scheduled surgery; resume therapy after surgery based clinical judgement of adequate wound healing.

Dosing: Geriatric

Refer to adult dosing.

Dosing: Adjustment for Toxicity

Recommended Lenvatinib Dose Reductions for Adverse Reactions				
Indication	**Usual lenvatinib dosage**	**First dose reduction to:**	**Second dose reduction to:**	**Third dose reduction to:**
Endometrial carcinoma (advanced)[a]	20 mg once daily	14 mg once daily	10 mg once daily	8 mg once daily
Hepatocellular carcinoma (unresectable); ≥60 kg	12 mg once daily	8 mg once daily	4 mg once daily	4 mg once every other day
Hepatocellular carcinoma (unresectable); <60 kg	8 mg once daily	4 mg once daily	4 mg once every other day	Discontinue therapy
Renal cell carcinoma (advanced)[b]	18 mg once daily	14 mg once daily	10 mg once daily	8 mg once daily
Thyroid cancer (differentiated)	24 mg once daily	20 mg once daily	14 mg once daily	10 mg once daily

[a]When used in combination with pembrolizumab, interrupt one or both drugs or dose reduce lenvatinib as appropriate. No dose reductions are recommended for pembrolizumab; refer to pembrolizumab monograph for dosage adjustment for toxicity.

[b]When used in combination with everolimus, for adverse reactions of both lenvatinib and everolimus, reduce the lenvatinib dose first and then the everolimus dose (refer to Everolimus monograph for dosage adjustment for toxicity).

Table has been converted to the following text.

Recommended lenvatinib dose reductions for adverse reactions

Indication:

Endometrial carcinoma (advanced):

Usual lenvatinib dosage: 20 mg once daily

First dose reduction to: 14 mg once daily

Second dose reduction to: 10 mg once daily

Third dose reduction to: 8 mg once daily

When used in combination with pembrolizumab, interrupt one or both drugs or dose reduce lenvatinib as appropriate. No dose reductions are recommended for pembrolizumab; refer to pembrolizumab monograph for dosage adjustment for toxicity.

Hepatocellular carcinoma (unresectable); ≥60 kg:

Usual lenvatinib dosage: 12 mg once daily

First dose reduction to: 8 mg once daily

Second dose reduction to: 4 mg once daily

Third dose reduction to: 4 mg once every other day

Hepatocellular carcinoma (unresectable); <60 kg:

Usual lenvatinib dosage: 8 mg once daily

First dose reduction to: 4 mg once daily

Second dose reduction to: 4 mg once every other day

Third dose reduction to: Discontinue therapy

Renal cell carcinoma (advanced):

Usual lenvatinib dosage: 18 mg once daily

First dose reduction to: 14 mg once daily

Second dose reduction to: 10 mg once daily

Third dose reduction to: 8 mg once daily

When used in combination with everolimus, for adverse reactions of both lenvatinib and everolimus, reduce the lenvatinib dose first and then the everolimus dose (refer to everolimus monograph for dosage adjustment for toxicity).

Thyroid cancer (differentiated):

Usual lenvatinib dosage: 24 mg once daily

First dose reduction to: 20 mg once daily

Second dose reduction to: 14 mg once daily

Third dose reduction to: 10 mg once daily

Arterial thrombotic event (any grade): Permanently discontinue therapy.

Cardiac:

Cardiac dysfunction:

Grade 3: Withhold therapy until improves to ≤ grade 1 or baseline. Depending on the severity and persistence of the cardiac dysfunction, resume therapy at a reduced dose or discontinue.

Grade 4: Permanently discontinue therapy.

Hypertension:

Grade 3: Withhold therapy for grade 3 hypertension that persists despite optimal antihypertensive therapy. When hypertension is controlled at ≤ grade 2, resume therapy at a reduced dose.

Grade 4: Permanently discontinue therapy.

QT prolongation: QT prolongation >500 msec or >60 msec increase from baseline: Withhold therapy until improves to ≤480 msec or baseline, then resume therapy at a reduced dose.

Gastrointestinal toxicity:

Diarrhea: Initiate prompt management of diarrhea or dehydration/hypovolemia. Based on the severity, withhold lenvatinib and upon recovery, resume lenvatinib at a reduced dose or permanently discontinue.

Fistula formation (grade 3 or 4): Permanently discontinue therapy.

Gastrointestinal perforation (any grade): Permanently discontinue therapy.

