DRUG NAME: Alectinib

SYNONYM(S): CH5424802, RO5424802[1]

COMMON TRADE NAME(S): ALECENSARO®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Alectinib is a potent tyrosine kinase receptor inhibitor selective for ALK (anaplastic lymphoma kinase) and RET (Rearranged During Transfection) genes. Alectinib induces tumour cell death by inhibiting ALK phosphorylation and ALK-mediated downstream signalling pathways. Activity against many acquired ALK resistance mutations has been demonstrated. Alectinib also inhibits LTK (leukocyte tyrosine kinase receptor) and GAK (cyclin-G-associated kinase).[2-4]

PHARMACOKINETICS:

Oral Absorption	bioavailability = 37%; time to peak concentration = 4-6 h; high-fat, high-calorie meal increases exposure 3-fold	
Distribution	extensive distribution into tissues; concentrations in CSF approximate the free concentrations in plasma	
	cross blood brain barrier?	yes
	volume of distribution	4000 L (parent drug); 10,000 L (M4)
	plasma protein binding	>99%
Metabolism	mainly via CYP 3A4	
	active metabolite(s)	M4
	inactive metabolite(s)	no information found
Excretion	mainly hepatic elimination	
	urine	<0.5%
	feces	98% (84% as parent drug; 6% as M4)
	terminal half life	32.5 h (parent drug); 30.7 h (M4)
	clearance	81.9 L/h (parent drug); 217 L/h (M4)

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Lung cancer, non-small cell

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:

- ***bradycardia*** has been reported; use with caution in patients with bradycardia at baseline or with history of syncope, arrhythmia, or heart disease, and those taking other medications which decrease heart rate[2]
- ***gastrointestinal (GI) perforation*** has been reported and may be fatal; use with caution in patients with history of diverticulitis, metastases to the gastrointestinal tract, or taking other medications with a risk of GI perforation[2]

Special populations: Alectinib is not recommended in patients under 18 years old. In animal studies, decreased bone formation and lesions in continuously growing incisor teeth were reported in immature test subjects.[2]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in the Ames test. Alectinib was aneugenic in both mammalian *in vitro* mutation tests and *in vitro* chromosome tests.[2]

Fertility: No adverse effects were seen on male or female reproductive organs in animal toxicology studies.[2]

Pregnancy: In animal studies, alectinib caused embryo-fetal toxicity (e.g., low body weight and retarded ossification) and abortion. Effective contraception is recommended during treatment and for at least three months after treatment has ended.[2]

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

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.[5,6]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (14-56%, severe 2%)
	hemorrhage (severe <1%); has been fatal
	leukopenia (3%)
	lymphopenia (21-22%, severe 4-5%)[2,4]
	neutropenia (3%, severe <1%)
cardiac	***atrioventricular block, complete*** (<1%, severe <1%)
	bradycardia (8-20%)[2,4]; see paragraph following **Side Effects** table
	endocarditis (severe <1%); has been fatal
eye	vision disorders (10%)
gastrointestinal	*emetogenic potential: low*[7]
	constipation (34%)
	diarrhea (16%, severe 1%)
	gastrointestinal perforation (<1%, severe <1%)
	nausea (18%)
	vomiting (12%, severe <1%)
general disorders and administration site conditions	edema (30%, severe <1%)
	fatigue (33-41%, severe 1%)[2]
	mucosal inflammation (3%)
hepatobiliary	***drug-induced liver injury*** (<1%, severe <1%); see paragraph following **Side Effects** table

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
infections and infestations	upper respiratory tract infection (10%)[8]
	lung infection (2%, severe 1%)[8]
investigations	activated partial thromboplastin time prolonged (6%, severe 1%)[8]
	alkaline phosphatase increase (7-47%, severe ≤1%)
	ALT increase (14-34%, severe 3-5%); see paragraph following **Side Effects** table
	AST increase (16-51%, severe 3-4%); see paragraph following **Side Effects** table
	bilirubin increase (15-39%, severe 2-3%); see paragraph following **Side Effects** table
	creatine phosphokinase increase (12-43%, severe 4-5%); see paragraph following **Side Effects** table
	creatinine increase (6-28%, severe <1%)
	QTc prolongation (1%, severe <1%)
	weight increase (11%, severe <1%)
metabolism and nutrition	hyperglycemia (35-36%, severe 2%)[2,4]
	hypoalbuminemia (6%, severe 1%)[8]
	hypocalcemia (32%, severe <1%)
	hypokalemia (29%, severe 4%)
	hyponatremia (20%, severe 2%)
	hypophosphatemia (21%, severe 3%)
musculoskeletal and connective tissue	arthralgia (10%)
	back pain (12%)[4]
	hemiparesis (2%, severe 1%)[8]
	muscular weakness (6-41%, severe <1%)[2,4]
	myalgia (29%, severe 1%); see paragraph following **Side Effects** table
nervous system	dizziness (10%)
	dysgeusia (6%)
	headache (17%, severe <1%)
	peripheral neuropathy (4%)
	seizure (3%, severe 1%)[8]
psychiatric disorders	insomnia (11%)[8]
renal and urinary	***renal insufficiency*** (8%)[9]; see paragraph following **Side Effects** table
respiratory, thoracic and mediastinal	cough (19%)[4]
	dyspnea (16%, severe 1%)[2,4]
	eosinophilic pneumonia (<1%, severe <1%)
	interstitial lung disease/pneumonitis (<1%, severe <1%)
skin and subcutaneous tissue	alopecia (5%)
	dry skin (6%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	photosensitivity reaction (10%); see paragraph following **Side Effects** table
	pruritus (4%)
	rash (18%, severe <1%)
vascular	***pulmonary embolism*** (1%, severe 1%)[2,4]; has been fatal

