

DRUG NAME: Ceritinib

SYNONYM(S): LDK378¹

COMMON TRADE NAME(S): ZYKADIA®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Ceritinib is a second-generation, orally active, selective inhibitor of anaplastic lymphoma kinase (ALK). Ceritinib blocks autophosphorylation of ALK, which inhibits downstream signaling proteins and prevents proliferation of ALK-dependent cancer cells. Ceritinib also inhibits insulin-like growth factor 1 receptor, insulin receptor, and ROS1. Ceritinib is twenty times more potent at inhibiting ALK than crizotinib and has better brain penetration, plus retains activity against several crizotinib resistance mutations.¹⁻³

PHARMACOKINETICS:

Oral Absorption	time to peak: 4-6 hours; bioavailability increases with food (AUC increased 58% and C _{max} 43%), particularly with high-fat meals (AUC increased 73% and C _{max} 41%)	
Distribution	slight preferential distribution to red blood cells relative to plasma	
	cross blood brain barrier?	yes; in animals, brain-to-blood exposure ratio ~15%
	volume of distribution	4230 L
	plasma protein binding	97%; independent of drug concentration
Metabolism	primarily hepatic, via CYP3A enzyme	
	active metabolite(s)	no information found
	inactive metabolite(s)	11 identified; low circulating plasma levels
Excretion	mean apparent clearance lower at steady state	
	urine	1.3%
	feces	92% (68% as unchanged drug)
	terminal half life	41 hours
	clearance	33.2-88.5 L/h

Adapted from standard reference² unless specified otherwise.

USES:

Primary uses:

*Lung cancer, non-small cell

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:

- **bradycardia** is reported; use with caution in patients with baseline heart rate less than 60 beats/minute or having a history of syncope, other rhythm disorders, ischemic heart disease, or congestive heart failure, as well as patients taking other medications which decrease heart rate²
- **QT interval prolongation** has been reported; avoid in congenital long QT syndrome and use caution in patients with a history of, or predisposition to, QT prolongation or taking other medications that prolong the QT interval or disrupt electrolyte levels²
- **hyperglycemia** is reported; assess glucose tolerance prior to ceritinib therapy and initiate or optimize antihyperglycemic medication²

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test. Ceritinib is aneugenic in mammalian *in vitro* chromosome tests, but is not clastogenic in other mammalian *in vivo* chromosome tests.²

Fertility: no information found

Pregnancy: In animal studies, skeletal anomalies were observed during organogenesis and embryolethality was observed at doses equivalent to the human dose. Females of child-bearing potential and males should use effective contraception during treatment and for three months following completion of therapy.²

Breastfeeding is not recommended during and for two weeks following completion of therapy due to the potential secretion into breast milk.^{2,4}