Hemorrhage: Withhold therapy; upon recovery (depending on severity), resume therapy at a reduced dose or permanently discontinue treatment.

Hypocalcemia: Administer calcium replacement therapy as necessary; withhold therapy and resume at a reduced dose or permanently discontinue depending on the severity.

Reversible posterior leukoencephalopathy syndrome (any grade): Withhold therapy until fully resolved; depending on severity and persistence of neurologic symptoms, resume at a reduced dose or discontinue.

Wound healing complications: Permanently discontinue lenvatinib.

Other adverse reactions:

Persistent or intolerable grade 2 or 3 adverse reaction: Withhold therapy until improves to ≤ grade 1 or baseline and then resume therapy at a reduced dose.

Grade 4 laboratory abnormality: Withhold therapy until improves to ≤ grade 1 or baseline and then resume therapy at a reduced dose.

Grade 4 adverse reaction: Permanently discontinue therapy.

Administration

Lenvatinib is associated with a moderate emetic potential; antiemetics are recommended to prevent nausea and vomiting (Hesketh 2017).

Oral: Administer orally at the same time each day. May be administered with or without food.

Capsules may be swallowed whole or dissolved in a small glass of liquid. To dissolve in liquid, measure 15 mL of water or apple juice into a glass; add whole capsule (do not break or crush capsule) and leave in liquid for at least 10 minutes, then stir for at least 3 minutes. Administer liquid, then add 15 mL of additional water or apple juice to glass, swirl a few times and then swallow additional liquid.

Storage

Store at 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F).

Drug Interactions

Amiodarone: QT-prolonging Kinase Inhibitors (Highest Risk) may enhance the QTc-prolonging effect of Amiodarone. Management: Consider alternatives to this drug combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

Amisulpride: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Amisulpride. Management: Consider alternatives to this combination. Patients with other risk factors (eg, older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations) are likely at greater risk for these toxicities. *Consider therapy modification*

Azithromycin (Systemic): QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Azithromycin (Systemic). Management: Consider alternatives to this combination. Patients with other risk factors (eg, older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations) are likely at greater risk for these toxicities. *Consider therapy modification*

Chloroquine: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Chloroquine. Management: Consider alternatives to this combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

Citalopram: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Citalopram. *Avoid combination*

Clarithromycin: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Clarithromycin. *Avoid combination*

Clofazimine: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Clofazimine. Management: Consider alternatives to this combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

CloZAPine: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of CloZAPine. Management: Consider alternatives to this combination. Patients with other risk factors (eg, older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations) are likely at greater risk for these toxicities. *Consider therapy modification*

Dasatinib: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Dasatinib. Management: Consider alternatives to this combination. Patients with other risk factors (eg, older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations) are likely at greater risk for these toxicities. *Consider therapy modification*

Domperidone: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Domperidone. *Avoid combination*

Doxepin-Containing Products: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Doxepin-Containing Products. Management: Consider alternatives to this combination. Patients with other risk factors (eg, older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations) are likely at greater risk for these toxicities. *Consider therapy modification*

Dronedarone: QT-prolonging Kinase Inhibitors (Highest Risk) may enhance the QTc-prolonging effect of Dronedarone. Management: Consider alternatives to this drug combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

Droperidol: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Droperidol. Management: Consider alternatives to this combination. Patients with other risk factors (eg, older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations) are likely at greater risk for these toxicities. *Consider therapy modification*

Encorafenib: May enhance the QTc-prolonging effect of QT-prolonging Agents (Highest Risk). Management: Consider alternatives to this combination. Patients with other risk factors (eg, older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations) are likely at greater risk for these toxicities. *Consider therapy modification*

Entrectinib: May enhance the QTc-prolonging effect of QT-prolonging Agents (Highest Risk). *Avoid combination*

Escitalopram: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Escitalopram. Management: Consider alternatives to this combination. Patients with other risk factors (eg, older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations) are likely at greater risk for these toxicities. *Consider therapy modification*

Fexinidazole [INT]: May enhance the QTc-prolonging effect of QT-prolonging Agents (Highest Risk). *Avoid combination*

Fingolimod: May enhance the QTc-prolonging effect of QT-prolonging Agents (Highest Risk). Management: Monitor for QTc interval prolongation and ventricular arrhythmias (including TdP) with a continuous overnight ECG when fingolimod is combined with QT prolonging drugs. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Monitor therapy*

