Drug Monograph

A - Drug Name

lenvatinib

COMMON TRADE NAME(S): Lenvima®

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B - Mechanism of Action and Pharmacokinetics

Lenvatinib is a multiple receptor tyrosine kinase inhibitor (TKI) that selectively inhibits vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR) and VEGFR3 (FLT4) as well as other proangiogenic and oncogenic pathway-related receptors.

Absorption	Lenvatinib is rapidly absorbed with a tmax reached 1 to 4 hours post-dose. Food slows the rate of absorption, but does not affect the extent of absorption.	
	Bioavailability	data from a mass-balance study suggests about 85%
Distribution	PPB	98-99% (mainly to albumin)
Metabolism	Active metabolites	yes
	Inactive metabolites	yes
Elimination	Plasma concentrations decline bi-exponentially following C_{max}.	
	Half-life	28 hours (terminal)
	Feces	64%

	Urine	25%

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C - Indications and Status

Health Canada Approvals:

- For the treatment of patients with locally recurrent or metastatic, progressive, radioactive-iodine refractory differentiated thyroid cancer (DTC).
- In combination with everolimus for the treatment of advanced renal cell carcinoma (RCC) following prior vascular endothelial growth factor (VEGF)-targeted therapy.
- For the first-line treatment of adult patients with unresectable hepatocellular carcinoma (HCC).*

*Efficacy and safety data for Child-Pugh Class B and Class C are not available.

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D - Adverse Effects

Emetogenic Potential: Moderate – Consider prophylaxis daily

Extravasation Potential: Not applicable

The following table lists adverse effects that occurred in ≥5% of patients in the phase III SELECT trial in DTC patients comparing lenvatinib vs placebo, where there was at least a 5% difference between arms. Severe adverse events from other studies or post-marketing are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (rare)	E
	Arterial thromboembolism (5%) (may be severe)	E
	Bradycardia (11%)	E
	Cardiotoxicity (5%)	E D
	Hypertension (73%) (44% severe)	E
	Hypotension (9%)	E

	Other - Artery dissection or aneurysm (rare)	L
	QT interval prolonged (12%) (2% severe)	E
	Venous thromboembolism (3%) (severe)	E
Dermatological	Alopecia (12%)	E
	Hand-foot syndrome (32%)	E
	Other (7%) - hyperkeratosis	E
	Rash (19%)	E
Gastrointestinal	Abdominal pain (31%)	E
	Anorexia, weight loss (54%)	E
	Constipation (29%)	E
	Dehydration (9%) (may be severe)	E
	Diarrhea (67%) (9% severe)	E
	Dry mouth (17%)	E
	Dyspepsia (13%)	E
	GI obstruction (rare)	E
	GI perforation (2% fistulas; may be severe)	E
	Mucositis (41%) (5% severe)	E
	Nausea, vomiting (47%) (may be severe)	E
General	Edema - limbs (21%)	E
	Fatigue (43%)	E
	Wound dehiscence (rare)	E
Hematological	Hemorrhage (35%) (2% severe)	E
	Myelosuppression (14%)	E D
Hepatobiliary	↓ albumin (49%)	E
	↑ Amylase / lipase (12%) (may be severe)	E
	Cholecystitis (rare)	E
	Hepatotoxicity (8%) (including hepatic encephalopathy)	E
	↑ LFTs (52%) (4% severe)	E
	Pancreatitis (rare)	E
Hypersensitivity	Hypersensitivity (rare)	E
Infection	Infection (12%)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (40%) (low Ca, K, Na, Mg; 9% severe)	E
	Hyperglycemia (53%) (<1% severe)	E