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.⁵

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
blood and lymphatic system/ febrile neutropenia	anemia (9%, severe 4%)
	leukopenia (47%, severe 2%)
	lymphocytopenia (73%, severe 28%)
	neutropenia (27%, severe 2%)
cardiac	bradycardia (3%); see paragraph following Side Effects table
	pericardial effusion (severe 2%)
	pericarditis (severe 2%)
eye	vision disorders , including blurred vision, vision impairment, floaters, flashing lights (9%)
gastrointestinal (see paragraph following Side Effects table)	emetogenic potential: high-moderate ⁶
	abdominal pain (54%, severe 2%)
	constipation (29%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i>	
	<i>diarrhea</i> (86%, severe 1-6%)
	dyspepsia, gastroesophageal reflux disease, dysphagia (16%, severe 1%)
	<i>nausea</i> (80%, severe 2-4%)
	<i>pancreatitis</i> (<1%); has been fatal
	<i>vomiting</i> (60%, severe 4%)
general disorders and administration site conditions	<i>fatigue, asthenia</i> (52%, severe 5%)
	pyrexia (15%, severe 1%) ^{2,7}
	non-cardiac chest pain (severe 1%)
hepatobiliary	hepatotoxicity, drug induced liver injury (<1%); see paragraph following Side Effects table
infections	pneumonia (severe 4%)
investigations (see paragraph following Side Effects table)	<i>ALT increase</i> (43%, severe 27%)
	amylase increase (28%, severe 6%)
	<i>AST increase</i> (31%, severe 8%)
	bilirubin increase (3%, severe <1%)
	creatinine increase (15%)
	lipase increase (8%, severe 5%)
	<i>QT interval prolongation</i> (4%, severe 1%)
	uric acid increase (47%, severe 8%)
metabolism and nutrition	appetite decrease (34%, severe 1%)
	dehydration (severe 2%)
	hyperglycemia (8-12%, severe 2-6%); see paragraph following Side Effects table
	hypophosphatemia (6%, severe 3%)
nervous system	convulsions (7%, severe 4%) ^{2,7}
	headache (21%, severe 1-2%) ^{2,7}
	<i>neuropathy</i> ; including both sensory and motor (17%, severe <1%)
renal and urinary	renal impairment (2%, severe <1%)
	renal failure (2%, severe <1%)
respiratory, thoracic and mediastinal	dyspnea (26%, severe 3-5%) ^{2,7}
	<i>interstitial lung disease/pneumonitis</i> (4%, severe 3%); see paragraph following Side Effects table
	pneumothorax (severe 2%)
	respiratory failure (severe 2%)
skin and subcutaneous tissue	rash (16%); includes maculopapular rash, dermatitis acneiform

Adapted from standard reference² unless specified otherwise.

Bradycardia has occurred during treatment with ceritinib. Monitor heart rate and blood pressure regularly and if possible, avoid or discontinue concurrent medications known to cause bradycardia. For symptomatic bradycardia, withhold ceritinib until asymptomatic or heart rate increases to greater than 60 beats/minute. Consider ceritinib dose reduction when treatment resumes. Ceritinib should be permanently discontinued for life-threatening bradycardia that occurs in the absence of other concurrent medications which cause bradycardia.²

Gastrointestinal toxicity occurs in 98% of patients and may be reported as nausea, diarrhea, abdominal pain, or vomiting. Symptoms occur early in treatment, with a median time to onset of 4-8 days. Symptoms are managed with anti-diarrheal agents, anti-nauseants, and fluid replacement as required. If symptoms are severe or persistent despite supportive treatment, hold ceritinib until symptoms improve. If ceritinib is to be restarted, consider dose reduction.^{2,8}

Patients with diabetes or taking corticosteroids have an increased risk of grade 3 or 4 **hyperglycemia**. Temporary treatment interruption is recommended for persistently high blood glucose levels (e.g., greater than 13.9 mmol/L) despite optimal anti-hyperglycemic therapy. Ceritinib dose reduction is recommended if treatment resumes. Ceritinib may need to be discontinued permanently in patients who cannot achieve adequate glucose control.^{2,8}

Severe, life-threatening, or fatal **interstitial lung disease (ILD)/pneumonitis** have been reported. Monitor for symptoms indicative of pneumonitis such as dyspnea, shortness of breath, cough, or chest pain, with or without accompanying fever. Hold ceritinib until other potential causes are excluded and permanently discontinue ceritinib if any grade, treatment-related ILD/pneumonitis is diagnosed. Most cases of ILD/pneumonitis improve or resolve with treatment discontinuation.^{2,8}

Concentration-dependent **QT interval prolongation** has occurred. Monitor electrolytes and ECGs regularly during treatment. Ceritinib is not recommended in patients with congenital long QT syndrome, uncorrected electrolyte abnormalities, or taking other QT prolonging medications. Withhold ceritinib if QTc interval exceeds 500 milliseconds and dose reduce when therapy is resumed. Permanently discontinue ceritinib in patients who experience torsades de pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia.^{2,9}