Flecainide: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Flecainide. Management: Consider alternatives to this combination. Patients with other risk factors (eg, older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations) are likely at greater risk for these toxicities. *Consider therapy modification*

Flupentixol: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Flupentixol. *Avoid combination*

Gadobenate Dimeglumine: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Gadobenate Dimeglumine. Management: Consider alternatives to this combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

Gemifloxacin: QT-prolonging Kinase Inhibitors (Highest Risk) may enhance the QTc-prolonging effect of Gemifloxacin. Management: Consider alternatives to this drug combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with

additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

Gilteritinib: May enhance the QTc-prolonging effect of QT-prolonging Agents (Highest Risk). Management: Consider alternatives to this combination. If use is necessary, monitor for QTc interval prolongation and arrhythmias. *Consider therapy modification*

Halofantrine: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Halofantrine. Management: Consider alternatives to this combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

Haloperidol: QT-prolonging Kinase Inhibitors (Highest Risk) may enhance the QTc-prolonging effect of Haloperidol. Management: Consider alternatives to this drug combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

Inotuzumab Ozogamicin: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Inotuzumab Ozogamicin. Management: Consider alternatives to this combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

Levofloxacin-Containing Products (Systemic): QT-prolonging Kinase Inhibitors (Highest Risk) may enhance the QTc-prolonging effect of Levofloxacin-Containing Products (Systemic). Management: Consider alternatives to this drug combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

Lofexidine: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Lofexidine. Management: Consider alternatives to this combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

Methadone: QT-prolonging Kinase Inhibitors (Highest Risk) may enhance the QTc-prolonging effect of Methadone. Management: Consider alternatives to this drug combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

Midostaurin: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Midostaurin. Management: Consider alternatives to this combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

Moxifloxacin (Systemic): QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Moxifloxacin (Systemic). *Avoid combination*

Nilotinib: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Nilotinib. *Avoid combination*

OLANZapine: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of OLANZapine. Management: Consider alternatives to this combination. Patients with other risk factors (eg, older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease,

and higher drug concentrations) are likely at greater risk for these toxicities. *Consider therapy modification*

Ondansetron: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Ondansetron. Management: Consider alternatives to this combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

Osimertinib: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Osimertinib. Management: Consider alternatives to this combination. Patients with other risk factors (eg, older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations) are likely at greater risk for these toxicities. *Consider therapy modification*

Pentamidine (Systemic): QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Pentamidine (Systemic). Management: Consider alternatives to this combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

Pilsicainide: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Pilsicainide. Management: Consider alternatives to this combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

Pimozide: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Pimozide. Management: Consider alternatives to this combination. Patients with other risk factors (eg, older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations) are likely at greater risk for these toxicities. *Avoid combination*

Piperaquine: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Piperaquine. *Avoid combination*

Probucol: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Probucol. *Avoid combination*

Propafenone: May enhance the QTc-prolonging effect of QT-prolonging Kinase Inhibitors (Highest Risk). Management: Consider alternatives to this drug combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

QT-prolonging Agents (Indeterminate Risk - Avoid): May enhance the QTc-prolonging effect of QT-prolonging Agents (Highest Risk). Management: Monitor for QTc interval prolongation and ventricular arrhythmias when these agents are combined. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Monitor therapy*

QT-prolonging Agents (Indeterminate Risk - Caution): May enhance the QTc-prolonging effect of QT-prolonging Agents (Highest Risk). Management: Monitor for QTc interval prolongation and ventricular arrhythmias when these agents are combined. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Monitor therapy*

QT-prolonging Class IA Antiarrhythmics (Highest Risk): QT-prolonging Kinase Inhibitors (Highest Risk) may enhance the QTc-prolonging effect of QT-prolonging Class IA Antiarrhythmics

(Highest Risk). Management: Consider alternatives to this drug combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

QT-prolonging Class III Antiarrhythmics (Highest Risk): QT-prolonging Kinase Inhibitors (Highest Risk) may enhance the QTc-prolonging effect of QT-prolonging Class III Antiarrhythmics (Highest Risk). Management: Consider alternatives to this drug combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. **Exceptions:** Dronedarone. *Consider therapy modification*

QT-prolonging Kinase Inhibitors (Highest Risk): May enhance the QTc-prolonging effect of other QT-prolonging Kinase Inhibitors (Highest Risk). *Avoid combination*

