Crizotinib: Drug information

(For additional information see "Crizotinib: Patient drug information ")

For abbreviations and symbols that may be used in Lexicomp (show table)

Brand Names: US

Xalkori

Brand Names: Canada

Xalkori

Pharmacologic Category

Antineoplastic Agent, Anaplastic Lymphoma Kinase Inhibitor; Antineoplastic Agent, Tyrosine Kinase Inhibitor

Dosing: Adult

Note: Crizotinib is associated with a moderate emetic potential; antiemetics may be needed to prevent nausea and vomiting.

Non-small cell lung cancer (NSCLC), metastatic (ALK- or ROS1-positive): Oral: 250 mg twice daily, continue treatment until disease progression or unacceptable toxicity

Missed doses: If a dose is missed, take as soon as remembered unless it is <6 hours prior to the next scheduled dose (skip the dose if <6 hours before the next dose); do not take 2 doses at the same time to make up for a missed dose. If vomiting occurs after dose, administer the next dose at the regularly scheduled time.

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

CrCl 30 to 89 mL/minute: No dosage adjustment necessary.

CrCl <30 mL/minute not requiring dialysis: Initial: 250 mg once daily.

Dosing: Hepatic Impairment

Hepatotoxicity **prior to** treatment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); crizotinib undergoes extensive hepatic metabolism and systemic exposure may be increased with impairment; use with caution.

Hepatotoxicity **during** treatment:

Grade 3 or 4 ALT or AST elevation (ALT or AST >5 x ULN) with ≤ grade 1 total bilirubin elevation (total bilirubin ≤1.5 x ULN): Withhold treatment until recovery to baseline or ≤ grade 1 (<3 x ULN), then resume at a reduced dose (200 mg twice daily).

Recurrent grade 3 or 4 ALT or AST elevation with ≤ grade 1 total bilirubin elevation: Withhold treatment until recovery to baseline or ≤ grade 1, then resume at the next lower reduced dose (250

mg once daily).

Recurrent grade 3 or 4 ALT or AST elevation on 250 mg once daily: Permanently discontinue.

Grade 2, 3, or 4 ALT or AST elevation (ALT or AST >3 x ULN) with concurrent grade 2, 3, or 4 total bilirubin elevation (>1.5 x ULN) in the absence of cholestasis or hemolysis: Permanently discontinue.

Dosing: Adjustment for Toxicity

Note: If dose reduction is necessary, reduce dose to 200 mg orally twice daily; if necessary, further reduce to 250 mg once daily. If unable to tolerate 250 mg once daily, permanently discontinue therapy.

Hematologic toxicity (except lymphopenia, unless lymphopenia is associated with clinical events such as opportunistic infection):

Grade 3 toxicity (WBC 1,000 to 2,000/mm^3, ANC 500 to 1,000/mm^3, platelets 25,000 to 50,000/mm^3), grade 3 anemia: Withhold treatment until recovery to ≤ grade 2, then resume at the same dose and schedule.

Grade 4 toxicity (WBC <1,000/mm^3, ANC <500/mm^3, platelets <25,000/mm^3), grade 4 anemia: Withhold treatment until recovery to ≤ grade 2, then resume at 200 mg twice daily.

Recurrent grade 4 toxicity on 200 mg twice daily: Withhold treatment until recovery to ≤ grade 2, then resume at 250 mg once daily.

Recurrent grade 4 toxicity on 250 mg once daily: Permanently discontinue.

Nonhematologic toxicities:

Cardiovascular toxicities:

QTc prolongation:

Grade 3 QTc prolongation (QTc >500 msec without life-threatening signs or symptoms) on at least 2 separate ECGs: Withhold treatment until recovery to baseline or to ≤ grade 1 (QTc <481 msec), then resume at 200 mg twice daily.

Recurrent grade 3 QTc prolongation at 200 mg twice daily: Withhold treatment until recovery to baseline or to ≤ grade 1, then resume at 250 mg once daily.

