Ceritinib: Drug information

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

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

Brand Names: US

Zykadia

Brand Names: Canada

Zykadia

Pharmacologic Category

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

Dosing: Adult

Note: Ceritinib is associated with a moderate emetic potential (Roila 2016); antiemetics may be needed to prevent nausea and vomiting.

Non-small cell lung cancer (ALK-positive), metastatic: Oral: 750 mg once daily; continue until disease progression or unacceptable toxicity.

Missed doses: If a dose is missed, take the missed dose unless the next dose is due within 12 hours. If vomiting occurs, do not administer an additional dose, patients should continue with the next scheduled dose.

Dosage adjustment for concomitant therapy:

Strong CYP3A4 inhibitors: Avoid concomitant use of strong CYP3A inhibitors; if concurrent administration cannot be avoided, reduce ceritinib dose by approximately one-third (rounded to the nearest multiple of the 150 mg strength). After discontinuation of the strong CYP3A inhibitor, resume ceritinib therapy at the dose used prior to initiation of the CYP3A4 inhibitor.

Strong CYP3A4 inducers: Avoid concurrent use of strong CYP3A inducers (eg, carbamazepine, phenytoin, rifampin, and St John's wort) during treatment with ceritinib.

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

CrCl ≥30 to 90 mL/minute: No dosage adjustment is necessary.

CrCl <30 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Dosing: Hepatic Impairment

Preexisting mild impairment (total bilirubin ≤ULN and AST >ULN **or** total bilirubin >1 to 1.5 times ULN and any AST): No dosage adjustment is necessary.

Preexisting moderate or severe impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). Ceritinib is primarily metabolized and eliminated hepatically; exposure is likely increased in patients with hepatic impairment.

Hepatotoxicity during treatment:

ALT or AST >5 times ULN with total bilirubin ≤2 times ULN: Interrupt therapy until recovery to baseline or ALT/AST ≤3 times ULN, then resume with a 150 mg dose reduction.

ALT or AST >3 times ULN with total bilirubin >2 times ULN in the absence of cholestasis or hemolysis: Permanently discontinue therapy.

Dosing: Adjustment for Toxicity

Note: Over half of patients initiating treatment required at least 1 dose reduction; the median time to the first dose reduction was 7 weeks. Discontinue if patients are unable to tolerate 300 mg daily.

Cardiac:

Bradycardia:

Symptomatic bradycardia (not life-threatening): Interrupt therapy and evaluate concomitant medications known to cause bradycardia.

Upon recovery to asymptomatic bradycardia or to a heart rate ≥60 beats per minute, adjust the dose.

Alternatively, the following recommendations have been made: Upon recovery to asymptomatic bradycardia or to a heart rate ≥60 beats per minute. If concomitant medication is identified and discontinued or its dose adjusted, reinitiate ceritinib at its previous dose. If no concomitant medication is identified or if it is identified but not discontinued or not dose-adjusted, reinitiate ceritinib with the dose reduced by 150 mg (Zykadia Canadian product labeling 2016).

Symptomatic bradycardia (life-threatening or requiring intervention) in patients taking concomitant medications known to cause bradycardia/hypotension: Interrupt therapy until recovery to asymptomatic bradycardia or to a heart rate ≥60 beats per minute.

If the concomitant medication can be adjusted or discontinued, resume ceritinib therapy with the dose reduced by 150 mg.

Alternatively, the following recommendations have been made: If concomitant medication can be discontinued or its dose adjusted, resume ceritinib with the dose reduced by 300 mg; monitor frequently; permanently discontinue ceritinib for recurrence (Zykadia Canadian product labeling 2016).

Symptomatic bradycardia (life-threatening) in patients not taking concomitant medications known to cause bradycardia/hypotension: Permanently discontinue therapy.

QTc prolongation:

QTc interval >500 msec on at least 2 separate ECGs: Interrupt therapy until QTc interval is <481 msec or recovers to baseline if baseline QTc is ≥481 msec, then resume therapy with a 150 mg dose reduction.

