DRUG NAME: Lenvatinib

SYNONYM(S): E7080[1], ER 20349200[2], lenvatinib mesylate[2]

COMMON TRADE NAME(S): LENVIMA®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Lenvatinib is an oral small molecule, multikinase inhibitor of vascular endothelial-derived growth factor receptors (VEGFR), fibroblast growth factor receptors (FGFR), platelet derived growth factor receptor-α (PDGFRα), KIT, and RETwhich are known to play a role in pathogenic angiogenesis, tumour growth and cancer progression. Lenvatinib's broad spectrum of antitumour activity and potent inhibition of FGFR1 differentiates it from other multikinase inhibitors with antiangiogenic properties.[2,3]

PHARMACOKINETICS:

Oral Absorption	T_{max} = 1-4 hours; food slows the rate, but not the extent, of absorption[4,5]	
Distribution	highly plasma protein bound to albumin; minor binding to α1-acid glycoprotein and ϒ-globulin	
	cross blood brain barrier?	no information found
	volume of distribution	43-121 L
	plasma protein binding[2]	98-99%
Metabolism	major metabolism by cytochrome P450 3A4; minor metabolism by aldehyde oxidase and non-enzymatic processes[2,5,6]	
	active metabolite(s)	yes (degree of relative activity unknown)
	inactive metabolite(s)	yes
Excretion	plasma concentrations decline bi-exponentially following C_{max}	
	urine[2]	64%
	feces[2]	25%
	terminal half life[2]	28 hours

Adapted from standard reference[5] unless specified otherwise.

USES:

Primary uses:

*Endometrial cancer
*Liver cancer
*Renal cell cancer
*Thyroid cancer

*Health Canada approved indication

Other uses:

Developed: 1 October 2017
Revised: 1 August 2020

SPECIAL PRECAUTIONS:

Caution:
- ***hypertension*** should be controlled prior to starting treatment[5]
- ***impaired wound healing*** is associated with VEGF inhibitors; consider holding lenvatinib before surgery and resume after surgical wounds are fully healed[5]
- ***QTc prolongation*** is reported; caution in patients with a history of or predisposition to QTc prolongation or who are taking concurrent medications known to prolong QTc interval[5]
- ***bradycardia*** and/or ***prolonged PR interval*** is reported; caution in patients who are taking other medications that decrease the heart rate or prolong the PR interval[7]
- risk of ***GI perforation*** or ***fistula*** is increased in patients with prior surgery or radiotherapy[5]
- lenvatinib impairs ***exogenous thyroid suppression***, including in patients with normal TSH at baseline; monitor TSH starting prior to treatment and initiate or adjust thyroid replacement therapy as required[8]

Special populations:
- patients 75 years or older are more likely to experience grade 3 or 4 hypertension, proteinuria, decreased appetite, dehydration, and fatal adverse events[5]
- patients with body weight below 60 kg or with comorbidities such as hypertension, hepatic, or renal impairment may have a reduced tolerability to lenvatinib[5]
- Asian patients may experience a higher incidence of adverse effects compared with Caucasian patients.[5]
- safety in children is not known; in animal studies, growth retardation, secondary delay of physical development, and reproductive organ immaturity was observed[5,9]

Carcinogenicity: no information found.

Mutagenicity: Not mutagenic in Ames test and in mammalian *in vitro* mutation test. Lenvatinib is not clastogenic in mammalian *in vivo* chromosome tests.[5]

Fertility: In animal toxicology studies, decreased menstruation and other non-specified ovarian and testicular changes were reported, sometimes at exposures below the anticipated clinical exposure in humans.[5,10]

Pregnancy: In animal studies, lenvatinib caused embryolethality and significant embryo and fetal toxicity at doses below the recommended clinical dose. Fetal external, visceral, and skeletal anomalies were observed.
Male patients should use effective contraception during treatment and females of reproductive potential should use effective contraception during treatment and for at least one month following completion of therapy.[5]

Breastfeeding is not recommended due to the potential secretion into breast milk.[5]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[11,12] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.[1]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	lymphopenia (7%, severe 1%)
	thrombocytopenia (14%, severe 2%)