Recurrent grade 3 QTc prolongation at 250 mg once daily: Permanently discontinue.

Grade 4 QTc prolongation: QTc >500 msec or ≥60 msec change from baseline with life-threatening symptoms: Permanently discontinue.

Bradycardia:

Grade 2 bradycardia (symptomatic with medical intervention indicated) or grade 3 bradycardia (severe/medically significant with intervention indicated): Withhold until recovery to asymptomatic bradycardia or to a heart rate of ≥60 beats/minute and evaluate concomitant medications. If contributing concomitant medication is identified and discontinued (or dose adjusted), then resume crizotinib at the previous dose. If no contributing concomitant medication is identified (or cannot be discontinued or dose adjusted), resume crizotinib at a reduced dose.

Grade 4 bradycardia (life-threatening with urgent intervention indicated): Withhold until recovery to asymptomatic bradycardia or to a heart rate of ≥60 beats/minute and evaluate concomitant medications. If contributing concomitant medication is identified and discontinued (or dose adjusted), then resume crizotinib at 250 mg once daily with frequent monitoring. If no contributing concomitant medication is identified, permanently discontinue crizotinib. Permanently discontinue for recurrence.

Hepatotoxicity: Refer to dosage adjustment in hepatic impairment.

Ocular toxicity: Visual loss (grade 4 visual disorder) or new onset of severe visual loss (best corrected vision less than 20/200 in one or both eyes): Discontinue during evaluation of severe vision loss.

Pulmonary toxicity: Interstitial lung disease (ILD)/pneumonitis (any grade; not attributable to disease progression, infection, other pulmonary disease or radiation therapy): Permanently discontinue.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, Oral:

Xalkori: 200 mg, 250 mg

Generic Equivalent Available (US)

No

Prescribing and Access Restrictions

Available through specialty pharmacies. Further information may be obtained from the manufacturer, Pfizer, at 1-877-744-5675, or at http://www.pfizerpro.com

Administration

Crizotinib is associated with a moderate emetic potential; antiemetics may be needed to prevent nausea and vomiting.

Swallow capsules whole (do not crush, dissolve, or open capsules). Administer with or without food. If vomiting occurs after dose, administer the next dose at the regularly scheduled time.

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage. NIOSH recommends single gloving for administration of intact tablets or capsules (NIOSH 2016).

Use **Non-small cell lung cancer, metastatic:** Treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive (as detected by an approved test) or are ROS1-positive

Medication Safety Issues

Sound-alike/look-alike issues:

Crizotinib may be confused with afatinib, alectinib, brigatinib, cabozantinib, ceritinib, cobimetinib, erlotinib, gefitinib, PONATinib

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Adverse Reactions

>10%:

Cardiovascular: Edema (31% to 49%), bradycardia (5% to 14%)

Central nervous system: Fatigue (27% to 29%), neuropathy (19% to 25%; includes dysesthesia, gait disturbance, hypoesthesia, muscular weakness, neuralgia, peripheral neuropathy, parasthesia, peripheral sensory neuropathy, polyneuropathy, burning sensation in skin), headache (22%), dizziness (18% to 22%)

Dermatologic: Skin rash (9 % to 11%)

Endocrine & metabolic: Hypophosphatemia (28% to 32%), hypokalemia (18%)

Gastrointestinal: Diarrhea (60% to 61%), nausea (55% to 56%), vomiting (46% to 47%), constipation (42% to 43%), decreased appetite (30%), abdominal pain (26%), dysgeusia (26%), dyspepsia (8% to 14%)

Genitourinary: Decreased estimated GFR (eGFR) (<90 mL/min/1.73 m^2: 76%; <60 mL/min/1.73 m^2: 38%; <30 mL/min/1.73 m^2: 4%)

Hematologic & oncologic: Neutropenia (49% to 52%; grades 3/4: 11% to 12%), lymphocytopenia (48% to 51%; grades 3/4: 7% to 9%)