QTc prolongation in combination with torsades de pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia: Permanently discontinue therapy.

Gastrointestinal:

Severe or intolerable nausea, vomiting, or diarrhea (despite appropriate management): Interrupt therapy until improved, then resume treatment with a 150 mg dose reduction.

Lipase or amylase elevation >2 times ULN: Interrupt therapy and monitor serum lipase and amylase; upon recovery to <1.5 times ULN, resume treatment with a 150 mg dose reduction.

Metabolic: Persistent hyperglycemia >250 mg/dL (despite optimal antihyperglycemic therapy): Interrupt therapy until hyperglycemia is adequately controlled, then resume therapy with a 150 mg dose reduction. If hyperglycemia cannot be controlled, discontinue ceritinib permanently.

Pulmonary: Treatment-related interstitial lung disease/pneumonitis (any grade): Permanently discontinue therapy.

Dosage Forms

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

Capsule, Oral:

Zykadia: 150 mg [contains fd&c blue #2 (indigotine)]

Generic Equivalent Available (US)

No

Administration

Ceritinib is associated with a moderate emetic potential (Roila 2016); antiemetics may be needed to prevent nausea and vomiting.

Administer orally on an empty stomach (at least 2 hours before or 2 hours after a meal).

Hazardous Drugs Handling Considerations

Hazardous agent (meets NIOSH 2016 criteria). This medication is not on the NIOSH (2016) list; however, it meets the criteria for a hazardous drug. Drugs are classified as hazardous based on their properties; the properties of a hazardous drug include one or more of the following characteristics: carcinogenic, teratogenic (or other developmental toxicity), reproductive toxicity, organotoxic at low doses, genotoxic, and/or new agents with structural or toxicity profiles similar to existing hazardous agents.

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 anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Medication Safety Issues

Sound-alike/look-alike issues:

Ceritinib may be confused with alectinib, brigatinib, cobimetinib, crizotinib

High alert medication:

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

Adverse Reactions

>10%:

Central nervous system: Fatigue (52%), neuropathy (17%; including paresthesia, muscular weakness, gait disturbance, peripheral neuropathy, hypoesthesia, peripheral sensory neuropathy, dysesthesia, neuralgia, peripheral motor neuropathy, hypotonia, polyneuropathy)

Dermatologic: Skin rash (16%; including maculopapular rash, acneiform dermatitis)

Endocrine & metabolic: Increased serum glucose (49%; grades 3/4: 13%), decreased serum phosphate (36%)

Gastrointestinal: Diarrhea (86%; grades 3/4: 6%), nausea (80%; grades 3/4: 4%), vomiting (60%; grades 3/4: 4%), abdominal pain (54%), decreased appetite (34%), constipation (29%), increased serum lipase (28%), disease of esophagus (16%; including dyspepsia, gastroesophageal reflux disease, dysphagia)

Hematologic & oncologic: Decreased hemoglobin (84%)

Hepatic: Increased serum ALT (80%; grades 3/4: 27%), increased serum AST (75%; grades 3/4: 13%), increased serum bilirubin (15%; grades 3/4: 1%)

Renal: Increased serum creatinine (58%)

1% to 10%:

Cardiovascular: Prolonged Q-T interval on ECG (4%; >60 msec increase from baseline: 3%; >500 msec: <1%), bradycardia (3%), sinus bradycardia (1%)

Ophthalmic: Visual disturbance (9%; including vision impairment, blurred vision, photopsia, accommodation disorder, presbyopia, reduced visual acuity)

Respiratory: Interstitial pulmonary disease (4%; grades 3/4: 3%)

Contraindications

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

Canadian labeling: Known hypersensitivity to ceritinib or any component of the formulation; congenital long QT syndrome or persistent Fridericia-corrected electrocardiogram interval (QTcF) of >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 adjust ceritinib dose. Permanently discontinue for life-threatening bradycardia due to ceritinib; if life-threatening bradycardia occurs and concurrent medications associated with bradycardia can be discontinued or dose adjusted, restart ceritinib at a reduced dose (with frequent monitoring).