QT-prolonging Miscellaneous Agents (Highest Risk): QT-prolonging Kinase Inhibitors (Highest Risk) may enhance the QTc-prolonging effect of QT-prolonging Miscellaneous Agents (Highest Risk). Management: Consider alternatives to this drug combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

QT-prolonging Moderate CYP3A4 Inhibitors (Moderate Risk): QT-prolonging Kinase Inhibitors (Highest Risk) may enhance the QTc-prolonging effect of QT-prolonging Moderate CYP3A4 Inhibitors (Moderate Risk). QT-prolonging Moderate CYP3A4 Inhibitors (Moderate Risk) may increase the serum concentration of QT-prolonging Kinase Inhibitors (Highest Risk). Management: Consider alternatives to this drug combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. **Exceptions:** Nilotinib; Ribociclib. *Consider therapy modification*

QT-prolonging Strong CYP3A4 Inhibitors (Moderate Risk): QT-prolonging Kinase Inhibitors (Highest Risk) may enhance the QTc-prolonging effect of QT-prolonging Strong CYP3A4 Inhibitors (Moderate Risk). QT-prolonging Strong CYP3A4 Inhibitors (Moderate Risk) may increase the serum concentration of QT-prolonging Kinase Inhibitors (Highest Risk). Management: Consider alternatives to this drug combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

QUEtiapine: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of QUEtiapine. *Avoid combination*

Ribociclib: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Ribociclib. *Avoid combination*

RisperiDONE: QT-prolonging Agents (Highest Risk) may enhance the CNS depressant effect of RisperiDONE. QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of RisperiDONE. Management: Consider alternatives to this drug combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

Sodium Stibogluconate: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Sodium Stibogluconate. Management: Consider alternatives to this combination. If combined, monitor for QTc interval prolongation and ventricular arrhythmias. Patients with

additional risk factors for QTc prolongation may be at even higher risk. *Consider therapy modification*

Sparfloxacin: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Sparfloxacin. *Avoid combination*

Thioridazine: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Thioridazine. *Avoid combination*

Vemurafenib: QT-prolonging Agents (Highest Risk) may enhance the QTc-prolonging effect of Vemurafenib. Management: Consider alternatives to this combination. Patients with other risk factors (eg, older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease, and higher drug concentrations) are likely at greater risk for these toxicities. *Consider therapy modification*

Adverse Reactions

>10%:

Cardiovascular: Hypertension (45% to 73%), peripheral edema (14% to 21%)

Central nervous system: Fatigue (44% to 67%), headache (10% to 38%), voice disorder (24% to 31%), mouth pain (25%), dizziness (15%), insomnia (12%)

Dermatologic: Palmar-plantar erythrodysesthesia (27% to 32%), skin rash (14% to 21%), alopecia (12%)

Endocrine & metabolic: Increased thyroid stimulating hormone level (57% to 70%), weight loss (31% to 51%), hypothyroidism (21%), increased gamma-glutamyl transferase (grades 3/4: 17%), hyponatremia (grades 3/4: 15%)

Gastrointestinal: Diarrhea (39% to 67%), decreased appetite (34% to 54%), nausea (20% to 47%), stomatitis (11% to 41%; grades 3/4: <1%), vomiting (16% to 36%), abdominal pain (30% to 31%), constipation (16% to 29%), dysgeusia (18%), xerostomia (17%), dyspepsia (13%)

Genitourinary: Proteinuria (26% to 34%), urinary tract infection (11%)

Hematologic & oncologic: Hemorrhage (23% to 35%, including carotid artery hemorrhage; grades ≥3: 2%)

Hepatic: Increased serum aspartate aminotransferase (grades ≥3: 5% to 12%)

Neuromuscular & skeletal: Arthralgia (≤62%), myalgia (≤62%)

Renal: Renal insufficiency (7% to 14%)

Respiratory: Cough (24%), epistaxis (12%)

Miscellaneous: Fever (15%)

1% to 10%:

Cardiovascular: Hypotension (9%), prolonged QT interval on ECG (8% to 9%; >500 msec: 2%), cardiac failure (≤7%), ventricular dysfunction (≤7%), arterial thromboembolism (2% to 5%),

cardiac abnormality (> grade 3: 3%), pulmonary embolism (3%), reduced ejection fraction (ejection fraction reduced by >20%: 2%)

Dermatologic: Hyperkeratosis (7%)