Hepatic: Increased serum ALT (76% to 79%), increased serum AST (61% to 66%)

Neuromuscular & skeletal: Limb pain (16%)

Ophthalmic: Visual disturbance (60% to 71%; onset: <2 weeks; includes blurred vision, diplopia, photophobia, photopsia, visual acuity decreased, visual brightness, visual field defect, visual impairment, vitreous floaters)

Respiratory: Upper respiratory tract infection (26% to 32%)

Miscellaneous: Fever (19%)

1% to 10%:

Cardiovascular: Pulmonary embolism (6%), prolonged Q-T interval on ECG (5% to 6%), syncope (1% to 3%)

Endocrine & metabolic: Weight loss (10%), weight gain (8%), diabetic ketoacidosis (≤2%),

decreased plasma testosterone (1%; hypogonadism)

Gastrointestinal: Dysphagia (10%), esophagitis (2% to 6%)

Hepatic: Hepatic failure (1%)

Infection: Sepsis (≤5%)

Neuromuscular & skeletal: Muscle spasm (8%)

Renal: Renal cyst (3% to 5%)

Respiratory: Adult respiratory distress syndrome (≤5%), interstitial pulmonary disease (≤5%; grades 3/4: 1%; includes acute respiratory distress syndrome, pneumonitis), pneumonia (≤5%), respiratory failure (≤5%), dyspnea (2%)

Frequency not defined:

Cardiovascular: Cardiac arrhythmia, septic shock

<1%, postmarketing, and/or case reports: Hepatotoxicity

Contraindications

There are no contraindications listed in the manufacturer's US labeling.

Canadian labeling: Known hypersensitivity to crizotinib or any component of the formulation; congenital long QT syndrome or with persistent Fridericia-corrected QT interval (QTcF) ≥500 msec

Warnings/Precautions

Concerns related to adverse effects:

• Bradycardia: Symptomatic bradycardia may occur; heart rate <50 beats/minute has occurred. If possible, avoid concurrent use with other agents known to cause bradycardia (eg, beta blockers, nondihydropyridine calcium channel blockers, clonidine, digoxin). Monitor heart rate and blood pressure regularly. If symptomatic bradycardia (not life-threatening) occurs, withhold treatment until recovery to asymptomatic bradycardia or to a heart rate of ≥60 beats/minute, evaluate concurrent medications, and potentially reduce crizotinib dose. Permanently discontinue for life-threatening bradycardia due to crizotinib; if life-threatening bradycardia occurs and concurrent medications associated with bradycardia can be discontinued or dose adjusted, restart crizotinib at a reduced dose (with frequent monitoring).

• Gastrointestinal toxicity: Crizotinib is associated with a moderate emetic potential; antiemetics may be needed to prevent nausea and vomiting.

• Hepatotoxicity: Fatalities due to crizotinib-induced hepatotoxicity have occurred. Grade 3 or 4 ALT increases (usually asymptomatic and reversible) have been observed in clinical trials. May require dosage interruption and/or reduction; permanent discontinuation was necessary in some cases. Elevations in ALT or AST >5 x ULN were observed; concurrent ALT or AST elevations ≥3 x ULN and total bilirubin elevations ≥2 x ULN (without alkaline phosphatase elevations) occurred rarely. Transaminase elevation onset generally was within 2 months of treatment initiation. Monitor liver function tests, including ALT, AST, and total bilirubin, every 2 weeks during the first 2 months of

therapy, then monthly and as clinically necessary.