Developed: 1 October 2017
Revised: 1 August 2020

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
cardiac	***arterial thromboembolic event*** (5%, severe 3%)[1,5]; includes cerebrovascular accident, transient ischemic attack, and myocardial infarction; requires treatment discontinuation
	cardiac failure (<1%); see paragraph following **Side Effects** table
endocrine	hypothyroidism (5%); may require thyroid replacement therapy[8]
	TSH increase (61%)
gastrointestinal	*emetogenic potential:* low-moderate[13]
	abdominal pain (32%, severe 2%)
	constipation (29%, severe <1%)
	diarrhea (67%, severe 9%); see paragraph following **Side Effects** table
	dry mouth (17%, severe <1%)
	dyspepsia (13%, severe <1%)
	flatulence (6%)
	gastrointestinal fistula (2%, severe <1%)[1]
	gastrointestinal perforation (<1%); requires treatment discontinuation
	nausea (47%, severe 2%)
	oropharyngeal pain (25%, severe 1%)
	stomatitis (41%, severe 5%)
	vomiting (36%, severe 2%); see paragraph following **Side Effects** table
general disorders and administration site conditions	asthenia (25%, severe 6%)
	fatigue (43%, severe 5%)
	malaise (5%)
	peripheral edema (21%, severe <1%)
hepatobiliary	***hepatic failure*** (severe <1%)[1,5]; see paragraph following **Side Effects** table
infections and infestations	pneumonia (severe 4%)
	urinary tract infection (12%, severe 1%)
investigations (see paragraph following **Side Effects** table)	ALT increase (severe 4%)
	AST increase (severe 5%)
	left ventricular ejection fraction decrease (5%)
	QT interval prolongation (8-9%, severe 2%)[1,5]
	weight loss (51%, severe 13%)
metabolism and nutrition	***anorexia*** (54%, severe 7%)
	dehydration (9%, severe 2%)
	hypoalbuminemia (10%)
	hypocalcemia (13%, severe 5%); may require supplementation[8]

Developed: 1 October 2017
Revised: 1 August 2020

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hypokalemia (14%, severe 3%)
	hypomagnesemia (severe <1%)
musculoskeletal and connective tissue	arthralgia (26%)
	back pain (18%, severe 2%)
	myalgia (19%, severe 2%)
	pain in extremity (15%, severe 1%)
nervous system	dizziness (15%)
	dysgeusia (18%)
	headache (38%, severe 3%)
	posterior reversible encephalopathy syndrome (<1%, severe 0%)[1]; dose interruption, adjustment, or discontinuation may be necessary
psychiatric	insomnia (12%)
renal and urinary (see paragraph following **Side Effects** table)	***proteinuria*** (34%, severe 11%)
	renal impairment, including acute renal failure (4-14%, severe 2-3%)[1,5]
respiratory, thoracic and mediastinal	cough (24%)
	dysphonia (32%, severe 1%)
	epistaxis (12%); see paragraph following **Side Effects** table
skin and subcutaneous tissue	alopecia (12%)
	palmar-plantar erythrodysesthesia syndrome (32%, severe 3%)
	rash (19%)
vascular	***hemorrhage*** (35%, severe 2%); includes serious tumour related bleeds and fatal intracranial hemorrhagic events in patients with brain metastases; see paragraph following **Side Effects** table
	hypertension (73%, severe 44%), see paragraph following **Side Effects** table
	hypotension (9%, severe 2%)
	venous thromboembolic events, including pulmonary embolism (2-5%, severe 4%)[1,5]

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Cardiac dysfunction has been reported, including decreased left or right ventricular function, cardiac failure, and/or pulmonary edema. Decreased ejection fraction is the most commonly reported of these events, in some cases with greater than 20% reduction in ejection fraction. Monitor patients for clinical symptoms of cardiac decompensation such as fatigue, shortness of breath, peripheral edema, and cyanosis as dose interruption, adjustment, or discontinuation of therapy may be necessary.[5,9]

Hypertension is commonly reported. Median time to onset is 16 days. Blood pressure should be controlled prior to starting lenvatinib and monitored frequently (e.g., up to every two weeks) for the first few months of therapy, with regular monitoring thereafter. Hypertension may be treated with a combination of standard antihypertensive therapy and lenvatinib dose interruption or reduction. Permanently discontinue lenvatinib for life-threatening hypertension or severe hypertension which persists despite optimal antihypertensive therapy.[5]

Developed: 1 October 2017
Revised: 1 August 2020

QTc prolongation has been reported and may increase the risk of ventricular arrhythmias, including torsades de pointes. Because lenvatinib can cause hypocalcemia, hypokalemia, and hypomagnesemia, which are known risk factors for the development of torsades de pointes, electrolyte disturbances should be corrected in all patients. Temporary dose interruption and electrolyte replacement therapy may be necessary. Obtain electrocardiograms at baseline and as needed during treatment in patients at risk for QT prolongation (e.g., congenital long QT syndrome, history of cardiac disease, or receiving concurrent therapy with QT/QTc interval-prolonging drugs). Patients should report any new chest pain, palpitations, dizziness, and/or fainting.[5,10,14]