• Gastrointestinal toxicity: Diarrhea, nausea, vomiting, or abdominal pain occurred in the majority of patients in clinical trials; over one-third of patients required dose reductions due to severe or persistent gastrointestinal toxicity. Manage symptoms medically with appropriate therapy (eg, antidiarrheals, antiemetics, fluid replacement) as indicated. May require therapy interruption and dosage reduction. Ceritinib is associated with a moderate emetic potential (Roila 2016); antiemetics may be needed to prevent nausea and vomiting. If vomiting occurs, do not administer an additional dose; continue with the next scheduled dose.

• Hepatotoxicity: Hepatotoxicity has been observed in patients treated with ceritinib in clinical trials, including ALT levels >5 times ULN in over one-quarter of patients. Concurrent ALT elevations >3 times ULN with total bilirubin >2 times ULN (with normal alkaline phosphatase) occurred rarely. Monitor liver function tests (eg, ALT, AST, total bilirubin) monthly and as clinically necessary, more frequently in patients who develop transaminase abnormalities. May require therapy interruption, dosage reduction, and/or discontinuation.

• Hyperglycemia: Hyperglycemia, including grade 3 and 4 toxicity, has been observed in ceritinib-treated patients. The risk of grade 3 or 4 hyperglycemia increases significantly in diabetic patients or those with glucose intolerance; risk is also increased in patients receiving corticosteroids. Monitor fasting blood glucose levels at baseline and as clinically necessary, particularly in patients with diabetes. May require initiation or optimization of antihyperglycemic therapy. Temporarily interrupt therapy for hyperglycemia until adequately controlled; reduce dose upon recovery. If adequate glycemic control is not possible with medical management, permanently discontinue ceritinib.

• Pancreatitis: Although rare, pancreatitis (with fatality) has been reported. Grade 3 to 4 lipase and amylase elevations occurred in clinical trials. Monitor lipase and amylase prior to treatment and periodically during treatment as clinically necessary. May require treatment interruption and dose reduction.

• Pulmonary toxicity: Severe and life-threatening interstitial lung disease (ILD)/pneumonitis (some

fatal) may occur. Monitor for signs/symptoms of pulmonary toxicity; permanently discontinue in patients diagnosed with treatment-related ILD/pneumonitis.

• QTc prolongation: QTc interval prolongation has occurred in clinical studies, and may be concentration-dependent. QT prolongation may lead to an increased risk for ventricular tachyarrhythmias (eg, torsades de pointes) or sudden death. Avoid use in patients with congenital long QTc syndrome. Correct electrolyte abnormalities prior to initiating therapy. Periodically monitor ECG and electrolytes in patients with heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications known to prolong the QTc interval. QT prolongation may require treatment interruption, dosage reduction, or discontinuation. Permanently discontinue in patients who develop QTc interval prolongation in combination with torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia.

Disease-related concerns:

• Hepatic impairment: Use with caution in patients with hepatic impairment (has not been studied in patients with moderate or severe impairment). Ceritinib is metabolized and eliminated hepatically; systemic exposure and toxicities may be increased in patients with hepatic dysfunction.

Concurrent drug therapy issues:

• Drug-drug 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.

• Drugs affecting gastric pH: In vitro studies indicate that ceritinib solubility and bioavailability may be decreased at higher pH; concurrent use with proton pump inhibitors, H_2-receptor antagonists, or antacids has not been evaluated.

Metabolism/Transport Effects

Substrate of CYP3A4 (major), P-glycoprotein; **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; **Inhibits** CYP2C9 (moderate), CYP3A4 (strong)

Drug Interactions

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

Ado-Trastuzumab Emtansine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Ado-Trastuzumab Emtansine. Specifically, strong CYP3A4 inhibitors may increase concentrations of the cytotoxic DM1 component. *Risk X: Avoid combination*

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

Alitretinoin (Systemic): CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alitretinoin (Systemic). Management: Consider reducing the alitretinoin dose to 10 mg when used together with strong CYP3A4 inhibitors. Monitor for increased alitretinoin effects/toxicities if combined with a strong CYP3A4 inhibitor. *Risk D: Consider therapy modification*

