Drug Monograph

A - Drug Name

ceritinib

COMMON TRADE NAME(S): Zykadia™

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B - Mechanism of Action and Pharmacokinetics

Ceritinib is an anaplastic lymphoma kinase (ALK) inhibitor. It inhibits autophosphorylation of ALK and ALK-mediated phosphorylation of downstream cell signaling and proliferation of ALK-dependent cancer cells. It also inhibits insulin-like growth factor 1 receptor (IGF-IR), insulin receptor (INSR), and ROS1.

Absorption	Bioavailability	Not determined. AUC and C_{max} increased dose proportionally over 50 to 750 mg (fasted).
	Peak plasma levels	C_{max}: 4 to 6 hours (fasted).
	Effects with food	750 mg dosing: Exposure increased with a high-fat meal (AUC 58%). No clinically significant difference observed in steady state exposure between 450 mg dosing with food vs 750 mg fasted dosing.
Distribution	Slight preferential distribution to RBCs relative to plasma.	
	PPB	97%
	Cross blood brain barrier?	Yes (animals)

Metabolism	Inactive metabolites	Yes
Elimination	Feces	91%; 68% as unchanged drug
	Urine	1.3%
	Half-life	Terminal: 41 hours

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C - Indications and Status

Health Canada Approvals:

- Non-small cell lung cancer (NSCLC).

(Includes conditional approvals)
Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Moderate – Consider prophylaxis daily

The following related adverse effects were reported in ≥ 1% of patients receiving ceritinib in the open-label Phase III study in previously untreated ALK-positive locally advanced or metastatic NSCLC (750 mg daily, fasting). Severe adverse effects from other studies or post-marketing are also included. The overall safety profile of ceritinib at the recommended dose of 450 mg with food was consistent with ceritinib 750 mg fasted, except for a reduction in gastrointestinal adverse drug reactions.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Atrial fibrillation (maybe severe)	E
	Bradycardia (3%)	E
	Pericarditis (4%)	E
	QT interval prolonged (11%) (maybe severe)	E

	Venous thromboembolism (1%)	E
Dermatological	Rash (20%)	E
Gastrointestinal	Abdominal pain (40%) (4% severe)	E
	Anorexia, weight loss (34%)	E
	Constipation (19%)	E
	Diarrhea (85%) (5% severe)	E
	Nausea, vomiting (69%) (5% severe)	E
General	Fatigue (44%) (7% severe)	E
Hematological	Anemia (15%)	E
Hepatobiliary	↑ Amylase / lipase (10%) (pancreatitis rare)	E
	↑ LFTs (69%) (50% severe)	E
Metabolic / Endocrine	Hyperglycemia (11%) (6% severe)	E
	↓ PO4 (4%)	E
Musculoskeletal	Musculoskeletal pain (19%)	E
Ophthalmic	Visual disorders (4%)	E
Renal	Creatinine increased (22%) (2% severe)	E
Respiratory	Pneumonitis (2%)	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 ceritinib include diarrhea, ↑ LFTs, nausea, vomiting, fatigue, abdominal pain, anorexia, weight loss, creatinine increased, rash, constipation and musculoskeletal pain.

Ceritinib produces concentration-dependent **increases in QTc** that may cause serious ventricular arrhythmias, including Torsades de Pointes. Symptomatic bradycardia has been reported; heart rate of < 50 beats/minute has occurred.

As compared to the 750 mg daily (fasted) dosing, the incidence and severity of **GI toxicity** appeared to be lower in a clinical study that used ceritinib 450 mg daily with food (e.g. diarrhea 76% vs 56%; nausea 50% vs 45%, vomiting 56% vs 35%; severe 12% vs 1%).

Although rare, **pancreatitis** (with fatality) has been reported.

Hyperglycemia has been reported and may be severe. Risk is higher in patients with diabetes and/or concurrent steroid use.

Severe **interstitial lung disease (ILD)/pneumonitis** including grade 3 or 4 events and fatalities has been reported.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Electrolyte abnormalities (hypokalemia, hypomagnesemia, and hypocalcemia) should be corrected prior to starting treatment.

Patients must have documented ALK-positive status based on a validated ALK assay.

