Drug Monograph

A - Drug Name

alectinib

COMMON TRADE NAME(S): Alecensaro®

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B - Mechanism of Action and Pharmacokinetics

Alectinib is a highly selective and potent ALK and RET (Rearranged during Transfection) tyrosine kinase inhibitor. It inhibits ALK phosphorylation and ALK-mediated downstream signalling pathways (STAT 3 and PI3K/AKT) and induces apoptosis. Alectinib has shown activity against mutant forms of the ALK enzyme, including mutations responsible for resistance to crizotinib.

Absorption	Rapidly absorbed	
	Bioavailability	37% (under fed conditions)
	T max	~4-6 hours
	Time to reach steady state	7 days
	Effects with food	Exposure increased 3-fold after a high-fat, high-calorie meal vs fasting
Distribution	Extensive distribution into tissues	
	PPB	> 99% (human plasma proteins)
	Cross blood brain barrier?	Yes (alectinib). CNS penetration of M4 metabolite has not been studied.

Metabolism	Main enzymes involved	CYP3A4
	Active metabolites	Yes (M4 has shown similar *in vitro* potency and activity to alectinib)
Elimination	Feces	98% (84% alectinib and 6% M4)
	Urine	<0.5%
	Half-life	~33 hours (alectinib) and ~31 hours (M4)

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C - Indications and Status

Health Canada Approvals:

- Non-small cell lung cancer (NSCLC)

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Low – No routine prophylaxis; PRN recommended

The following table lists adverse effects that occurred in ≥ 2% of patients treated with alectinib in the Phase III clinical trial in first-line NSCLC. Severe adverse effects from other studies or post-marketing are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Atrioventricular block (rare)	E D
	Bradycardia (11%)	E
	QT interval prolonged (rare)	E D
	Venous thromboembolism (rare)	E
Dermatological	Dry skin (4%)	E

	Photosensitivity (5%)	E D
	Rash (15%)	E
Gastrointestinal	Constipation (34%)	E
	Diarrhea (12%)	E
	GI perforation (rare)	E D
	Mucositis (3%)	E
	Nausea, vomiting (14%)	E
General	Edema (22%)	E
	Fatigue (26%)	E D
Hematological	Anemia (20%) (5% severe)	E D
	Hemolytic anemia (rare)	E
Hepatobiliary	Drug-induced liver injury (rare)	E
	↑ LFTs (21%) (5% severe)	E
Musculoskeletal	Musculoskeletal pain (23%)	E
	↑CPK (5%) (3% severe)	E
Nervous System	Dizziness (8%)	E
	Dysgeusia (3%)	E
Ophthalmic	Visual disorders (5%)	E
Renal	Creatinine increased (8%) (1% severe)	E
	Nephrotoxicity (3%)	E
Respiratory	Other - Pneumonitis / eosinophilic pneumonia (rare)	E D

* "*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 alectinib include constipation, fatigue, musculoskeletal pain, edema, ↑ LFTs, anemia, rash, nausea, vomiting, diarrhea and bradycardia.

Bradycardia correlates with plasma levels and is reversible. Patients should be informed about symptoms of bradycardia and advised to report these to the health care team.

Hepatotoxicity usually occurs during the first 3 months of therapy and is usually transient and reversible.

Myalgia and elevations of creatinine phosphokinase (CPK) have been observed and usually present early.

Hemolytic anemia has been reported during post-marketing. If suspected, initiate appropriate laboratory testing.

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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.

Patients must have documented ALK-positive status, based on a validated ALK assay, prior to starting treatment with alectinib.

Patients must avoid sun exposure while on treatment and for at least 7 days after the last dose, and must use UVA/B sunscreen and lip balm (at least SPF 50).

Adults:

Oral: 600 mg BID

Dosage with Toxicity:

Dose level	Dose (mg) BID
Starting Dose	600
-1	450
-2	300
-3	Discontinue

Toxicity	Action
GI perforation	Discontinue.
ILD/pneumonitis of any Grade	Hold; if confirmed, discontinue.
Grade 3 Renal Impairment	Hold until serum creatinine recovers to baseline or ≤ Grade 1, then resume at 1 dose level ↓.
Grade 4 Renal Impairment	Discontinue.
≥ Grade 3 ALT or AST elevation (> 5 x ULN) **and** Total bilirubin ≤ 2 x ULN	Hold until recovery to baseline or ≤ Grade 1; Resume at 1 dose level ↓.
≥ Grade 2 ALT or AST elevation (> 3 x ULN) **and** Total bilirubin ≥ 2 x ULN (in absence of cholestasis or hemolysis)	Discontinue.
Grade 2 to 3 Bradycardia (HR < 60 bpm) (symptomatic)	Hold until recovery to ≤ Grade 1 (asymptomatic) bradycardia or HR of ≥ 60 bpm. Evaluate concomitant medications; if contributing, discontinue or reduce dose of concomitant drug. Resume at previous dose. If no concomitant medication contributing, or contributing medication not stopped/reduced: resume at 1 dose level ↓
Grade 4 Bradycardia (HR < 60 bpm) (life-threatening consequences, urgent intervention required)	Discontinue if no contributing concomitant medication. If contributing concomitant medication is discontinued or reduced: Hold until recovery to ≤ Grade 1 (asymptomatic) bradycardia or HR of ≥ 60 bpm, with frequent monitoring. Resume at 1 dose level ↓. If recurs: discontinue.
CPK elevation > 5 x ULN	Hold until recovery to baseline or ≤ 2.5 x ULN; resume at same dose.
CPK elevation > 10 x ULN **or** 2nd Occurrence of CPK elevation > 5 x ULN	Hold until recovery to baseline or ≤ 2.5 x ULN; resume at 1 dose level ↓.
Hemolytic anemia with hemoglobin of < 100 g/L (≥ Grade 2)	Hold until recovery, then resume at 1 dose level ↓. OR Discontinue.