Adapted from standard reference[2] unless specified otherwise.

Bilirubin elevations of greater than three times upper limit of normal [ULN]) and ***transaminase elevations*** of greater than five times ULN) have been reported. These test abnormalities generally occur within the first three months of treatment and are usually reversible with treatment interruption or dose reduction. However, biopsy confirmed ***drug-induced liver injury*** has occurred in some patients. Monitor liver function regularly during treatment and increase test frequency if clinically indicated. Hold alectinib for AST/ALT elevations more than 5 times ULN. Treatment may be resumed at a lower dose following recovery to grade 1 or baseline levels. Permanently discontinue alectinib in patients experiencing AST/ALT elevations more than 3 times ULN with bilirubin more than 2 times ULN in the absence of cholestasis or hemolysis.[2-4]

Bradycardia has been reported in up to 20% of patients and may be symptomatic. Monitor heart rate and blood pressure regularly throughout treatment. Withhold alectinib for symptomatic, non-life threatening bradycardia. Treatment may be resumed once patient is asymptomatic or after heart rate increases to 60 beats per minute or greater. Adjust any concurrent bradycardic/hypotensive medications and consider alectinib dose reduction if needed. Permanently discontinue alectinib for recurrent life-threatening bradycardia or life-threatening bradycardia which occurs in the absence of concurrent bradycardic/hypotensive medications.[2,4]

Myalgia has been reported in up to 29% of patients. It is sometimes severe and may be associated with elevated creatine phosphokinase (CPK). Patients should report any unexplained muscle pain or weakness. Management of symptoms may require alectinib dose modification or temporary discontinuation of treatment.[2]

Photosensitivity has been reported. Prolonged sun exposure should be avoided. If exposure is unavoidable, the use of broad-spectrum sun screen and lip balm of at least SPF 50 are recommended during treatment and for 7 days after treatment discontinuation.[2]

Renal insufficiency has been reported and is sometimes fatal. Withhold alectinib for grade 3 renal impairment. Resume treatment at a reduced dose once serum creatinine is less than 1.5 times ULN. Permanently discontinue alectinib for grade 4 renal impairment.[4]

Up to 10% of patients report ***vision disorders*** such as diplopia, blurry vision, vitreous floaters, asthenopia, and reduced visual acuity. Patients experiencing vision disorders should be cautious when driving or operating machinery.[2]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
proton pump inhibitors, H_2 blockers, antacids[2]	no effect on alectinib pharmacokinetics		

Alectinib and M4 are substrates and weak inhibitors of CYP 3A. Dose adjustment of alectinib is not required.[10]

Alectinib inhibits CYP 2C8 *in vitro;* clinical significance is unknown.[2]

Alectinib and M4 are inhibitors of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) *in vitro*. Plasma levels of P-gp or BCRP substrates with a narrow therapeutic index should be monitored during coadministration with alectinib.[2]

M4 is a substrate of P-gp *in vitro;* clinical significance is unknown.[2]

SUPPLY AND STORAGE:

Oral: Hoffmann-La Roche Limited supplies alectinib as 150 mg capsules. Capsules contain lactose. Store at room temperature. Protect from light.[2]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy.

***Adults*:**

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

Oral: ***600 mg PO twice daily[2,11]***

Administer with food.[2]

Concurrent radiation: no information found

Dosage in renal failure: CrCl ≥ 30 mL/min: no adjustment required[2]
CrCl < 30 mL/min: no information found

$$\text{calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure: mild impairment (bilirubin ≤ 1.5 x ULN and any AST): no adjustment required[2]
moderate hepatic impairment (Child-Pugh B): no information found
severe hepatic impairment (Child-Pugh C): 450 mg PO twice daily[2]

Dosage in dialysis: no information found; however alectinib and its M4 metabolite are extensively protein bound so hemodialysis is not expected to enhance clearance[3]

Children: safety and efficacy not established[2]

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