DRUG NAME: Crizotinib

SYNONYM(S):

COMMON TRADE NAME(S): XALKORI®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Crizotinib is an orally administered selective small molecule tyrosine kinase inhibitor which targets anaplastic lymphoma kinase (ALK), hepatocyte growth factor receptor (HGFR, c-Met), ROS (ROS1, c-ros), and Recepteur d'Origine Nantais (RON) tyrosine kinases. Crizotinib demonstrates potent growth inhibitory activity and induces apoptosis in tumour cell lines exhibiting ALK and ROS1 fusion events or ALK or MET gene amplification. Antitumour efficacy is dose-dependent. A validated assay should be used to confirm ALK-positive or ROS1-positive disease prior to treatment.[1-3]

PHARMACOKINETICS:

Oral Absorption	aqueous solubility is pH dependent; median time to peak concentration is 4 h; high fat meal reduces AUC and Cmax by ~14%	
Distribution	extensive distribution to tissues	
	cross blood brain barrier?	yes
	volume of distribution	1772 L (following IV administration)
	plasma protein binding	91% ; may be independent of drug concentration
Metabolism	primary metabolic pathways in humans: oxidation of piperidine ring to crizotinib lactam and O-desalkylation with subsequent Phase 2 conjugation of O-dealkylated metabolites; *in vitro* studies demonstrate CYP 3A4/5 are major enzymes involved in metabolic clearance	
	active metabolite(s)	crizotinib lactam (~2.5-8 fold less potent than parent)
	inactive metabolite(s)	O-desalkyl crizotinib and O-desalkyl crizotinib lactam
Excretion	mean apparent clearance may be lower at steady state, possibly due to autoinhibition of CYP 3A following repeated dosing	
	urine	22% (2% unchanged drug)
	feces	63% (53% unchanged drug)
	terminal half life	42 h
	clearance	65-100 L/h
Ethnicity	steady state Cmax and AUC were ~1.5-1.6 fold higher in Asians than non-Asians	

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:

*Lung cancer, non-small cell

*Health Canada approved indication

Other uses:

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SPECIAL PRECAUTIONS:

Contraindications:
- patients with congenital long QT syndrome or with persistent corrected electrocardiogram interval (QTc) of ≥500 msec[1]

Caution:
- ***vision disorders*** have been reported; ability to drive or operate machinery may be compromised.[1]
- ***bradycardia*** has been reported; caution is required in patients with a low heart rate at baseline, or who have a history of syncope, arrhythmia, other rhythm disorders, ischemic or congestive heart disease, or are taking other medications which decrease heart rate[1]
- ***QTc prolongation*** has been reported; caution is required in patients with a history of or predisposition to QTc prolongation or who are taking other medications known to prolong QTc interval. Obtain baseline ECG and correct electrolyte disturbances prior to treatment.[1]
- potentially ***phototoxic***; minimize exposure to sunlight and other UV emitting sources[1]

Special populations: Safety and efficacy in ***pediatric*** patients has not been established. In toxicology studies, decreased bone formation in growing long bones was observed in immature animals.[1]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in bacterial reverse mutation assays. Crizotinib is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests. A positive kinetochore assay suggests an aneugenic mechanism.[1]

Fertility: In toxicology studies in rats, reversible effects on male and female reproductive organs were seen, including testicular pachytene spermatocyte and single cell necrosis of ovarian follicles.[1]

Pregnancy: FDA Pregnancy Category D.[4] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Crizotinib has been shown to be fetotoxic, but not teratogenic in pregnant rats and rabbits. Adequate contraception is recommended during treatment and for 90 days following completion of treatment.[1]

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	disseminated intravascular coagulation (<1%)
	leukopenia (3-5%, severe <1%)
	lymphopenia (2-3%, severe 2%)
	neutropenia (5-9%, severe 3-6%); may require dose modification
cardiac	***bradycardia*** (4-11%)[1,7]; see paragraph following **Side Effects** table
	QT prolongation (<2%, severe 1%); see paragraph following **Side Effects** table