Dosage with Hepatic Impairment:

Pre-existing Hepatic impairment	Alectinib Dose
Mild or Moderate	No dose adjustment required.
Severe	450 mg twice daily.

Dosage with Renal Impairment:

Renal Impairment	Alectinib Dose
Mild or Moderate (CrCl ≥ 30 mL/min)	No dose adjustment required
Severe (CrCl < 30 mL/min)	Has not been studied

Dosage in the elderly:

No dose adjustment required. Fatal adverse events and adverse events leading to treatment withdrawal were more common in patients 65 years or older compared to younger patients.

Children:

Safety and efficacy have not been established. Non-clinical studies showed effects on bone and dentition.

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F - Administration Guidelines

- Alectinib should be taken with food (fasted state decreases exposure three fold).
- Capsules should not be opened or dissolved.
- If a dose is missed the next dose should be taken at the next scheduled time.
- If vomiting occurs, a repeat dose should not be taken; the next dose should be taken at the next scheduled time.
- Avoid grapefruit, grapefruit juice, products with grapefruit extract, star fruit, Seville oranges, pomegranate, and other similar fruits that inhibit CYP3A4 during alectinib treatment due to risk for increased toxicity.
- Store between 15-30ºC in the original package.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Use with caution in patients who are at risk for gastrointestinal perforation (e.g., concomitant use of medications with GI perforation risk, history of diverticulitis, metastases to the GI tract).
- Use with caution in patients with hepatic impairment or renal impairment.
- Use with caution in patients who have bradycardia at baseline (< 60 bpm), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, AV block, ischemic heart disease, CHF or who are on medications that lower HR.
- Vision disorders, asthenia, fatigue and dizziness have been reported. Patients with these symptoms should use caution when driving or operating machines.
- Contains lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

Other Drug Properties:

- Carcinogenicity: Unknown
- Phototoxicity: Likely

Pregnancy and Lactation:

- Mutagenicity: Probable
- Abortifacient effects: Yes
- Embryotoxicity: Yes

- Fetotoxicity: Yes
  Alectinib 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

- CYP3A4 is the primary enzyme responsible for metabolism of alectinib and M4 (active metabolite). M4 has shown similar in vitro potency and activity to alectinib against ALK.
- Alectinib is not a substrate of P-gp while M4 is a substrate of P-gp
- Alectinib and M4 are not substrates of BCRP or OATP 1B1/B3
- Medications that increase gastric pH do not appear to have an effect on alectinib or M4 exposure.
- Neither alectinib nor M4 are inhibitors of CYP1A2, 2B6, 2C9, 2C19, or 2D6. Alectinib is a weak inhibitor of 3A4 and 2B6.
- No dose adjustment is necessary with CYP3A4 substrates.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Strong CYP3A inducers (i.e. phenytoin, rifampin, carbamazepine, phenobarbital, St. John's Wort, etc.)	↓ alectinib exposure and ↑ M4 exposure	↑ metabolism of alectinib	Caution; monitor closely
Strong CYP3A inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ alectinib exposure and ↓ M4 exposure	↓ metabolism of alectinib	Caution; monitor closely
CYP 2C8 substrates (i.e. paclitaxel, sorafenib, amiodarone)	↑ substrate concentration and/or toxicity (in vitro)	↓ metabolism of substrate	Caution; monitor closely

BCRP substrates (i.e. topotecan)	↑ substrate concentration and/or toxicity (in vitro)	↓ metabolism of substrate	Caution with drugs with narrow therapeutic index
P-glycoprotein substrates (i.e. verapamil, digoxin, morphine, ondansetron)	↑ substrate concentration and/or toxicity (in vitro)	↓ metabolism of substrate	Caution with drugs with narrow therapeutic index
Drugs that lower heart rate (e.g. alpha2-adrenoceptor agonists, beta blockers, non-dihydropyridine Ca channel blockers, digoxin, cholinesterase inhibitors, sphingosine-1 phosphate receptor modulators)	↑ risk of bradycardia	Additive	Avoid if possible; if not possible, monitor closely

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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, every 2 weeks during the first 3 months of treatment, then at each visit or as clinically indicated; more frequent with abnormal LFTs.
Blood CPK levels	Every 2 weeks for the first month, and as clinically indicated

Renal function tests	Baseline, at each visit, and as clinically indicated
Electrolytes, including serum calcium and potassium	Baseline, at each visit, and as clinically indicated
Blood pressure and heart rate	Baseline, at each visit, and as clinically indicated.
ECG	Baseline and as required to evaluate QTc, AV block.
CBC	Baseline and as clinically indicated, or if hemolytic anemia suspected
Clinical toxicity assessment for photosensitivity, rash, edema, fatigue, myalgia, dizziness, headache, visual disorders, respiratory and GI 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)

- alectinib - Treatment of non-small cell lung cancer, according to specific criteria

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K - References

Ou SI, Ahn JS, De Petris L, et al: Alectinib in Crizotinib-Refractory ALK-Rearranged Non-Small-Cell Lung Cancer: A Phase II Global Study. J Clin Oncol, 2015.

Product monograph: Alectinib (Alecensaro). Hoffmann-La Roche Limited. May 9, 2022.

Shaw AT, Gandhi L, Gadgeel S, et al: Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. Lancet Oncol 17:234-42, 2016

April 2024 Updated pregnancy/breastfeeding 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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