Endocrine & metabolic: Dehydration (9%), hypocalcemia (grades 3/4: 9%), hypokalemia (grades 3/4: 3% to 6%), hypercalcemia (>5%), hypercholesterolemia (>5%), hyperkalemia (>5%), hypoalbuminemia (3% to >5%), hypoglycemia (>5%), hypomagnesemia (>5%)

Gastrointestinal: Infection of mouth (≤10%), increased serum lipase (grades 3/4: 4% to 6%), increased serum amylase (>5%), gastrointestinal fistula (≤2%), gastrointestinal perforation (≤2%)

Hematologic & oncologic: Thrombocytopenia (grades 3/4: 2% to 10%), lymphocytopenia (grades 3/4: 8%), neutropenia (grades 3/4: 7%), anemia (grades 3/4: 4%)

Hepatic: Hepatic encephalopathy (8%), hyperbilirubinemia (>5%), increased serum alanine aminotransferase (grades ≥3: 4% to 8%), increased serum alkaline phosphatase (>5%), hepatic failure (3%)

Renal: Increased serum creatinine (grades 3/4: 2% to 3%)

Respiratory: Pulmonary edema (≤7%), pneumonia (4%)

<1%, postmarketing, and/or case reports: Aortic dissection, cholecystitis, fistula, hepatitis, nephrotic syndrome, pancreatitis, pneumothorax, reversible posterior leukoencephalopathy syndrome, tumor hemorrhage, wound healing impairment

Warnings/Precautions

Concerns related to adverse effects:

• Cardiac effects: Hypertension commonly occurred in patients treated with lenvatinib in clinical trials (including grade 3 and 4 events); the median time to onset of new or worsening hypertension was 16 to 35 days. Serious complications have been reported secondary to poorly controlled hypertension. Blood pressure should be controlled prior to initiating therapy; monitor frequently throughout treatment. Serious (≥ grade 3) and fatal cardiac dysfunction has been reported with lenvatinib, including cardiomyopathy, left or right ventricular dysfunction, decreased left or right ejection fraction (>20% from baseline), heart failure, cardiac failure, or ventricular hypokinesia. Monitor for clinical signs/symptoms of cardiac dysfunction. QT/QTc prolongation was also observed in lenvatinib-treated patients, including prolongation >500 msec and increases >60 msec from baseline. Monitor electrolytes (baseline and periodically) and correct electrolyte abnormalities in all patients; obtain electrocardiograms in patients with congenital long QT syndrome, heart failure, bradyarrhythmias, or in those on concomitant medications known to prolong the QT interval. Cardiac adverse effects (hypertension, cardiac dysfunction, or QT prolongation) may require treatment interruption, dosage reduction, or discontinuation.

• Fistula formulation/GI perforation: Fistulas and GI perforations have been reported with lenvatinib. Permanently discontinue lenvatinib in patients who develop GI perforation (any severity) or grade 3 or 4 fistula.

• GI toxicity: Lenvatinib is associated with a moderate emetic potential; antiemetics are recommended to prevent nausea and vomiting (Hesketh 2017). Diarrhea has commonly occurred in patients receiving lenvatinib; grade 3 events have been reported. When used in combination with everolimus, diarrhea was the most frequent cause of dose interruption and/or

reduction, and diarrhea recurred despite dose reduction. When diarrhea occurs, initiate prompt management of diarrhea or dehydration/hypovolemia. Based on the severity, withhold lenvatinib and upon recovery, resume lenvatinib at a reduced dose or permanently discontinue.

• Hemorrhage: Serious and fatal hemorrhagic events may occur with lenvatinib. Hemorrhagic events (any grade) occurred in over 25% of patients treated with lenvatinib (either as a single agent or in combination with everolimus); epistaxis and hematuria were the most frequently reported hemorrhagic events. Fatal intracranial hemorrhage was observed in a patient who had CNS metastases at baseline and received lenvatinib; cerebral hemorrhage has been reported in patients who received lenvatinib in combination with everolimus (including rare fatal cases). Serious tumor-related bleeding events (including cases of fatal hemorrhage) have been observed. Serious and fatal carotid artery hemorrhages were reported more frequently in patients with anaplastic thyroid carcinoma (ATC) than with other tumor types. Safety and efficacy of lenvatinib have not been established in the treatment of ATC. Consider the risk of severe or fatal hemorrhage associated with tumor infiltration/invasion of major blood vessels. Monitor for bleeding; may require therapy interruption, dosage reduction, or permanent discontinuation.