Almotriptan: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Almotriptan. Management: Limit initial almotriptan adult dose to 6.25 mg and maximum adult dose to 12.5 mg/24-hrs when used with a strong CYP3A4 inhibitor. Avoid concurrent use in patients with impaired hepatic or

renal function. *Risk D: Consider therapy modification*

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

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

Antidiabetic Agents: Hyperglycemia-Associated Agents may diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

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

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

ARIPiprazole: CYP3A4 Inhibitors (Strong) may increase the serum concentration of ARIPiprazole. Management: See full interaction monograph for details. *Risk D: Consider therapy modification*

ARIPiprazole Lauroxil: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of ARIPiprazole Lauroxil. Management: Please refer to the full interaction monograph for details concerning the recommended dose adjustments. *Risk D: Consider therapy modification*

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

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

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

Axitinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Axitinib. Management: Avoid concurrent use of axitinib with any strong CYP3A inhibitor whenever possible. If a strong CYP3A inhibitor must be used with axitinib, a 50% axitinib dose reduction is recommended. *Risk X: Avoid combination*

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

Bedaquiline: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Bedaquiline. Management: Limit the duration of concomitant administration of bedaquiline with CYP3A4 inhibitors to no more than 14 days, unless the benefit of continued administration is judged to outweigh the possible risks. Monitor for toxic effects of bedaquiline. *Risk D: Consider therapy modification*

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

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

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

Bosentan: CYP3A4 Inhibitors (Strong) 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*

Bosentan: CYP2C9 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 (Strong) may increase the serum concentration of Bosutinib. *Risk X: Avoid combination*

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*

Brentuximab Vedotin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Brentuximab Vedotin. Specifically, concentrations of the active monomethyl auristatin E (MMAE) component may be increased. *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 (Strong) may increase the serum concentration of Brexpiprazole. Management: Reduce brexpiprazole dose to 50% of usual with a strong CYP3A4 inhibitor; reduce to 25% of usual if used with both a moderate CYP3A4 inhibitor and a CYP2D6 inhibitor, or if a strong CYP3A4 inhibitor is used in a CYP2D6 poor metabolizer. *Risk D: Consider therapy modification*

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

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

Budesonide (Nasal): CYP3A4 Inhibitors (Strong) may increase the serum concentration of Budesonide (Nasal). *Risk C: Monitor therapy*

Budesonide (Oral Inhalation): CYP3A4 Inhibitors (Strong) may increase the serum concentration of Budesonide (Oral Inhalation). *Risk C: Monitor therapy*

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

Budesonide (Topical): CYP3A4 Inhibitors (Strong) 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*

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

Cabazitaxel: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Cabazitaxel.

Management: Concurrent use of cabazitaxel with strong inhibitors of CYP3A4 should be avoided when possible. If such a combination must be used, consider a 25% reduction in the cabazitaxel dose. *Risk D: Consider therapy modification*

Cabozantinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Cabozantinib. Management: Avoid use of a strong CYP3A4 inhibitor with cabozantinib if possible. If combined, cabozantinib dose adjustments are recommended and vary based on the cabozantinib product used and the indication for use. See monograph for details. *Risk D: Consider therapy modification*

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

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

Cannabis: CYP2C9 Inhibitors (Moderate) may increase the serum concentration of Cannabis. More specifically, tetrahydrocannabinol serum concentrations may be increased. *Risk C: Monitor therapy*

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

Cariprazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Cariprazine. Management: Cariprazine dose reductions of 50% are required; specific recommended management varies slightly for those stable on cariprazine versus those just starting cariprazine. See prescribing information or full interaction monograph for details. *Risk D: Consider therapy modification*

Cilostazol: CYP3A4 Inhibitors (Strong) 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 strong inhibitors of CYP3A4. *Risk D: Consider therapy modification*