	Hypoglycemia (19%) (mild to moderate)	E
	Hypothyroidism (21%)	E D
	Other - ↑ TSH (61%)	E D
	↑ Triglycerides (15%)	E
Musculoskeletal	Fracture (rare)	D L
	Musculoskeletal pain (26%)	E
	Rhabdomyolysis (rare)	E
Neoplastic	Secondary malignancy (adenocarcinoma; rare)	D L
Nervous System	Dizziness (15%)	E
	Dysgeusia (18%)	E
	Headache (38%)	E
	Insomnia (12%)	E
	Posterior reversible encephalopathy syndrome (PRES) (rare)	E
	Seizure (rare)	E
Ophthalmic	Retinal vascular disorder (retinal vein thrombosis; rare)	E
Renal	Creatinine increased (87%) (3% severe)	E
	Proteinuria (34%) (may be severe)	E
Respiratory	Cough, dyspnea (24%)	E
	Dysphonia (31%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for lenvatinib include creatinine increased, hypertension, diarrhea, anorexia, weight loss, hyperglycemia, ↑ LFTs, ↓ albumin, nausea, vomiting, fatigue and mucositis.

Hypertension was commonly reported and may be severe. Median time to onset was 16-35 days. Serious complications, including aortic dissection, have been reported secondary to poorly controlled hypertension.

Cardiac failure was reported in in less than 1% of DTC patients, but decreases in left ventricular ejection fraction (LVEF) were seen in 5% of DTC patients and 10% of RCC patients receiving combination treatment. **Arterial thromboembolic events** were reported as well, including fatal cases.

Severe cases of **artery dissection** (with or without hypertension) and **artery aneurysm** (including

rupture) have been reported in patients using VEGFR TKIs.

QT prolongation has been reported and may lead to severe ventricular arrhythmias, including Torsades de pointes.

Grade 3 or 4 **renal failure** was reported in up to 3% of patients, with the primary risk factor being dehydration secondary to diarrhea or vomiting. HCC Patients with baseline renal impairment had a higher incidence of fatigue, hypothyroidism, dehydration, diarrhea, decreased appetite, proteinuria and hepatic encephalopathy. These patients also had a higher incidence of renal reactions and arterial thromboembolic events.

Proteinuria was common and may be severe. The median time to onset for RCC patients was 6 weeks for any grade and 20 weeks for grades 3 or 4.

Lenvatinib impairs exogenous thyroid suppression and may elevate thyroid stimulating hormone (TSH) levels in both DTC and RCC patients. TSH should be monitored regularly and thyroid medication adjusted as required.

Diarrhea was reported more commonly in RCC patients on combination treatment (81%; 19% grade 3, 4).

Serious **gastrointestinal perforation** or **fistulas** have been reported, mainly in patients with prior surgery or radiotherapy. Reports of non-GI fistulae (e.g. respiratory, genitourinary, cutaneous) have been observed across various indications.

Wound healing complications, including fistula formation and wound dehiscence, may occur.

Severe tumour-related **hemorrhage**, including fatal intracranial hemorrhage in patients with brain metastases has been reported. Epistaxis and hematuria were the most frequently reported hemorrhagic events.

Posterior-reversible encephalopathy syndrome (PRES) has been reported rarely and may be associated with hypertension.

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E - Dosing

Refer to protocol by which the patient is being treated.

Lenvatinib is associated with a moderate emetic potential; antiemetics may be considered to prevent nausea and vomiting.

Blood pressure should be well controlled and electrolyte abnormalities should be corrected prior to starting treatment.

Adequate washout period is required between lenvatinib and other systemic anticancer

treatments (e.g. sorafenib). In DTC and RCC studies, the minimum washout period was 3 weeks. In HCC, washout period from prior locoregional therapies was 4 weeks.

Adults:

DTC patients:

lenvatinib 24 mg PO daily

RCC patients:

lenvatinib 18 mg PO daily in combination with everolimus 5 mg PO daily

HCC patients:

In patients with body weight (BW) of ≥60 kg: lenvatinib 12 mg PO daily

In patients with body weight (BW) of <60 kg: lenvatinib 8 mg PO daily

Dosage with Toxicity:

The dosing and dose modifications described here relate to lenvatinib use only.

Refer to the everolimus drug monograph for dosage modifications for RCC patients. For toxicities related to both lenvatinib and everolimus, reduce the lenvatinib dose first and then the everolimus dose.

Reduced doses should not be increased.