• Ocular toxicities: Ocular toxicities (eg, blurred vision, diplopia, photophobia, photopsia, visual acuity decreased, visual brightness, visual field defect, visual impairment, and/or vitreous floaters) commonly occur. Onset is generally within 1 week of treatment initiation. Grade 4 visual field defect with vision loss had been reported (rare); optic atrophy and optic nerve disorder have been reported as potential causes of vision loss. Discontinue with new onset of severe visual loss (best corrected vision less than 20/200 in one or both eyes). Obtain ophthalmic evaluation (including best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography, and other evaluations as appropriate). The risks of restarting crizotinib after severe vision loss have not been evaluated; the decision to resume therapy should consider the potential benefits of treatment.

• Pulmonary toxicity: Severe, life-threatening, and potentially fatal interstitial lung disease (ILD)/pneumonitis has been associated with crizotinib. Onset was generally within 3 months of treatment initiation. Monitor for pulmonary symptoms which may indicate ILD/pneumonitis; exclude other potential causes (eg, disease progression, infection, other pulmonary disease, or radiation therapy). Permanently discontinue if treatment-related ILD/pneumonitis is confirmed.

• QT prolongation: QTc prolongation has been observed. Monitor ECG and electrolytes in patients with heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications known to prolong the QT interval. May require treatment interruption, dosage reduction, or discontinuation. Avoid use in patients with congenital long QT syndrome.

Disease-related concerns:

• Hepatic impairment: Use with caution in patients with hepatic impairment; has not been studied; patients with ALT or AST >2.5 times ULN (>5 times ULN if due to liver metastases) and total bilirubin >1.5 times ULN were excluded from studies. Crizotinib is extensively metabolized in the liver and liver impairment is likely to increase crizotinib levels.

• Renal impairment: Reduce initial dose in patients with severe renal impairment not requiring dialysis.

Concurrent drug therapy issues:

• Drug-drug/drug-food interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information. Avoid concomitant use with strong CYP3A4 inhibitors and inducers and with CYP3A4 substrates.

Other warnings/precautions:

• ALK or ROS1 positivity: Approved for use only in patients with metastatic non-small cell lung cancer (NSCLC) who test positive for the abnormal anaplastic lymphoma kinase (ALK) gene or ROS1 rearrangements. The Vysis ALK break-apart FISH probe kit is approved to test for the ALK gene abnormality. An approved test is not currently available for detection of ROS1 rearrangements; in clinical trials, ROS1 positivity was determined by laboratory-developed break-apart FISH or RT-PCR.

Metabolism/Transport Effects

Substrate of CYP3A4 (major), P-glycoprotein; **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; **Inhibits** CYP3A4

(moderate), OCT1, OCT2

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Alfentanil: Crizotinib may increase the serum concentration of Alfentanil. *Risk X: Avoid combination*

AmLODIPine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of AmLODIPine. *Risk C: Monitor therapy*

Apixaban: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Apixaban. *Risk C: Monitor therapy*

Aprepitant: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Aprepitant. *Risk X: Avoid combination*

ARIPiprazole: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of ARIPiprazole. Management: Monitor for increased aripiprazole pharmacologic effects. Aripiprazole dose adjustments may or may not be required based on concomitant therapy and/or indication. Consult full interaction monograph for specific recommendations. *Risk C: Monitor therapy*

Asunaprevir: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Asunaprevir. *Risk X: Avoid combination*

Avanafil: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Avanafil. Management: The maximum avanafil adult dose is 50 mg per 24-hour period when used together with a moderate CYP3A4 inhibitor. Patients receiving such a combination should also be monitored more closely for evidence of adverse effects. *Risk D: Consider therapy modification*

Blonanserin: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Blonanserin. *Risk C: Monitor therapy*

Bosentan: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Bosentan: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Bosentan. Management: Concomitant use of both a CYP2C9 inhibitor and a CYP3A inhibitor or a single agent that inhibits both enzymes with bosentan is likely to cause a large increase in serum concentrations of bosentan and is not recommended. See monograph for details. *Risk C: Monitor therapy*

Bosutinib: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Bosutinib. *Risk X: Avoid combination*

Bradycardia-Causing Agents: May enhance the bradycardic effect of other Bradycardia-Causing Agents. *Risk C: Monitor therapy*