Adults:

450 mg Orally Daily with food

Dosage with Toxicity:

Dose level	Ceritinib dose (mg/day)
0	450
-1	300
-2	150
-3	Discontinue

Toxicity	Severity	Ceritinib Dose
Nausea, vomiting or diarrhea	Grade 3 or intolerable, despite optimal antiemetic and antidiarrheal therapy.	Hold until improved, restart at ↓ 1 dose level.
Hyperglycemia (> 250 mg/dL or 14 mmol/L)	Persistent hyperglycemia despite optimal anti-hyperglycemic therapy.	Hold until controlled, restart at ↓ 1 dose level. Discontinue if adequate control cannot be achieved with optimal medical management.
Bradycardia (HR < 60 bpm)	Symptomatic, non-life-threatening	Hold until asymptomatic or heart rate ≥ 60 bpm. If medication(s) contributing to bradycardia/hypotension is discontinued or dose adjusted, restart ceritinib at same dose. If no contributing medication(s) is identified or cannot be discontinued/dose adjusted, restart ceritinib at ↓ 1 dose level.
	Life-threatening	Hold until asymptomatic or heart rate ≥ 60 bpm. If medication(s) contributing to bradycardia/hypotension is discontinued or dose adjusted, restart ceritinib at ↓ 1 dose level. Discontinue permanently: • If potentiating medications cannot be identified and discontinued • For recurrence
Prolonged QTcF	> 500 msec on at least 2 separate ECGs	Hold until baseline or < 481 msec, restart at ↓ 1 dose level.
	Torsades de pointes or polymorphic ventricular tachycardia or signs and symptoms of other serious arrhythmia	Discontinue.
Elevated LFTs	AST or ALT > 5 x ULN AND total bilirubin ≤ 1.5 x ULN	Hold until baseline or ≤ 3 x ULN, restart at ↓ 1 dose level.
	AST or ALT > 3 x ULN AND total bilirubin > 2 x ULN (without cholestasis or hemolysis)	Discontinue.

Elevated lipase or amylase	> 2 x ULN	Hold until ≤ 1.5 x ULN, restart at ↓ 1 dose level if pancreatitis is ruled out. If pancreatitis is confirmed, discontinue and manage appropriately.
Suspected ILD/pneumonitis	Any grade	Hold and investigate; discontinue if confirmed.

Dosage with Hepatic Impairment:

Hepatic Impairment	Ceritinib Dose
Mild to moderate impairment (Child-Pugh classes A and B)	No dosage adjustment necessary.
Severe impairment (Child-Pugh class C)	Reduce the dose by approximately one-third (rounded to the nearest multiple of the 150 mg strength).

Dosage with Renal Impairment:

Creatinine Clearance	Ceritinib Dose
≥ 30 to 90 mL/minute	No dosage adjustment necessary.
< 30 mL/minute; patients on dialysis	Use with caution; No data available.

Dosage in the elderly:

No overall differences in efficacy were observed between patients ≥ 65 years and younger patients.

Children:

Safety and efficacy has not been established in pediatric patients.

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F - Administration Guidelines

- Administer ceritinib at the same time each day with food. Food can range from a snack to a full meal.
- Capsules should be swallowed whole with water and not be chewed or crushed.
- Avoid grapefruit or grapefruit juice as they may inhibit CYP3A in the gut wall and may increase the bioavailability of ceritinib.
- If a dose is missed it may be taken as soon as possible, unless the next dose is due within 12 hours.
- If vomiting occurs after taking the dose, do not take a replacement dose. Continue with the next scheduled dose.
- Store at room temperature, between 15^{o}C to 30^{o}C.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components
- Patients with congenital long QT syndrome or with a persistent QTcF > 500 msec

Other Warnings/Precautions:

Not recommended for use in:

- ALK-negative patients
- Patients who are taking medications known for QT prolongation

Use with caution in:

- Patients who are at risk of prolonged QT (electrolyte imbalances, cardiovascular disease, diabetes, autonomic neuropathy, females, older patients).
- Patients with baseline bradycardia (HR < 60 bpm), history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular block, ischemic heart disease or congestive heart failure, or taking agents known to cause bradycardia or hypotension.
- Patients with severe renal impairment requiring peritoneal dialysis or hemodialysis (ceritinib has not been studied in these patients).

Other Drug Properties:

- Carcinogenicity: Unknown
  Carcinogenicity studies have not been performed.