Dose Levels:

Dose level	Lenvatinib DTC / RCC monotherapy dose	Lenvatinib RCC dose when in combination with everolimus	≥60 kg BW Lenvatinib HCC dose (mg daily, unless otherwise stated)	<60 kg BW Lenvatinib HCC dose (mg daily, unless

	(mg daily)	(mg daily)		otherwise stated)
0	24	18	12	8
-1	20	14	8+	4+
-2	14	10	4	4 every other day
-3	10	8	4 every other day	Discontinue
-4	Discontinue			N/A

+ No dose adjustment required for first occurrence of hematologic toxicity or proteinuria

No recommendations are available for resuming lenvatinib in patients with grade 4 adverse reactions that resolve.

Toxicity	Severity	Action
Hypertension	≥ 140/90	Treat with anti-hypertensives
	Grade 3 that persists despite optimal antihypertensive therapy	Hold until recovery to ≤ grade 2; resume at 1 dose level ↓.*
	Grade 4, life-threatening	Discontinue
Cardiotoxicity or hemorrhage	Grade 3	Hold until recovery to ≤ grade 1 or baseline; resume at 1 dose level ↓* or discontinue depending on severity and persistence.
	Grade 4	Discontinue
Nephrotoxicity or hepatotoxicity	Grade 3	Hold until recovery to ≤ grade 1 or baseline; resume at 1 dose level ↓* or discontinue depending on severity and persistence.
	Grade 4	Discontinue
Hepatic failure	Grade 3 or 4	Discontinue
Proteinuria	≥ 2 g proteinuria / 24 h (≥ 2+ on urine dipstick)	Hold until proteinuria < 2 g / 24 h; resume at 1 dose level ↓.*†
	Nephrotic syndrome	Discontinue
Nausea, vomiting, diarrhea**	Persistent and intolerable Grade 2	Hold until recovery to ≤ grade 1 or baseline; resume at 1 dose level ↓.

	or Grade 3	
	Grade 4 despite medical management	Discontinue
QT prolongation	Grade 3 or 4	Hold until recovery to ≤ grade 1 or baseline; resume at 1 dose level ↓.*
PRES	Any	Hold until resolved; resume at 1 dose level ↓* or discontinue depending on the severity and persistence of neurologic symptoms.
Arterial thromboembolism		Discontinue
GI perforation or fistula		
Wound healing complications		
Other treatment-related toxicity	Persistent and intolerable Grade 2 Or Grade 3 Or Grade 4 lab abnormalities considered non-life-threatening	Medically manage. Hold until recovery to ≤ grade 1 or baseline; resume at 1 dose level ↓.*†
	Grade 4 (except lab abnormalities considered non-life-threatening)	Discontinue
Major surgery		Hold at least 6 days prior to scheduled surgery, resume after adequate wound healing.

*For each occurrence of toxicity, reduce dose in succession based on the previous dose level (see dose levels table).

**Initiate prompt medical management in order to reduce the risk of development of renal impairment or failure.

†For patients with HCC and hematologic toxicity or proteinuria, may restart when recovery to ≤ Grade 2.

Dosage with Hepatic Impairment:

Lenvatinib exposure increases in severe hepatic impairment.

Childs classification of hepatic impairment	Starting dose DTC / RCC monotherapy (mg daily)	Starting dose RCC when in combination with everolimus (mg daily)	Starting Dose HCC (≥60 kg BW) (mg daily)	Starting Dose HCC (<60 kg BW) (mg daily)
A	24	18	12	8
B	24	18	No data	
C	14	10	No data: not recommended for use	

Dosage with Renal Impairment:

Lenvatinib exposure increases with severe renal impairment.

Creatinine clearance (ml/min)	Starting dose DTC / RCC monotherapy (mg daily)	Starting dose RCC when in combination with everolimus (mg daily)	Starting Dose HCC (≥60 kg BW) (mg daily)	Starting Dose HCC (<60 kg BW) (mg daily)
50-80	24	18	12	8
30-49	24	18	12	8
< 30	14	10	No data	
End stage renal failure	No data: not recommended for use			

Dosage in the elderly:

No dosage adjustment is recommended. Use with caution and monitor patients closely.