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
eye	***vision disorders*** (59-62%); see paragraph following **Side Effects** table
gastrointestinal	*emetogenic potential:* low-moderate[8]
	constipation (27-42%, severe ≤2%)[1,2]; primarily grade 1
	diarrhea (43-60%)[1,2]; primarily grade 1
	dyspepsia (2-8%)
	esophageal related disorder (4-11%); includes gastroesophageal reflux disease, odynophagia, esophageal pain or ulcer, esophagitis
	nausea (49-57%); primarily grade 1
	vomiting (35-43%); primarily grade 1
general disorders and administration site conditions	edema (28-31%)[1,2]
	fatigue (14-27%, severe 1-2%)
hepatobiliary	***hepatic failure*** (<1%); see paragraph following **Side Effects** table
investigations	***ALT increase*** (13-14%, severe 4-7%); see paragraph following **Side Effects** table
	AST increase (8-11%, severe <3%); see paragraph following **Side Effects** table
metabolism and nutrition	appetite decrease (17-21%)
nervous system	CNS hemorrhage (<1%)
	dizziness (13-22%, severe 1%)[1,2]
	dysgeusia (8-26%)[1,2]
	neuropathy (11-19%, severe <1%)[1,7]; see paragraph following **Side Effects** table
renal and urinary	renal cyst (1%, severe <1%); doesn't appear to be associated with renal impairment
respiratory, thoracic and mediastinal	cough (<4%)
	dyspnea (3-13%, severe 2-4%)[1,2]
	pneumonitis (1-2%, severe <2%); see paragraph following **Side Effects** table
skin and subcutaneous tissue	alopecia[2] (8%)
	rash (7-9%)
vascular	arteriosclerotic cardiovascular disease (<1%)
	deep vein thrombosis (<1%)
	hypotension (1-2%)

Adapted from standard reference[1] unless specified otherwise.

Symptomatic ***bradycardia*** may occur with crizotinib; heart rate less than 50 beats/min has been reported in up to 11% of patients.[7] Monitor heart rate and blood pressure regularly and, if possible, avoid or discontinue concurrent use of other medications known to cause bradycardia. For symptomatic, non-life threatening bradycardia, withhold crizotinib until asymptomatic or heart rate increases to greater than 60 beats/min. Consider dose reduction when treatment resumes. Permanently discontinue crizotinib for life-threatening bradycardia, unless associated with concurrent medications known to cause bradycardia or hypotension. In these patients, review and adjust concurrent therapy as necessary and withhold crizotinib until the patient is asymptomatic or heart rate increases to greater than

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60 beats/min; crizotinib may be restarted at 250 mg once daily with increased monitoring.[4,7] Refer to protocol by which patient is being treated.

Various ***neuropathies*** have been reported, including neuralgia, paresthesia, sensory disturbance, and peripheral motor and sensorimotor neuropathy. Most commonly, neuropathy is sensory in nature and grade one or two in severity.[1,7]

Severe, life-threatening or fatal treatment-related ***pneumonitis*** has been reported in about 2% of patients. Cases occurred within 2 months of treatment initiation. Monitor for pulmonary symptoms during treatment and hold crizotinib treatment if symptoms of pneumonitis occur. Permanently discontinue crizotinib if treatment-related pneumonitis is diagnosed.[1]

QT interval prolongation without accompanying arrhythmia has been observed with crizotinib, and may be exposure dependent. Periodic ECG and electrolyte monitoring is suggested. Crizotinib should be withheld until recovery for grade 3 QTc prolongation (increases of ≥500 msec) and dose reduced when therapy is resumed. Permanent discontinuation is recommended for patients who experience grade 4 QTc prolongation (increases of ≥500 msec or more than a 60 msec increase from baseline AND signs/symptoms of serious arrhythmias or torsades de pointes).[1] Refer to protocol by which patient is being treated.

Transaminase elevations are reported and generally occur within the first two months of treatment. Monitor for drug-induced ***hepatoxicity*** as fatalities due to hepatic failure have been reported. Routine monitoring of liver function tests should include a period of increased frequency of testing during the first two months of treatment, as well as regular monthly testing thereafter. More frequent retesting is also indicated following grade 2 (or greater) elevations of ALT, AST, or bilirubin. Hold crizotinib for grade 3 or 4 transaminase elevations. After recovery of transaminases to a grade 1 or baseline level, crizotinib may be resumed at the next lower dose level (e.g., 200 mg twice daily, 250 mg daily). Crizotinib should be permanently discontinued in patients who experience grade 2 (or greater) elevation in total bilirubin concurrently with grade 2 (or greater) transaminase elevation or who cannot tolerate crizotinib at 250 mg daily.[3]

