Drug Monograph

A - Drug Name

crizotinib

COMMON TRADE NAME(S): Xalkori®

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B - Mechanism of Action and Pharmacokinetics

Crizotinib is a selective inhibitor of the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase (including oncogenic variants). It also demonstrated activity as an inhibitor of the Hepatocyte Growth Factor Receptor.

Absorption	Bioavailability	43% (range 32%-66%)
	Effects with food	High-fat meal ↓ bioavailability by 14% (single dose)
	Time to reach steady state	15 days
	Peak plasma levels	4 hours (range: 2 - 9.33 hours)
Distribution	Extensively distributed into tissues	
	PPB	91% (independent of drug concentration)
	Distribution Sites	Extensively distributed to liver, uveal tract, adrenal gland, small intestine and pituitary gland.

Metabolism	Active metabolites	Yes
	Inactive metabolites	Yes
Elimination	Reduced clearance at steady state may be due to CYP3A autoinhibition by repeated crizotinib dosing.	
	Half-life	42 hours
	Urine	22% of dose (2.3% unchanged)
	Feces	63% of dose (53% unchanged)

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C - Indications and Status

Health Canada Approvals:

- Monotherapy for treatment of locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive.
- Monotherapy for treatment of patients with ROS1-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC.

Notes:

- ALK or ROS1 positivity should be determined using a validated test.
- Approval for ROS1-positive NSCLC was based on objective response rate and duration of response in a small single-arm study.
- An overall survival benefit has not been demonstrated with crizotinib.

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D - Adverse Effects

Emetogenic Potential: Moderate – Consider prophylaxis daily

The following adverse events are from a phase III study in previously untreated ALK-positive patients; life-threatening effects are included from other studies.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial thromboembolism (rare)	E
	Bradycardia (14%)	I E
	Hypotension (5%)	E
	QT interval prolonged (6%)	E
	Venous thromboembolism (4%)	E
Dermatological	Rash (11%)	E D
Gastrointestinal	Abdominal pain (26%)	E
	Anorexia (30%)	E D
	Constipation (43%) (2% severe)	E
	Diarrhea (61%) (2% severe)	E
	Dyspepsia (14%)	E
	Dysphagia (10%)	E
	Mucositis (6%)	E
	Nausea, vomiting (56%) (2% severe)	E
General	Edema (49%) (<1% severe)	E
	Fatigue (29%)	E
	Fever (19%)	E
Hematological	Disseminated intravascular coagulation (rare)	E
	Hemorrhage (CNS; rare)	E
	Myelosuppression ± infection (21%) (11% severe)	E
Hepatobiliary	↑ LFTs (36%) (14% severe)	E
Infection	Infection (32%) (URTI)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (5%) (↓ K, ↓Na; severe)	E
Musculoskeletal	Musculoskeletal pain (16%)	E
Nervous System	Dizziness (18%)	E
	Dysgeusia (26%)	E
	Neuropathy (21%)	E D
	Syncope (<1%)	E
Ophthalmic	Visual disorders (71%) (1% severe)	E D
Renal	Creatinine increased (5%) (may be severe)	E D
	Other (5%) Renal cyst	E D

Respiratory	Cough, dyspnea (18%) (may be severe)	E
	Pneumonitis (1%)	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 crizotinib include visual disorders, diarrhea, nausea, vomiting, edema, constipation, ↑ LFTs, infection, anorexia, fatigue and abdominal pain.

Increased cardiovascular side effects such as **bradycardia** (which may occur several weeks after the start of therapy), **QTc prolongation** and **hypotension** were reported. Crizotinib should be used with caution in patients with increased QTc or at risk of bradycardia.

Visual disorders including diplopia, photopsia, blurred vision, vitreous floaters and general visual impairment have been reported and are usually mild in nature, but may result in severe visual loss with optic nerve atrophy. Ophthalmological evaluation is required if vision disorder persists or worsens. The onset of vision disorder was generally reported within the first week of drug administration. Discontinue crizotinib with new onset severe visual loss.

Gastrointestinal events including nausea, diarrhea, vomiting and constipation were most commonly reported but mild in nature and responded to supportive care (antiemetic and/or antidiarrheal and/or laxative medications), dose interruption or reduction. Median times to onset for diarrhea and constipation were 13 and 17 days, respectively.

CNS hemorrhage has been reported in pediatric patients with intracranial disease.

Fatalities due to crizotinib-induced **hepatotoxicity** have occurred rarely. Transaminase elevation onset was generally reported within 2 months of treatment initiation. Less than 1% of patients had concurrent elevations in ALT and/or AST ≥3 x ULN and total bilirubin ≥2 x ULN without significant elevations of alkaline phosphatase.