In the DTC study, patients aged 75 and older had a higher incidence of toxicity, including severe and fatal adverse events, compared to younger patients, leading to treatment discontinuation (21% vs 14%). Patients 75 years or older were more likely to experience grade 3-4 hypertension, proteinuria, decreased appetite, and dehydration compared to patients < 65 years old.

In the RCC, study patients aged 65 and older had a higher incidence of cough, dyspnea,

lethargy, nausea, peripheral swelling and vomiting compared to younger patients.

In the HCC study, patients ≥75 years appeared to have lower tolerability and were more likely to experience hypertension, proteinuria, decreased appetite, asthenia, dehydration, dizziness and hepatic encephalopathy. Arterial thromboembolic events also occurred at an increased incidence in this age group.

Body weight

In patients with DTC and RCC, no adjustment of starting dose is required based on body weight. In the DTC study, patients with body weight <60 kg had a higher incidence of hand-foot syndrome, proteinuria, severe electrolyte abnormalities and a trend towards severe anorexia.

Lenvatinib PK was affected by body weight in patients with HCC. Refer to the dosing section for starting doses.

Dosage based on gender:

No adjustment of starting dose is required based on gender.

In the DTC study, females had a higher incidence of hypertension (including severe hypertension), proteinuria and hand-foot syndrome, while males had a higher incidence of cardiotoxicity, GI perforation and fistulas.

In the RCC study, females had a higher incidence of hepatotoxicity, while males had a higher incidence of hemorrhage, nephrotoxicity, proteinuria and hand-foot syndrome.

In HCC patients, females had a higher incidence of hypertension, fatigue and ECG QT prolongation. Hepatic failure events were observed in male patients only.

Dosage based on ethnicity:

No adjustment of starting dose is required based on race.

In the DTC study, Asian patients had a higher incidence of peripheral edema, hypertension, fatigue, hand-foot syndrome, proteinuria, thrombocytopenia and elevated TSH levels compared to Caucasian patients.

In HCC patients, Asian patients had a higher incidence of proteinuria and hand-foot syndrome compared to Caucasian patients, while Caucasian patients had a higher incidence of fatigue, hepatic encephalopathy and acute kidney injury, anxiety, asthenia, thrombocytopenia, and vomiting.

Children:

Safety and efficacy have not been established in pediatric patients. Animal studies suggest the potential for impaired bone growth in children. Lenvatinib should not be used in children younger than 2 years of age.

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F - Administration Guidelines

- Lenvatinib should be taken at the same time daily, with or without food.
- Capsules should be swallowed whole with water.
- If the patient has difficulty swallowing, capsule(s) may be added (without breaking or crushing) to a tablespoon of water or apple juice in a small glass. Capsule(s) should be left in the liquid for at least 10 minutes and stirred for at least 3 minutes to allow the capsule shell(s) to dissolve. The entire suspension should then be swallowed. After drinking, the glass should be filled with the same amount of water or apple juice, swirled a few times, then additional liquid should be swallowed.
- If a dose is missed and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time.
- Lenvatinib should be stored between 15-30^{o}C.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or to any ingredient in the formulation or component of the container.

Other Warnings/Precautions:

- The degree of tumour invasion of major blood vessels should be considered prior to treatment given the potential risk of hemorrhage associated with tumour shrinkage.

- Lenvatinib is not recommended in patients with congenital long QT syndrome or those who are taking medications known to prolong the QT interval.
- Use with caution in patients at risk of prolonged QT, including females, aged ≥ 65 years, family history of sudden cardiac death at < 50 years of age, pre-existing cardiac disease, history of arrhythmias, electrolyte disturbances or conditions leading to electrolyte disturbances, bradycardia, acute neurological events, diabetes mellitus and autonomic neuropathy.
- Use lenvatinib with caution in patients who are at risk for, or have a history of cardiac events or arterial thromboembolism. The drug has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.
- Patients with prior surgery or radiotherapy are at increased risk of GI perforation or fistulas.