Bretylium: May enhance the bradycardic effect of Bradycardia-Causing Agents. Bretylium may also enhance atrioventricular (AV) blockade in patients receiving AV blocking agents. *Risk C: Monitor therapy*

Brexpiprazole: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Brexpiprazole. Management: The brexpiprazole dose should be reduced to 25% of usual if used together with both a moderate CYP3A4 inhibitor and a strong or moderate CYP2D6 inhibitor, or if a moderate CYP3A4 inhibitor is used in a CYP2D6 poor metabolizer. *Risk C: Monitor therapy*

Bromocriptine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Bromocriptine. Management: The bromocriptine dose should not exceed 1.6 mg daily with use of a moderate CYP3A4 inhibitor. The Cycloset brand specifically recommends this dose limitation, but other bromocriptine products do not make such specific recommendations. *Risk D: Consider therapy modification*

Budesonide (Systemic): CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Budesonide (Systemic). *Risk X: Avoid combination*

Budesonide (Topical): CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Budesonide (Topical). Management: Per US prescribing information, avoid this combination. Canadian product labeling does not recommend strict avoidance. If combined, monitor for excessive glucocorticoid effects as budesonide exposure may be increased. *Risk D: Consider therapy modification*

Cannabis: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Cannabis. More specifically, tetrahydrocannabinol and cannabidiol serum concentrations may be increased. *Risk C: Monitor therapy*

Ceritinib: Bradycardia-Causing Agents may enhance the bradycardic effect of Ceritinib. Management: If this combination cannot be avoided, monitor patients for evidence of symptomatic bradycardia, and closely monitor blood pressure and heart rate during therapy. *Risk X: Avoid combination*

Cilostazol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Cilostazol. Management: Consider reducing the cilostazol dose to 50 mg twice daily in adult patients who are also receiving moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

Cobimetinib: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Cobimetinib. Management: Avoid the concomitant use of cobimetinib and moderate CYP3A4 inhibitors. If concurrent short term (14 days or less) use cannot be avoided, reduce the cobimetinib dose to 20 mg daily. *Risk X: Avoid combination*

Colchicine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Colchicine. Management: Reduce colchicine dose as directed when using with a moderate CYP3A4 inhibitor, and increase monitoring for colchicine-related toxicity. Use extra caution in patients with impaired renal and/or hepatic function. *Risk D: Consider therapy modification*

Conivaptan: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

CycloSPORINE (Systemic): Crizotinib may increase the serum concentration of CycloSPORINE (Systemic). *Risk X: Avoid combination*

CYP3A4 Inducers (Moderate): May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May decrease the serum concentration of Crizotinib. *Risk X: Avoid combination*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Crizotinib. *Risk X: Avoid combination*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4

Substrates. **Exceptions:** Alitretinoin (Systemic); Praziquantel; Vinorelbine. *Risk C: Monitor therapy*

Dabrafenib: May decrease the serum concentration of CYP3A4 Substrates. Management: Seek alternatives to the CYP3A4 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). *Risk D: Consider therapy modification*

Dapoxetine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Dapoxetine. Management: The dose of dapoxetine should be limited to 30 mg/day when used together with a moderate inhibitor of CYP3A4. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deflazacort: CYP3A4 Inhibitors (Moderate) may increase serum concentrations of the active metabolite(s) of Deflazacort. Management: Administer one third of the recommended deflazacort dose when used together with a strong or moderate CYP3A4 inhibitor. *Risk D: Consider therapy modification*

Dihydroergotamine: Crizotinib may increase the serum concentration of Dihydroergotamine. *Risk X: Avoid combination*

Domperidone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Domperidone. *Risk X: Avoid combination*