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

Colchicine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Colchicine. Management: Colchicine is contraindicated in patients with impaired renal or hepatic function who are also receiving a strong CYP3A4 inhibitor. In those with normal renal and hepatic function, reduce colchicine dose as directed. *Risk D: Consider therapy modification*

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

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

Corticosteroids: May enhance the hyperglycemic effect of Ceritinib. **Exceptions:** Hydrocortisone (Ophthalmic). *Risk C: Monitor therapy*

Corticosteroids (Systemic): CYP3A4 Inhibitors (Strong) may increase the serum concentration of Corticosteroids (Systemic). **Exceptions:** MethylPREDNISolone; PrednisoLONE (Systemic); PrediSONE. *Risk C: Monitor therapy*

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

CYP2C9 Substrates: Ceritinib may increase the serum concentration of CYP2C9 Substrates. Management: Concurrent use of ceritinib with a CYP2C9 substrate that has a narrow therapeutic index (e.g., warfarin, phenytoin) should be avoided when possible. *Risk C: Monitor therapy*

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

CYP3A4 Inducers (Strong): May decrease the serum concentration of Ceritinib. *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 Ceritinib. Management: If such combinations cannot be avoided, the ceritinib dose should be reduced by approximately one-third (to the nearest 150 mg). Resume the prior ceritinib dose after cessation of the strong CYP3A4 inhibitor. *Risk X: Avoid combination*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. **Exceptions:** Alitretinoin (Systemic); AmLODIPine; Buprenorphine; Gefitinib; HYDROcodone; Praziquantel; Telithromycin; Vinorelbine. *Risk D: Consider therapy modification*

CYP3A4 Substrates: Ceritinib may increase the serum concentration of CYP3A4 Substrates. Management: Use of ceritinib with a narrow therapeutic index CYP3A substrate (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus) should be avoided when possible. *Risk C: Monitor therapy*

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

Daclatasvir: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Daclatasvir. Management: Decrease the daclatasvir dose to 30 mg once daily if combined with a strong CYP3A4 inhibitor. No dose adjustment is needed when daclatasvir is used with darunavir/cobicistat. *Risk D: Consider therapy modification*

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

Dasatinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Dasatinib. Management: Use of this combination should be avoided; consider reducing dasatinib dose if a strong CYP3A4 inhibitor must be used. If using dasatinib 100 mg/day, consider reduction to 20 mg/day; if using dasatinib 140 mg/day, consider reduction to 40 mg/day. *Risk D: Consider therapy modification*

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

Deflazacort: CYP3A4 Inhibitors (Strong) 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*

Delamanid: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Delamanid. Management: Increase electrocardiogram (ECG) monitoring frequency if delamanid is combined with strong CYP3A4 inhibitors because the risk for QTc interval prolongation may be increased. Continue frequent ECG assessments throughout the full delamanid treatment period. *Risk D: Consider therapy*

modification

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

DOCEtaxel: CYP3A4 Inhibitors (Strong) may increase the serum concentration of DOCEtaxel. Management: Avoid the concomitant use of docetaxel and strong CYP3A4 inhibitors when possible. If combined use is unavoidable, consider a 50% docetaxel dose reduction and monitor for increased docetaxel toxicities. *Risk D: Consider therapy modification*

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

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

DOXOrubicin (Conventional): CYP3A4 Inhibitors (Strong) may increase the serum concentration of DOXOrubicin (Conventional). Management: Seek alternatives to strong 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: CYP2C9 Inhibitors (Moderate) may increase the serum concentration of Dronabinol. *Risk C: Monitor therapy*

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

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

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

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

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

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

Erlotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Erlotinib. Management: Avoid use of this combination when possible. When the combination must be used, monitor the patient closely for the development of severe adverse reactions, and if such severe reactions occur, reduce the erlotinib dose (in 50 mg decrements). *Risk D: Consider therapy modification*

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

Eszopiclone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eszopiclone. Management: Limit the eszopiclone dose to 2 mg daily when combined with strong CYP3A4 inhibitors and monitor for increased eszopiclone effects and toxicities (eg, somnolence, drowsiness, CNS depression). *Risk D: Consider therapy modification*