Other Drug Properties:

- Carcinogenicity: Unknown
  Carcinogenicity studies have not been conducted.

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Teratogenicity: Yes
  Lenvatinib is not recommended for use in pregnancy as it's likely to cause fetal harm. Highly effective contraception (including barrier method) should be used by both sexes during treatment, and for at least **1 month** after the last dose.
- Excretion into breast milk: Likely
  Observed in animal studies.
  Breastfeeding is not recommended.
- Fertility effects: Likely
  Animal studies suggest decreased male and female fertility.

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H - Interactions

Lenvatinib is extensively metabolized by CYP3A4. In vitro studies indicate that lenvatinib inhibits CYP 2C8, 1A2, 2B6, 2C9, 2C19, 2D6 and 3A4. Lenvatinib inhibited UGT1A1 and UGT1A4 as well as OAT1, OAT3, OCT1, OCT2, OATP1B1 and BSEP. It is not considered a strong inducer or inhibitor P450 or UGT enzymes.

Lenvatinib may be co-administered with CYP3A4 inhibitors and inducers, PGP inducers and inhibitors, BRCP inhibitors and drugs that effect gastric pH without dosage adjustment.

AGENT	EFFECT	MECHANISM	MANAGEMENT

Use of lenvatinib immediately following sorafenib or other anticancer drugs	Potential for additive toxicities	Additive	For DTC and RCC, use a minimum washout period of 3 weeks. For HCC, use a minimum washout period of 4 weeks after locoregional therapies
Drugs decrease heart rate and/or prolong PR interval (e.g. antiarrhythmics, beta blockers, non-dihydropyridine Ca channel blockers, digoxin, some HIV protease inhibitors, sphingosine-1 phosphate receptor modulators)	Decreased heart rate, prolonged PR interval	Additive	Avoid if possible; monitor closely if used together
Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	Prolonged QT, Torsades de pointes	Additive	Avoid if possible; monitor closely if used together
CYP3A4 substrates (e.g. cyclosporine, pimozide, tacrolimus, triazolo-	Reduced efficacy of substrate	Lenvatinib may induce CYP3A4	Use with caution with substrates that have a narrow therapeutic index

benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)			
P-glycoprotein substrates (i.e. verapamil, digoxin, morphine, ondansetron)	Reduced efficacy of substrate	Lenvatinib may induce PgP	Use with caution with substrates that have a narrow therapeutic index
Drugs that disrupt electrolyte levels (i.e. loop/thiazide diuretics, laxatives, amphotericin B, high dose corticosteroids)	Increased risk of arrhythmias	Additive	Avoid if possible; monitor closely if used together

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Blood pressure	Baseline, after 1 week, then every 2 weeks for the first 2 months, monthly thereafter while on treatment
CBC	Baseline and at each visit
ECG	Baseline and as clinically indicated
Liver function tests	Baseline, every 2 weeks for the first 2 months, then monthly during treatment
Renal function tests	Baseline and at each visit

Urine protein	Baseline and at each visit
TSH levels	Baseline and monthly during treatment
Serum calcium and electrolytes	Baseline, at least monthly and as clinically indicated
Clinical toxicity assessment for GI effects, infection, wound healing complications, bleeding, hypertension, thromboembolism, cardiac and neurologic effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- lenvatinib - For the treatment of patients with locally recurrent or metastatic, progressive, radioactive-iodine-refractory differentiated thyroid cancer (DTC) according to criteria
- lenvatinib - For the treatment of unresectable advanced hepatocellular carcinoma according to clinical criteria
- lenvatinib - In Combination with Pembrolizumab for First-Line Advanced or Metastatic Renal Cell Carcinoma
- lenvatinib - In Combination with Pembrolizumab for Advanced Endometrial Cancer

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K - References

Lenvatinib product monograph, Eisai Limited. December 19, 2018

Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015 Feb 12;372(7):621-30.

Scott LJ. Lenvatinib: first global approval. Drugs 2015;75:553-560

Product Monograph Update: Vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs). Health Canada InfoWatch, June 2020.

September 2023 Updated elimination section

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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