Pregnancy and Lactation:

- Clastogenicity: No
- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Genotoxicity: Yes
- Mutagenicity: No
- Pregnancy:
  Ceritinib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **3 months** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Unknown

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H - Interactions

Ceritinib is primarily metabolized by CYP3A, may inhibit CYP3A, CYP2C9, CYP2A6 and CYP2E1.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	↑ risk of prolonged QT and Torsades de Pointes	additive	Avoid concomitant use with QT prolonging agents if possible; closely monitor QT
Drugs that disrupt electrolyte levels (i.e. loop/thiazide diuretics, laxatives, amphotericin B, high dose corticosteroids)	↑ risk of prolonged QT	additive	Caution; closely monitor electrolytes
Drugs that lower heart rate (i.e. beta blockers, calcium channel blockers, digoxin)	↑ risk of bradycardia	additive	Avoid co-administration with agents that lower heart rate if possible; closely monitor HR
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ ceritinib concentration and/or toxicity (co-admin with ketoconazole ↑ ceritinib AUC 2.9 fold)	↓ metabolism of ceritinib	Avoid strong CYP3A4 inhibitors. If unavoidable, consider ceritinib dose reduction. Caution with concomitant use of moderate CYP3A4 inhibitors. Monitor for adverse reactions.
CYP3A4 inducers (i.e. phenytoin,	↓ ceritinib concentration and/or efficacy (co-admin	↑ metabolism of ceritinib	Avoid strong CYP3A4 inducers

rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	with rifampin ↓ ceritinib AUC by 70%)		
P-glycoprotein inhibitors (i.e. quinidine, verapamil, cyclosporine)	↑ ceritinib concentration and/or toxicity	inhibits drug efflux (in vitro data)	Caution and monitor with strong P-gp inhibitors
P-glycoprotein inducers (i.e. dexamethasone, rifampin)	↓ ceritinib concentration and/or efficacy	promotes drug efflux (in vitro data)	Caution and monitor with strong P-gp inducers
CYP3A4 substrates (e.g. midazolam, cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)	↑ substrate concentration and/or toxicity. (midazolam AUC ↑ 5.4x with co-admin)	ceritinib may inhibit CYP3A (in vitro data)	Avoid co-administration with substrates that have narrow therapeutic indices. If unavoidable, consider substrate dose reduction.
CYP 2C9 substrates (e.g. warfarin, meloxicam, fluvastatin)	↑ substrate concentration and/or toxicity	ceritinib may inhibit CYP2C9 (in vitro data)	Avoid co-administration with substrates that have narrow therapeutic indices. If unavoidable, consider substrate dose reduction. Increase INR monitoring with warfarin if concurrent use cannot be avoided.
CYP2A6 substrates (e.g. valproic acid, letrozole, disulfiram)	↑ substrate concentration and/or toxicity	ceritinib may inhibit CYP2A6 (in vitro data)	Caution with concomitant use of CYP2A6 substrates; monitor for adverse reactions.
CYP2E1	↑ substrate concentration	ceritinib may inhibit	Caution with

substrates (e.g. ethanol, acetaminophen)	and/or toxicity	CYP2E1 (in vitro data)	concomitant use of CYP2E1 substrates; monitor for adverse reactions.
Drugs that reduce gastric acid (antacids, H2-receptor blockers, proton pump inhibitors)	↓ ceritinib concentration, AUC, but no clinically significant changes in steady state exposure	ceritinib has pH dependent solubility (in vitro data)	If concurrent use necessary, give H2-blocker 10 hours before or 2 hours after ceritinib dose. Give antacids 2 hours before or 2 hours after ceritinib dose.

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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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests	Baseline and monthly thereafter; more frequently in patients that develop liver enzyme elevations during treatment
Lipase, amylase	Baseline and as clinically indicated; more frequently if abnormal or symptoms of pancreatitis
ECG	Baseline and as clinically indicated; more frequent in patients at risk for QT prolongation
Blood glucose	Baseline and as clinically indicated; more frequent if diabetic
Renal function tests and electrolytes	Baseline and as clinically indicated
Clinical toxicity assessment for gastrointestinal, skin, cardiac (blood pressure and heart rate), and respiratory toxicity	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)

- ceritinib - Second-line monotherapy of ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC, in patients who have experienced disease progression or intolerance to crizotinib, according to specific criteria

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K - References

Ceritinib product monograph, Novartis Pharmaceuticals Canada Inc. January 2020.

Ceritinib prescribing information. Novartis Pharmaceuticals Corp. (USA). August 2021.

Cho BC, Kim DW, Bearz A, et al. ASCEND-8: A Randomized Phase 1 Study of Ceritinib, 450 mg or 600 mg, Taken with a Low-Fat Meal versus 750 mg in Fasted State in Patients with Anaplastic Lymphoma Kinase (ALK)-Rearranged Metastatic Non-Small Cell Lung Cancer (NSCLC). J Thorac Oncol. 2017 Sep;12(9):1357-67.

Shaw AT, Engelman JA. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med. 2014 Jun 26;370(26):2537-9.

November 2024 Updated Pregnancy and Lactation 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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