Etizolam: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Etizolam. Management: Consider use of lower etizolam doses when using this combination; specific recommendations concerning dose adjustment are not available. Monitor clinical response to the combination closely. *Risk D: Consider therapy modification*

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

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. Management: Monitor patients closely for several days following initiation of this combination, and adjust fentanyl dose as necessary. *Risk D: Consider therapy modification*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4 mg daily in adult patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

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

Fluticasone (Nasal): CYP3A4 Inhibitors (Strong) may increase the serum concentration of Fluticasone (Nasal). *Risk X: Avoid combination*

Fluticasone (Oral Inhalation): CYP3A4 Inhibitors (Strong) may increase the serum concentration of Fluticasone (Oral Inhalation). Management: Use of orally inhaled fluticasone propionate with strong CYP3A4 inhibitors is not recommended. Use of orally inhaled fluticasone furoate with strong CYP3A4 inhibitors should be done with caution. Monitor patients using such a combination more closely. *Risk D: Consider therapy modification*

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

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

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

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

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 (Strong) 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 (Strong) 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 (Strong) may increase the serum concentration of Ibrutinib. Management: If a strong CYP3A inhibitor must be used short-term (e.g. antifungals and antibiotics for 7 days or less),

consider stopping ibrutinib until the CYP3A inhibitor is no longer needed. *Risk X: Avoid combination*

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

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

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

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

Irinotecan Products: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Irinotecan Products. Specifically, serum concentrations of SN-38 may be increased. CYP3A4 Inhibitors (Strong) may increase the serum concentration of Irinotecan Products. *Risk X: Avoid combination*

Isavuconazonium Sulfate: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Isavuconazonium Sulfate. Specifically, CYP3A4 Inhibitors (Strong) may increase isavuconazole serum concentrations. Management: Combined use is considered contraindicated per US labeling. Lopinavir/ritonavir (and possibly other uses of ritonavir doses less than 400 mg every 12 hours) is treated as a possible exception to this contraindication despite strongly inhibiting CYP3A4. *Risk X: Avoid combination*

Ivabradine: CYP3A4 Inhibitors (Strong) 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 (Strong) may increase the serum concentration of Ivacaftor. Management: Ivacaftor dose reductions are required; consult full monograph content for specific age- and weight-based recommendations. *Risk D: Consider therapy modification*

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

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

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

Lapatinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Lapatinib. Management: If an overlap in therapy cannot be avoided, consider reducing lapatinib adult dose to 500 mg/day during, and within 1 week of completing, treatment with the strong CYP3A4 inhibitor. *Risk X: Avoid combination*

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

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

Levomilnacipran: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Levomilnacipran. Management: Do not exceed a maximum adult levomilnacipran dose of 80 mg/day in patients also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

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

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

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

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

Manidipine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Manidipine. Management: Consider avoiding concomitant use of manidipine and strong CYP3A4 inhibitors. If combined, monitor closely for increased manidipine effects and toxicities. Manidipine dose reductions may be required. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Maraviroc. Management: Reduce the adult dose of maraviroc to 150 mg twice daily when used with a strong CYP3A4 inhibitor. Do not use maraviroc with strong CYP3A4 inhibitors in patients with Clcr less than 30 mL/min. *Risk D: Consider therapy modification*

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

MethylPREDNISolone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of MethylPREDNISolone. Management: Consider methylprednisolone dose reduction in patients receiving strong CYP3A4 inhibitors and monitor for increased steroid related adverse effects. *Risk D: Consider therapy modification*

Midostaurin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Midostaurin. Management: Seek alternatives to the concomitant use of midostaurin and strong CYP3A4 inhibitors if possible. If concomitant use cannot be avoided, monitor patients for increased risk of adverse reactions. *Risk D: Consider therapy modification*

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

Mirodenafil: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Mirodenafil. Management: Consider using a lower dose of mirodenafil when used with strong CYP3A4 inhibitors. Monitor for increased mirodenafil effects/toxicities with the use of this combination. *Risk D: Consider therapy modification*