Hemorrhagic events occur in over one-third of patients, with epistaxis being the most commonly reported hemorrhagic event. Serious tumour-related bleeding events and fatal cases have also been reported. Before initiating lenvatinib therapy, consider the degree of tumour invasion of major blood vessels as there is a risk of severe hemorrhage associated with tumour shrinkage. Any hemorrhage which requires medical intervention may also require either a temporary interruption in lenvatinib treatment, dose modification, or permanent discontinuation of lenvatinib, depending on the severity of the hemorrhage.[5,14,15]

Hepatotoxicity, including grade 3 transaminase elevations, acute hepatitis, and hepatic failure has occurred with lenvatinib. Patients with pre-existing hepatic impairment may experience an increased incidence of adverse reactions. Liver function tests should be monitored frequently for the first few months of therapy, with regular monitoring thereafter. Treatment interruption or dose reduction may be required for hepatotoxicity. Permanently discontinue lenvatinib if hepatic failure occurs.[5]

Proteinuria can occur while on anti-VEGF therapy. Dipstick urinalysis is recommended for monitoring throughout treatment. If proteinuria is detected, dose interruption, adjustment, or discontinuation may be necessary. Discontinue lenvantinib for nephrotic syndrome.[5]

Renal impairment and renal failure are reported. Untreated vomiting and diarrhea are considered the primary risk factors for renal impairment during treatment as these may lead to dehydration and hypovolemia. To reduce the risk of lenvatinib-induced renal impairment, promptly initiate active management of grade 1 diarrhea, vomiting, or other gastrointestinal symptoms with standard anti-diarrheal therapy, anti-emetics, and oral hydration. Intolerable grade 2 (or greater) diarrhea/vomiting may require temporary interruption of lenvatinib, dose reduction, or discontinuation of treatment depending on the reaction. If grade 3 or 4 renal failure/impairment occurs, withhold lenvatinib until it resolves and consider either resuming treatment at a reduced dose or discontinuing treatment depending on the severity and persistence of renal impairment.[5,10]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
ketoconazole[5]	minimal effects on lenvatinib exposure *in vivo*	inhibition of CYP3A4 by ketoconazole	no dose adjustment necessary
rifampin[5]	minimal effects on lenvatinib exposure *in vivo*	induction of CYP3A4 by rifampin	no dose adjustment necessary
proton pump inhibitors, H2 blockers, antacids[5,16]	no influence on lenvatinib pharmacokinetics	agents that increase gastric pH	no dose adjustment necessary

Concurrent therapy with drugs that prolong QT/QTc interval or disrupt electrolyte levels should be avoided if possible; periodic monitoring of ECG and electrolytes is suggested.[15]

SUPPLY AND STORAGE:

Oral: Eisai Limited supplies lenvatinib as 4 mg and 10 mg hard hypromellose capsules. Store at room temperature.[5]

Additional information: Lenvatinib capsules are packaged in blister cards in a dose-specific compliance configuration. Blister cards contain a five day supply of lenvatinib in daily dose configurations of 4 mg, 8 mg, 10 mg,

Developed: 1 October 2017
Revised: 1 August 2020

12 mg, 14 mg, 18 mg, 20 mg, or 24 mg. Each carton contains six blister cards for a 30 day supply. Store in original packaging.[8]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Oral[8,17,18]:	Cycle Length: ***24 mg*** (range 10-24 mg) ***PO once daily*** Administer with food or on an empty stomach. ***8-12 mg*** (range 4-12 mg) ***PO once daily*** or once every other day Administer with food or on an empty stomach.
Concurrent radiation:	no information found
Dosage in renal failure[8,17]:	recommended starting dose adjustments are based on indication mild/moderate renal impairment: no adjustment required severe renal impairment (CrCl <30 mL/min): refer to protocol by which patient is being treated end-stage renal disease: no information found
Dosage in hepatic failure[8,17]:	recommended starting dose adjustments are based on indication mild/moderate hepatic impairment: no adjustment required severe hepatic impairment (Child-Pugh C): refer to protocol by which patient is being treated
Dosage in dialysis:	not expected to be dialyzable[14]
***Children*:**	not indicated for use in children[5]

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Revised: 1 August 2020

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Developed: 1 October 2017
Revised: 1 August 2020