• Hepatotoxicity: Serious hepatic adverse reactions were observed in patients with malignancies other than hepatocellular cancer (HCC) who received lenvatinib; fatal events, including hepatic failure, acute hepatitis, and hepatorenal syndrome, have occurred. Hepatic encephalopathy (including hepatic encephalopathy, encephalopathy, metabolic encephalopathy, and hepatic coma) have been reported in lenvatinib-treated patients with HCC, including ≥ grade 3 events and hepatic failure. Monitor liver function tests at baseline and throughout therapy; monitor patients with HCC closely for signs of hepatic failure, including hepatic encephalopathy. Hepatotoxicity may require treatment interruption, dosage reduction, and/or permanent discontinuation. Reduce the initial dose for certain patients with preexisting hepatic impairment.

• Hypocalcemia: Grade 3 to 4 hypocalcemia has occurred in patients receiving lenvatinib; in most cases, hypocalcemia improved or resolved following calcium supplementation, with or without treatment interruption or dosage reduction. Monitor serum calcium levels at least monthly; replace calcium as necessary. Depending on the severity, hypocalcemia may require treatment interruption, dosage reduction, and/or permanent discontinuation.

• Hypothyroidism: Lenvatinib impairs exogenous thyroid suppression. Most patients with differentiated thyroid cancer (DTC) had a baseline thyroid stimulating hormone (TSH) level ≤0.5 milliunits/L, however, in patients with DTC with a normal baseline TSH, elevation of TSH level >0.5 milliunits/L was commonly observed. Grade 1 or 2 hypothyroidism also occurred in patients receiving lenvatinib for other indications; an elevation of TSH was commonly observed in patients with a normal or low TSH at baseline. Monitor thyroid function prior to lenvatinib initiation and at least monthly during lenvatinib treatment. Manage hypothyroidism according to standard medical practice.

• Palmar-plantar erythrodysesthesia: Palmar-plantar erythrodysesthesia (usually grades 1 to 2) was observed in nearly one-third of patients receiving lenvatinib.

• Renal toxicity: Proteinuria (including grade 3 toxicity) was commonly observed in clinical studies. Monitor for proteinuria at baseline and periodically throughout therapy. If urine dipstick for proteinuria is ≥2+, obtain a 24-hour urine protein. Withhold treatment for proteinuria ≥2 g/24 hours; upon recovery, resume at a reduced dose or permanently discontinue (depending on the severity). Discontinue for nephrotic syndrome. Serious renal impairment or failure may also occur (including ≥ grade 3 events and fatal renal failure); a primary risk factor for renal impairment is dehydration or hypovolemia due to diarrhea and vomiting; initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold lenvatinib for grade 3 or 4 renal

failure or impairment; resume at reduced dose or permanently discontinue depending on the severity of renal impairment/failure. Reduce the initial dose for certain patients with preexisting renal impairment.

• Reversible posterior leukoencephalopathy syndrome: Reversible posterior leukoencephalopathy syndrome (RPLS) has occurred (rarely). Confirm RPLS diagnosis with MRI. Withhold lenvatinib; depending on the severity and persistence of neurologic symptoms, resume at a reduced dose or permanently discontinue.

• Thromboembolic events: Arterial thromboembolic events, including ≥ grade 3 events, have been reported. Permanently discontinue lenvatinib if arterial thrombosis occurs; the safety of resuming therapy after such an event has not been established. Lenvatinib has not been studied in patients who have had an arterial thromboembolic event within the preceding 6 months.

• Wound healing complications: Wound healing complications, including fistula formation and wound dehiscence, may occur. Withhold lenvatinib for at least 6 days before scheduled surgery; treatment reinitiation should be guided by clinical judgment and wound healing assessment. Permanently discontinue in patients with wound healing complications.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

Special populations:

• Elderly: Patients ≥75 years of age appeared to have reduced tolerability for lenvatinib in some studies.

Monitoring Parameters

LFTs (at baseline, every 2 weeks for 2 months, and at least monthly thereafter); renal function; electrolytes (baseline and periodically); serum calcium at least monthly; thyroid function (TSH levels) at baseline and monthly or as clinically indicated; monitor for proteinuria at baseline and periodically during treatment (urine dipstick; if 2+ then 24-hour urine protein); verify pregnancy status prior to treatment initiation (in females of reproductive potential). Monitor BP after 1 week, then every 2 weeks for 2 months, and at least monthly thereafter; ECG in select patients (congenital long QT syndrome, heart failure, bradyarrhythmias, or in those on concomitant medications known to prolong the QT interval); monitor for clinical signs/symptoms of cardiac dysfunction, arterial thrombosis, reversible posterior leukoencephalopathy syndrome, fistula formation, GI perforation, bleeding/hemorrhagic events, diarrhea, dehydration, and wound healing complications; monitor patients with hepatocellular carcinoma closely for signs of hepatic failure, including hepatic encephalopathy. Monitor adherence.