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 (Strong) may increase the serum concentration of Naldemedine. *Risk*

C: Monitor therapy

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

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

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

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

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

Olaparib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Olaparib. Management: Avoid use of strong CYP3A4 inhibitors in patients being treated with olaparib. If such concurrent use cannot be avoided, the dose of olaparib should be reduced to 150 mg twice daily. *Risk X: Avoid combination*

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

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

OxyCODONE: CYP3A4 Inhibitors (Strong) may enhance the adverse/toxic effect of OxyCODONE. CYP3A4 Inhibitors (Strong) may increase the serum concentration of OxyCODONE. Serum concentrations of the active metabolite oxymorphone may also be increased. *Risk D: Consider therapy modification*

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

Panobinostat: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Panobinostat. Management: Reduce the panobinostat dose to 10 mg when it must be used with a strong CYP3A4 inhibitor. *Risk D: Consider therapy modification*

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

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

PAZOPanib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of PAZOPanib. Management: Avoid concurrent use of pazopanib with strong inhibitors of CYP3A4 whenever possible. If it is not possible to avoid such a combination, reduce pazopanib adult dose to 400 mg. Further dose reductions may also be required. *Risk D: Consider therapy modification*

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 (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

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

PONATinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of PONATinib. Management: Per ponatinib U.S. prescribing information, the adult starting dose of ponatinib should be reduced to 30 mg daily during treatment with any strong CYP3A4 inhibitor. *Risk D: Consider therapy modification*

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

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

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

PrednisoLONE (Systemic): CYP3A4 Inhibitors (Strong) may increase the serum concentration of PrednisoLONE (Systemic). *Risk C: Monitor therapy*

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

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*

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

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

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

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

Red Yeast Rice: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Red Yeast Rice. Specifically, concentrations of lovastatin and related compounds found in Red Yeast Rice may be increased. *Risk X: Avoid combination*

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

Repaglinide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Repaglinide. Management: The addition of a CYP2C8 inhibitor to this drug combination may substantially increase the magnitude of increase in repaglinide exposure. *Risk C: Monitor therapy*

Retapamulin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Retapamulin. Management: Avoid this combination in patients less than 2 years old. No action is required in other populations. *Risk C: Monitor therapy*

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

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

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

Ruxolitinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ruxolitinib. Management: This combination should be avoided under some circumstances. See monograph for details. *Risk D: Consider therapy modification*

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

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

SAXagliptin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of SAXagliptin. Management: Saxagliptin U.S. product labeling recommends limiting saxagliptin adult dose to 2.5 mg/day when used with a strong CYP3A4 inhibitor. Monitor for increased saxagliptin levels/effects. A similar recommendation is not made in the Canadian product labeling. *Risk D: Consider therapy modification*

Sildenafil: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sildenafil. Management: Use of sildenafil for pulmonary hypertension should be avoided with strong CYP3A4 inhibitors. When used for erectile dysfunction, starting adult dose should be reduced to 25 mg. Maximum adult dose with ritonavir or cobicistat is 25 mg per 48 hours. *Risk D: Consider therapy modification*

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

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

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

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

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

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

St John's Wort: May decrease the serum concentration of Ceritinib. *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 (Strong) may increase the serum concentration of Suvorexant. *Risk X: Avoid combination*

Tacrolimus (Systemic): CYP3A4 Inhibitors (Strong) may increase the serum concentration of Tacrolimus (Systemic). Management: Monitor clinical tacrolimus response closely and frequently monitor tacrolimus serum concentrations with concurrent use of any strong CYP3A4 inhibitor. Tacrolimus dose reductions and/or prolongation of the dosing interval will likely be required. *Risk D: Consider therapy modification*

Tadalafil: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Tadalafil. Management: Recommendations regarding use of tadalafil in patients also receiving strong CYP3A4 inhibitors may vary based on indication and/or international labeling. Consult appropriate product labeling. *Risk D: Consider therapy modification*

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

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

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

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

Tetrahydrocannabinol: CYP2C9 Inhibitors (Moderate) may increase the serum concentration of Tetrahydrocannabinol. *Risk C: Monitor therapy*