DOXOrubicin (Conventional): CYP3A4 Inhibitors (Moderate) may increase the serum concentration of DOXOrubicin (Conventional). Management: Seek alternatives to moderate CYP3A4 inhibitors in patients treated with doxorubicin whenever possible. One U.S. manufacturer (Pfizer Inc.) recommends that these combinations be avoided. *Risk D: Consider therapy modification*

Dronabinol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Dronabinol. *Risk C: Monitor therapy*

Eletriptan: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eletriptan. Management: The use of eletriptan within 72 hours of a moderate CYP3A4 inhibitor should be avoided. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: When used concomitantly with moderate inhibitors of CYP3A4, eplerenone dosing recommendations vary by indication and international labeling. See full drug interaction monograph for details. *Risk D: Consider therapy modification*

Ergotamine: Crizotinib may increase the serum concentration of Ergotamine. *Risk X: Avoid combination*

Everolimus: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Everolimus. Management: Everolimus dose reductions are required for patients being treated for subependymal giant cell astrocytoma or renal cell carcinoma. See prescribing information for specific dose adjustment and monitoring recommendations. *Risk D: Consider therapy modification*

FentaNYL: Crizotinib may increase the serum concentration of FentaNYL. *Risk X: Avoid combination*

Flibanserin: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Flibanserin. *Risk X: Avoid combination*

Fosaprepitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Grapefruit Juice: May increase the serum concentration of Crizotinib. *Risk X: Avoid combination*

GuanFACINE: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of GuanFACINE. Management: Reduce the guanfacine dose by 50% when initiating this combination. *Risk D: Consider therapy modification*

Highest Risk QTc-Prolonging Agents: Moderate Risk QTc-Prolonging Agents may enhance the QTc-prolonging effect of Highest Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

HYDROcodone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of HYDROcodone. *Risk C: Monitor therapy*

Hydroxychloroquine: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

HydrOXYzine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of HydrOXYzine. Management: This combination is specifically contraindicated in some non-U.S. labeling. *Risk D: Consider therapy modification*

Ibrutinib: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ibrutinib. Management: If a moderate CYP3A inhibitor must be used, consider reducing the dose of ibrutinib to 140mg daily and monitor closely for signs of toxicity. *Risk X: Avoid combination*

Idelalisib: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Ifosfamide: CYP3A4 Inhibitors (Moderate) may decrease serum concentrations of the active metabolite(s) of Ifosfamide. *Risk C: Monitor therapy*

Imatinib: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Imatinib. *Risk C: Monitor therapy*

Ivabradine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ivabradine. *Risk X: Avoid combination*

Ivabradine: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

Ivacaftor: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ivacaftor. Management: Ivacaftor dose reductions are required; consult full monograph content for specific age- and weight-based recommendations. No dose adjustment is needed when using ivacaftor/lumacaftor with a moderate CYP3A4 inhibitor. *Risk D: Consider therapy modification*

Lacosamide: Bradycardia-Causing Agents may enhance the AV-blocking effect of Lacosamide. *Risk C: Monitor therapy*

Lomitapide: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Lomitapide. *Risk X: Avoid combination*

Lurasidone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Lurasidone.

Management: Lurasidone US labeling recommends reducing lurasidone dose by half with a moderate CYP3A4 inhibitor. Some non-US labeling recommends initiating lurasidone at 20 mg/day and limiting dose to 40 mg/day; avoid concurrent use of grapefruit products. *Risk D: Consider therapy modification*

Manidipine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Manidipine. *Risk C: Monitor therapy*

MiFEPRIStone: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

Mirodenafil: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Mirodenafil. *Risk C: Monitor therapy*

Moderate Risk QTc-Prolonging Agents: May enhance the QTc-prolonging effect of other Moderate Risk QTc-Prolonging Agents. Management: Avoid such combinations when possible. Use should be accompanied by close monitoring for evidence of QT prolongation or other alterations of cardiac rhythm. *Risk D: Consider therapy modification*

Naldemedine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Naldemedine. *Risk C: Monitor therapy*

Naloxegol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Naloxegol. *Risk X: Avoid combination*

Netupitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

NiMODipine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of NiMODipine. *Risk C: Monitor therapy*

Olaparib: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Olaparib. Management: Avoid use of moderate CYP3A4 inhibitors in patients being treated with olaparib. If such concurrent use cannot be avoided, the dose of olaparib should be reduced to 200 mg twice daily. *Risk X: Avoid combination*

OxyCODONE: CYP3A4 Inhibitors (Moderate) may enhance the adverse/toxic effect of OxyCODONE. CYP3A4 Inhibitors (Moderate) may increase the serum concentration of OxyCODONE. Serum concentrations of the active metabolite Oxymorphone may also be increased. *Risk C: Monitor therapy*

Palbociclib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

P-glycoprotein/ABCB1 Inhibitors: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Crizotinib may enhance the QTc-prolonging effect of Pimozide. Crizotinib may increase the serum concentration of Pimozide. *Risk X: Avoid combination*

Probucol: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

Promazine: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents (Indeterminate Risk and Risk Modifying): May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk C: Monitor therapy*

QuiNIDine: Crizotinib may enhance the QTc-prolonging effect of QuiNIDine. Crizotinib may increase the serum concentration of QuiNIDine. *Risk X: Avoid combination*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine adult dose to a maximum of 500 mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Rupatadine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Rupatadine. *Risk C: Monitor therapy*

Ruxolitinib: May enhance the bradycardic effect of Bradycardia-Causing Agents. Management: Ruxolitinib Canadian product labeling recommends avoiding use with bradycardia-causing agents to the extent possible. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Sarilumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

SAXagliptin: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of SAXagliptin. *Risk C: Monitor therapy*

Sildenafil: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Sildenafil. *Risk C: Monitor therapy*

Siltuximab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Simeprevir: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Simeprevir. *Risk X: Avoid combination*

Sirolimus: Crizotinib may increase the serum concentration of Sirolimus. *Risk X: Avoid combination*

Sonidegib: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Sonidegib. Management: Avoid concomitant use of sonidegib and moderate CYP3A4 inhibitors when possible. When concomitant use cannot be avoided, limit CYP3A4 inhibitor use to less than 14 days and monitor for sonidegib toxicity (particularly musculoskeletal adverse reactions). *Risk D: Consider therapy modification*

St John's Wort: May decrease the serum concentration of Crizotinib. *Risk X: Avoid combination*

Stiripentol: May increase the serum concentration of CYP3A4 Substrates. Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. *Risk D: Consider therapy modification*

Suvorexant: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Suvorexant. *Risk D: Consider therapy modification*

Tacrolimus (Systemic): Crizotinib may increase the serum concentration of Tacrolimus (Systemic). *Risk X: Avoid combination*

Tetrahydrocannabinol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Tetrahydrocannabinol. *Risk C: Monitor therapy*

Ticagrelor: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ticagrelor. *Risk C: Monitor therapy*

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Tofacitinib: May enhance the bradycardic effect of Bradycardia-Causing Agents. *Risk C: Monitor therapy*

Tolvaptan: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Tolvaptan. *Risk X: Avoid combination*

Trabectedin: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Trabectedin. *Risk X: Avoid combination*

Udenafil: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Udenafil. *Risk C: Monitor therapy*

Ulipristal: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ulipristal. Management: This is specific for when ulipristal is being used for signs/symptoms of uterine fibroids (Canadian indication). When ulipristal is used as an emergency contraceptive, patients receiving this combination should be monitored for ulipristal toxicity. *Risk X: Avoid combination*

Venetoclax: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Venetoclax. Management: Reduce the venetoclax dose by at least 50% in patients requiring these combinations. *Risk D: Consider therapy modification*

Vilazodone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Vilazodone. *Risk C: Monitor therapy*

Vindesine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Vindesine. *Risk C: Monitor therapy*

Vinflunine: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

Xipamide: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk C: Monitor therapy*

Zopiclone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Zopiclone. Management: The starting adult dose of zopiclone should not exceed 3.75 mg if combined with a moderate CYP3A4 inhibitor. Monitor patients for signs and symptoms of zopiclone toxicity if these agents are combined. *Risk D: Consider therapy modification*

Food Interactions Grapefruit juice may increase serum crizotinib levels. Management: Avoid grapefruit and grapefruit juice.