Pregnancy Considerations

Based on the mechanism of action and findings from animal reproduction studies, lenvatinib may cause fetal harm if administered in pregnancy. Verify pregnancy status prior to initiating lenvatinib in females of reproductive potential. Females of reproductive potential should use effective contraception during lenvatinib treatment and for at least 30 days after completion of therapy.

Patient Education

What is this drug used for?

• It is used to treat thyroid cancer.

• It is used to treat kidney cancer.

• It is used to treat liver cancer.

• It may be given to you for other reasons. Talk with the doctor.

Frequently reported side effects of this drug

• Change in taste

• Loss of strength and energy

• Cough

• Constipation

• Lack of appetite

• Dry mouth

• Hair loss

• Heartburn

• Mouth pain

• Mouth sores

• Mouth irritation

• Muscle pain

• Joint pain

• Nausea

• Vomiting

• Trouble sleeping

• Change in voice

• Weight loss

Other side effects of this drug: Talk with your doctor right away if you have any of these signs of:

• Posterior reversible encephalopathy syndrome like confusion, not alert, vision changes, seizures, or severe headache.

• Liver problems like dark urine, fatigue, lack of appetite, nausea, abdominal pain, light-colored stools, vomiting, or yellow skin.

• Blood clots like numbness or weakness on one side of the body; pain, redness, tenderness, warmth, or swelling in the arms or legs; change in color of an arm or leg; chest pain; shortness of breath; fast heartbeat; or coughing up blood.

• Severe cerebrovascular disease like change in strength on one side is greater than the other, trouble speaking or thinking, change in balance, or vision changes.

• Bleeding like vomiting blood or vomit that looks like coffee grounds; coughing up blood; blood in the urine; black, red, or tarry stools; bleeding from the gums; abnormal vaginal bleeding; bruises without a reason or that get bigger; or any severe or persistent bleeding.

• Low thyroid level like constipation; trouble handling heat or cold; memory problems; mood changes; or burning, numbness, or tingling feeling.

• Fluid and electrolyte problems like mood changes, confusion, muscle pain or weakness, abnormal heartbeat, severe dizziness, passing out, fast heartbeat, increased thirst, seizures, loss of strength and energy, lack of appetite, unable to pass urine or change in amount of urine passed, dry mouth, dry eyes, or nausea or vomiting.

• Kidney problems like unable to pass urine, blood in the urine, change in amount of urine passed, or weight gain.

• Urinary tract infection like blood in the urine, burning or painful urination, passing a lot of urine, fever, lower abdominal pain, or pelvic pain.

• Heart problems like cough or shortness of breath that is new or worse, swelling of the ankles or legs, abnormal heartbeat, weight gain of more than five pounds in 24 hours, dizziness, or passing out.

• Severe headache

• Vision changes

• Severe dizziness

• Passing out

• Fast heartbeat

• Abnormal heartbeat

• Redness or irritation of palms or soles of feet

• Severe abdominal pain

• Impaired wound healing

• Severe or persistent diarrhea

• Signs of a significant reaction like wheezing; chest tightness; fever; itching; bad cough; blue skin color; seizures; or swelling of face, lips, tongue, or throat.

Note: This is not a comprehensive list of all side effects. Talk to your doctor if you have questions.

Consumer Information Use and Disclaimer: This information should not be used to decide whether or not to take this medicine or any other medicine. Only the healthcare provider has the knowledge and training to decide which medicines are right for a specific patient. This information does not endorse any medicine as safe, effective, or approved for treating any patient or health condition. This is only a brief summary of general information about this medicine. It does NOT include all information about the possible uses, directions, warnings, precautions, interactions, adverse effects, or risks that may apply to this medicine. This information is not specific medical advice and does not replace information you receive from the healthcare provider. You must talk with the healthcare provider for complete information about the risks and benefits of using this medicine.

Further information

Always consult your healthcare provider to ensure the information displayed on this page applies to your personal circumstances.