Pancreatitis is rare, but sometimes fatal. Withhold ceritinib for lipase or amylase elevation greater than two times upper limit of normal. Ceritinib may be resumed at a lower dose when lipase or amylase returns to less than 1.5 times the upper limit of normal. Monitor for signs and symptoms of pancreatitis and if suspected, withhold ceritinib and initiate appropriate management.²

Transaminase elevations have been reported, however the majority of cases are manageable and reversible with treatment interruption and/or dose reduction. Monitor transaminases and bilirubin regularly, with more frequent testing following transaminase elevations. Ceritinib should be permanently discontinued for ALT/AST elevation greater than 3 times ULN with concurrent total bilirubin elevation greater than 2 times ULN (in the absence of cholestasis or hemolysis).^{2,3,10}

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
esomeprazole ^{11,12}	ceritinib AUC and C _{max} decreased by 76% and 79% following single dose coadministration; however, at steady-state, the effect on ceritinib exposure is considered modest and not clinically meaningful (AUC and C _{max} decreased by 30% and 25%)	pH dependent solubility of ceritinib (reduced solubility of ceritinib with increasing pH)	clinical significance is unclear ¹¹⁻¹⁴ ; no change is recommended for administration with PPIs ¹¹ ; however, it is recommended to space the administration of H ₂ blockers (10 h before or 2 h after ceritinib) and antacids (2 h before or 2 h after ceritinib) ¹²

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit juice ^{2,15}	may increase plasma level of ceritinib	may inhibit CYP 3A4 metabolism of ceritinib in the intestinal wall	avoid grapefruit and grapefruit juice for duration of treatment with ceritinib
ketoconazole ^{2,4}	ceritinib AUC increased 2.9 fold and C _{max} increased 1.2 fold	strong inhibition of CYP3A by ketoconazole	avoid concurrent therapy; if unavoidable, consider reducing ceritinib dose by one-third (rounding dose to the nearest 150 mg)
rifampin ²	ceritinib AUC decreased 70% and C _{max} decreased 44%	strong induction of CYP3A by rifampin	avoid concurrent therapy

Ceritinib is a substrate of CYP3A. Moderate CYP3A inhibitors may increase ceritinib exposure; monitor for toxicity related to increased ceritinib exposure.²

Drugs that prolong QT/QTc interval or disrupt electrolyte levels should be avoided if possible during ceritinib therapy due to the risk of potentially fatal arrhythmias. Periodic monitoring of ECG and electrolytes is suggested.²

Ceritinib is a substrate of P-glycoprotein (P-gp) *in vitro*.² Clinical significance is unknown.

Ceritinib inhibits CYP3A and 2C9 metabolism *in vitro* and may increase plasma concentrations of drugs predominantly metabolized by these enzymes. Clinical significance is unknown. Monitor for side effects of CYP3A and CYP2C9 substrates.²

SUPPLY AND STORAGE:

Oral: Novartis Pharmaceuticals Canada Inc. supplies ceritinib as 150 mg hard gelatin capsules. Store at room temperature.²

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

Oral: **450 mg** (range 150-450 mg) **PO once daily**^{12,16,17} *BC Cancer usual dose noted in bold, italics*

Administer **with food** at the same time each day. Food can range from a snack to a full meal.¹²

Do not take with grapefruit or grapefruit juice.¹²

* **Food effect:** Food increases systemic exposure of ceritinib. There is no clinically significant difference between administering ceritinib 750 mg daily in a fasting state and the **recommended dosing regimen** of 450 mg daily with food.¹²

Concurrent radiation: no information found

	BC Cancer usual dose noted in <i>bold, italics</i>
<i>Dosage in renal failure:</i>	mild/moderate impairment: no adjustment required ² severe renal impairment (CrCl <30 mL/min): no information found
<i>Dosage in hepatic failure:</i>	mild impairment: no adjustment required ² moderate/severe impairment: no information found
<i>Dosage in dialysis:</i>	no information found
<u>Children:</u>	no information found

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