Severe or life-threatening **pneumonitis** was reported across clinical trials. Cases generally occurred within 3 months of starting therapy. Crizotinib should be discontinued if pneumonitis is confirmed.

Renal cysts have been reported, but are of uncertain clinical significance.

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E - Dosing

Use only in patients with known ALK-positive or ROS1-positive NSCLC confirmed using a

validated assay.

Avoid using concomitantly with strong CYP3A4 inducers/inhibitors, or CYP3A4 substrates with narrow therapeutic indices and associated with severe arrhythmias.

Electrolyte abnormalities should be corrected prior to initiating treatment.

Adults:

Oral: 250 mg twice daily

until disease progression or unacceptable toxicity

Dosage with Toxicity:

Dose Level	Crizotinib Dose
0	250mg twice daily
-1	200mg twice daily
-2	250 mg once daily
-3	Discontinue

Toxicity	Action
Grade 3 hematologic	Hold until recovery to ≤ grade 2; resume at same dose
Grade 4 hematologic	Hold until recovery to ≤ grade 2; resume at ↓ 1 dose level
Grade 3 or 4 AST/ALT WITH ≤ grade 1 bilirubin	Hold until recovery to ≤ grade 1 or baseline; resume at ↓ 1 dose level
Bilirubin ≥ grade 2 and AST/ALT ≥ grade 2 (in the absence of cholestasis or hemolysis)	Discontinue
QTc ≥ 500 msec without arrhythmia	Hold until ≤ 470 msec and correct electrolyte abnormalities; resume at ↓ 1 dose level
QTc ≥ 500 msec (or > 60 msec change from	Discontinue

baseline) and Torsade de Pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmias	
Grade 2 or 3 bradycardia (< 60 bpm; symptomatic, may be severe and medically significant, medical intervention indicated)	Hold until recovery to ≤ grade 1* Evaluate contributing medications: If contributing concomitant medication is identified and is adjusted or discontinued, resume at same dose If there is no contributing concomitant medication or if concomitant medications are not adjusted/ discontinued, resume at ↓ 1 dose level
Grade 4 bradycardia (life-threatening consequences, urgent intervention indicated)	Hold immediately Evaluate contributing medications: If contributing concomitant medication is identified and adjusted or discontinued, resume* at 250 mg once daily and monitor If no contributing concomitant medication identified, discontinue Discontinue with recurrence
Signs or symptoms of pneumonitis / interstitial lung disease	Hold and investigate; discontinue permanently if confirmed
Severe visual loss (best corrected vision < 20/200 in one or both eyes)	Discontinue and evaluate severe vision loss No data to support resuming; risk benefit must be assessed

*Do not restart until heart rate ≥ 60 bpm and asymptomatic

Dosage with Hepatic Impairment:

Hepatic Impairment	Crizotinib Starting dose
Mild	No dose adjustment necessary

Moderate (total bilirubin >1.5 to ≤3 x ULN and any AST)	200 mg twice daily
Severe (total bilirubin >3 x ULN and any AST)	250 mg once daily

Dosage with Renal Impairment:

Renal Impairment	Crizotinib Starting Dose
Mild or moderate	No dose adjustment necessary
Severe (CrCl < 30 mL/min) not requiring peritoneal dialysis or hemodialysis	250 mg once daily
Severe requiring peritoneal dialysis or hemodialysis	No data

Dosage in the elderly:

There were no overall differences in safety or efficacy between patients aged 65 or older and younger patients and dosage adjustment is not required. However, edema, constipation, dysgeusia and nausea were reported more frequently in older patients.

Dosage based on ethnicity:

Although exposure is higher in Asian patients, there is no increase in incidence of Grade 3 or 4 adverse events.

Children:

The safety and efficacy of crizotinib have not been established in the pediatric population. Effects on growth are likely. CNS hemorrhage was reported in pediatric trials.

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F - Administration Guidelines

- Swallow capsules whole with a glass of water. Do not crush, dissolve, or open capsules.
- Administer crizotinib with or without food.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during crizotinib treatment
- If a dose is missed, patient may take within 6 hours of missed dose. If more than 6 hours, the dose should be skipped and taken at the next planned time.
- Store at room temperature and away from children or pets.