Vision disorders, including diplopia, photopsia, blurry vision, impaired vision, and vitreous floaters, have been reported in 59-62% of patients. Greater than 95% of these patients had events that were considered mild in severity.[1] Events were most frequently described as trails of light following moving objects, particularly during changes in ambient lighting from dark to light. Median time to onset is 7-13 days, and the disorder often improves with length of time on treatment. Symptoms have rarely required treatment interruption/cessation. Consider ophthalmological evaluation if vision disorder is severe, persists, or worsens in severity. Crizotinib should be discontinued for new onset severe visual loss (i.e., best corrected vision less than 20/200 in one or both eyes.) The risks of resuming crizotinib following severe vision loss are not known. Patients experiencing vision disorders should be cautious when driving or operating machinery.[1,3,9]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
esomeprazole[10]	the extent of the change in total exposure of crizotinib is not considered clinically significant	pH dependent solubility; reduced crizotinib with increasing pH	starting dose adjustment is not required during concurrent therapy with proton pump inhibitors, H2 blockers or antacids
grapefruit juice[1,11]	may increase plasma level of crizotinib	may inhibit CYP 3A4 metabolism of crizotinib in the intestinal wall	avoid grapefruit and grapefruit juice for duration of treatment with crizotinib[1]
ketoconazole[1]	3 fold increase in crizotinib AUC; 1.4 fold increase in crizotinib Cmax	strong inhibition of CYP 3A4 by ketoconazole	avoid concurrent administration if possible

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AGENT	EFFECT	MECHANISM	MANAGEMENT
midazolam[1]	3.7 fold increase in midazolam AUC	moderate inhibition of CYP 3A by crizotinib	monitor for signs of toxicity due to midazolam
rifampin[1]	82% decrease in crizotinib AUC; 69% decrease in crizotinib Cmax	strong induction of CYP 3A4 by rifampin	avoid concurrent administration if possible

Drugs that prolong QT/QT_c interval or disrupt electrolyte levels should be avoided if possible during crizotinib therapy due to the risk of potentially fatal arrhythmias. Periodic monitoring of ECG and electrolytes is suggested.[1]

Crizotinib is a substrate and moderate inhibitor of CYP 3A. Avoid concurrent use of strong CYP 3A inhibitors and inducers as well as CYP 3A substrates with narrow therapeutic indices and/or associated with life-threatening arrhythmias.[1]

Crizotinib is an inhibitor of CYP 2B6 *in vitro*; clinical significance is unknown.[1]

Crizotinib is a substrate and inhibitor of p-glycoprotein; clinical significance is unknown.[1]

SUPPLY AND STORAGE:

Oral: Pfizer Canada Inc. supplies crizotinib as 200 mg and 250 mg hard gelatin capsules. Store at room temperature.[1]

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*:**

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

Oral[1,12]:

250 mg PO twice daily
Administer with food or on an empty stomach.

Concurrent radiation:

no information found

Dosage in myelosuppression:

modify according to protocol by which patient is being treated; if no guidelines available, refer to the following[1]:

- grade 3 toxicity: withhold crizotinib until recovery to grade 2 or less severity, then resume at same dose
- grade 4 toxicity: withhold crizotinib until recovery to grade 2 or less severity, then resume at 200 mg PO twice daily.
  In case of recurrence, withhold until recovery to grade 2 or less severity OR baseline, then resume at 250 mg PO once daily. Discontinue permanently in case of further grade 4 recurrence.

Dosage in renal failure:

- mild to moderate impairment (CrCl ≥30 mL/min): no adjustment required[1]
- severe impairment (CrCl<30 mL/min), not requiring dialysis: 50% dose reduction (to 250 mg once daily)[7]

$$\text{Calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{Serum Creatinine in } \mu\text{mol/L}}$$

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

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

Dosage in hepatic failure[3]:

	AST		Bilirubin	Starting Dose
mild	any	and	≤1.5xULN	100%
moderate	any	and	1.5-3xULN	80% (given as 200 mg BID)
severe	any	and	>3xULN	50% (given as 250 mg daily)

Dosage in dialysis: no published data, however physicochemical characteristics of drug suggest that drug removal is unlikely during dialysis[13]

Children: safety and efficacy not established[1]

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