Pregnancy Implications Adverse events have been observed in animal reproduction studies. Based on the mechanism of action, crizotinib may cause fetal harm if administered during pregnancy. Women

of childbearing potential should use adequate contraception during treatment and for at least 45 days after the last crizotinib dose; males with female partners of reproductive potential should use condoms during treatment and for at least 90 days after the final dose. The Canadian labeling recommends adequate contraception during treatment and for at least 90 days after the last dose for both males and females.

Breast-Feeding Considerations It is not known if crizotinib is excreted in breast milk. Due to the potential for serious adverse reactions in the nursing infant, the manufacturer recommends against breast-feeding during treatment and for 45 days after the final dose.

Dietary Considerations Avoid grapefruit and grapefruit juice.

Monitoring Parameters ALK or ROS1 positivity; CBC with differential monthly and as clinically appropriate (monitor more frequently if grades 3 or 4 abnormalities observed or with fever or infection), liver function tests every 2 weeks for the first 2 months, then monthly and as clinically appropriate (monitor more frequently if grades 2, 3, or 4 abnormalities observed); renal function (baseline and periodic). Monitor pulmonary symptoms (for interstitial lung disease [ILD]/pneumonitis). Monitor heart rate and blood pressure; monitoring ECG and electrolytes in patients with heart failure, bradycardia, bradyarrhythmias, electrolyte abnormalities, or who are taking medications known to prolong the QT interval. Obtain ophthalmic evaluation (including best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography, and other evaluations as appropriate) if severe visual loss occurs.

Mechanism of Action Tyrosine kinase receptor inhibitor, which inhibits anaplastic lymphoma kinase (ALK), Hepatocyte Growth Factor Receptor (HGFR, c-MET), ROS1 (c-ros), and Recepteur d'Origine Nantais (RON). ALK gene abnormalities due to mutations or translocations may result in expression of oncogenic fusion proteins (eg, ALK fusion protein) which alter signaling and expression and result in increased cellular proliferation and survival in tumors which express these fusion proteins. Approximately 2% to 7% of patients with NSCLC have the abnormal echinoderm microtubule-associated protein-like 4, or EML4-ALK gene (which has a higher prevalence in never smokers or light smokers and in patients with adenocarcinoma). Inhibition of ALK, ROS1, and c-Met phosphorylation is concentration-dependent. Crizotinib selectively inhibits ALK tyrosine kinase, which reduces proliferation of cells expressing the genetic alteration.

Pharmacodynamics/Kinetics

Distribution: V_{ss}: 1772 L

Protein binding: 91%

Metabolism: Hepatic, via CYP3A4/5 (oxidation and dealkylation)

Bioavailability: 43% (range: 32% to 66%); bioavailability is reduced 14% with a high-fat meal

Half-life elimination: Terminal: 42 hours

Time to peak: 4 to 6 hours

Excretion: Feces (63%; 53% as unchanged drug); urine (22%; 2% as unchanged drug)

Pricing: US

Capsules (Xalkori Oral)

200 mg (60): $17815.04

250 mg (60): $17815.04

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names Ksalkori (UA); Xalkori (AE, AR, AT, AU, BE, CH, CL, CN, CY, CZ, DE, DK, EE, ES, FR, GB, HK, HR, HU, ID, IE, IL, IS, JP, KR, KW, LB, LT, LU, MT, MY, NL, NO, NZ, PE, PH, PL, PT, QA, RO, SA, SE, SG, SI, SK, TH, TR)

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