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G - Special Precautions

Contraindications:

- Patients with congenital long QT syndrome or persistent QTcF ≥ 500 msec.
- 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 of QT prolongation or bradycardia (low potassium/magnesium, congenital QT prolongation, CHF, anti-arrhythmics, other QTc prolonging agents, prior anthracyclines, AV block, sick sinus, sinoatrial block or drugs leading to bradycardia etc.).
- Use with caution in patients who have bradycardia at baseline (< 60 bpm), and in patients with cardiac disease, history of arrhythmias or who are on medications that may reduce heart rate.
- Caution with driving or using machinery due to vision disorder including diplopia, photopsia, blurred vision, visual impairment and vitreous floaters.
- Caution in patients with a history of thrombotic events. Crizotinib has not been studied in patients who have had arterial thromboembolism or CHF within the last 3 months.
- Exercise caution in patients with hepatic impairment or severe renal impairment requiring dialysis.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: Documented in animals
- Fetotoxicity: Documented in animals
- Teratogenicity: No
- Fertility effects: Probable
  Crizotinib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **3 months** after the last dose.
- Breastfeeding: Not recommended

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H - Interactions

Crizotinib is metabolized via CYP3A4/5 and is susceptible to drug interactions with CYP3A4 inhibitors and inducers, which may be clinically relevant. The drug is a moderate inhibitor of CYP3A4 and also inhibits P-gp, CYP2B6, UGT and OCT in vitro (theoretical interaction potential).

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. ketoconazole, voriconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges, starfruit or pomegranate)	↑ crizotinib concentration and/or toxicity (up to 3.2-fold ↑ in exposure)	↓ metabolism of crizotinib	Avoid with strong CYP3A inhibitors; caution with moderate inhibitors
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ crizotinib concentration and/or efficacy (up to 82% ↓ in exposure)	↑ metabolism of crizotinib	Avoid with strong CYP3A inducers; caution with moderate inducers
Drugs that raise gastric pH (e.g. antacid, proton pump inhibitor, H2-receptor antagonist)	↓ bioavailability of crizotinib	↓ solubility of crizotinib	Caution; dose adjustment not required
CYP3A4 substrates (e.g. cyclosporine, pimozide,	↑ CYP3A4 substrate concentration and/or toxicity	↓ metabolism of CYP3A4 substrate	Avoid substrates with narrow therapeutic index and associated with severe arrhythmias

tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)			(dihydroergotamine, ergotamine and pimozide); caution with other CYP3A4 substrates
P-glycoprotein substrates (i.e. verapamil, digoxin, morphine, ondansetron)	Potentially ↑ P-gp substrate concentration and/or toxicity	↓ metabolism of P-gp substrate (in vitro)	Caution
CYP 2B6 substrates (i.e. bupropion, cyclophosphamide, selegiline)	Potentially ↑ CYP2B6 substrate concentration and/or toxicity	↓ metabolism of CYP2B6 substrates (in vitro)	Caution
Drugs that disrupt electrolyte levels (i.e. loop/thiazide diuretics, laxatives, amphotericin B, high dose corticosteroids)	↑ risk of life-threatening arrhythmias		Avoid where possible
Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	↑ risk of life-threatening arrhythmias	Additive	Avoid where possible
Drugs that decrease heart rate (e.g. antiarrhythmics, beta blockers, non-	↑ risk of bradycardia	Additive	Avoid where possible

dihydropyridine Ca channel blockers, cholinesterase inhibitors, sphingosine-1 phosphate receptor modulators)			
UGT substrates (e.g. raltegravir, irinotecan, morphine, naloxone)	Potentially ↑ substrate concentration and/or toxicity	↓ metabolism of UGT substrates (in vitro)	Caution
OCT substrates (e.g. metformin)	Potentially ↑ substrate concentration and/or toxicity	↓ metabolism of OCT substrates (in vitro)	Caution

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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.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	baseline and at each visit; more frequent if severe myelosuppression, fever and/or infection
Liver function tests	baseline, every 2 weeks during the first 2 months, then monthly and as clinically indicated (more frequent with hepatotoxicity)
Creatinine, electrolytes, including calcium, potassium and magnesium	baseline and as clinically indicated
ECG, heart rate and blood pressure	baseline and as clinically indicated
Renal imaging and urinalysis if renal cysts develop	As clinically indicated
Ophthalmoscopy and assessment of visual loss	As clinically indicated
Clinical toxicity assessment for signs of bleeding or infection and GI, ocular, hepatic, cardiac and nervous	At each visit

system effects, pneumonitis and venous thromboembolism	

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
MUGA, especially for patients with cardiac risk factors	baseline and as clinically indicated

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- crizotinib - First or second-line treatment for ALK-positive advanced NSCLC, according to specific criteria
- crizotinib - First-line treatment for ROS1-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC, according to specific criteria

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K - References

Kwak E, Bang Y, Camidge DR, Shaw, Solomon B. Anaplastic Lymphoma Kinase Inhibition in Non-Small-Cell Lung Cancer. NEJM 2010;363:1693-703.

Product Monograph: Xalkori® (crizotinib). Pfizer Canada Inc, January 21, 2019.

Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013 Jun 20;368(25):2385-94.

December 2020 Updated Supplementary Public Funding 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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