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

Ticagrelor: CYP3A4 Inhibitors (Strong) may decrease serum concentrations of the active metabolite(s) of Ticagrelor. CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ticagrelor. *Risk X: Avoid combination*

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

Tofacitinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Tofacitinib. Management: Reduce the adult dose of tofacitinib to 5 mg daily in patients receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Tolterodine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Tolterodine. Management: The maximum recommended adult dose of tolterodine is 2 mg/day when used together with a strong CYP3A4 inhibitor. *Risk D: Consider therapy modification*

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

Toremifene: CYP3A4 Inhibitors (Strong) may enhance the adverse/toxic effect of Toremifene. CYP3A4 Inhibitors (Strong) may increase the serum concentration of Toremifene. *Risk X: Avoid combination*

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

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

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

Ulipristal: CYP3A4 Inhibitors (Strong) 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 combo should be monitored for ulipristal toxicity. *Risk X: Avoid combination*

Valbenazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Valbenazine. Management: Reduce the valbenazine dose to 40 mg daily when combined with strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Vardenafil: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Vardenafil. Management: Recommendations regarding concomitant use of vardenafil with strong CYP3A4 inhibitors may vary depending on brand name (e.g., Levitra, Staxyn) or by international labeling. See full drug interaction monograph for details. *Risk D: Consider therapy modification*

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

Venetoclax: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Venetoclax. Management: These combinations are contraindicated during venetoclax initiation and ramp-up. In patients receiving steady venetoclax doses after completing ramp-up, reduce the venetoclax by at least 75% if strong CYP3A4 inhibitor use cannot be avoided. *Risk D: Consider therapy modification*

Vilazodone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Vilazodone. Management: Limit maximum adult vilazodone dose to 20 mg/day in patients receiving strong CYP3A4 inhibitors. The original vilazodone dose can be resumed following discontinuation of the strong CYP3A4 inhibitor. *Risk D: Consider therapy modification*

VinCRIStine (Liposomal): CYP3A4 Inhibitors (Strong) may increase the serum concentration of VinCRIStine (Liposomal). *Risk X: Avoid combination*

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

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

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

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

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

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

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

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

Food Interactions

A high-fat meal increases AUC and C_{max} by 73% and 41%, respectively and a low-fat meal increases AUC and C_{max} by 58% and 43%, respectively; systemic exposure when administered with a meal may exceed that of a typical dose, and may result in increased toxicity. Management: Administer on an empty stomach, at least 2 hours before or after a meal.

Grapefruit and grapefruit juice may inhibit the metabolism of ceritinib and increase its systemic exposure. Management: Avoid grapefruit juice during therapy.

Pregnancy Risk Factor

D (show table)

Pregnancy Implications

Adverse events were observed in animal reproduction studies. Based on its mechanism of action, ceritinib may cause fetal harm if administered to a pregnant woman. Women of reproductive potential should use effective contraception during treatment and for at least 2 weeks following therapy discontinuation.

Breast-Feeding Considerations

It is not known if ceritinib is excreted in breast milk. Due to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended by the manufacturer.

Dietary Considerations

Avoid grapefruit and grapefruit juice.

Monitoring Parameters

ALK positivity; renal function, liver function (ALT, AST, total bilirubin monthly and as clinically necessary, more frequently in patients who develop transaminase abnormalities), fasting blood glucose (baseline and as clinically necessary), lipase and amylase (baseline and periodically as clinically necessary); electrolytes (baseline and periodically thereafter); cardiac monitoring (heart rate and QTc interval; ECG in patients with heart failure, bradyarrhythmias, electrolyte abnormalities, or on concomitant medications known to prolong the QTc interval); blood pressure; signs/symptoms of gastrointestinal, pulmonary toxicity, and/or pancreatitis.

Mechanism of Action

Potent inhibitor of anaplastic lymphoma kinase (ALK), a tyrosine kinase involved in the pathogenesis of non-small cell lung cancer. 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. ALK inhibition reduces proliferation of cells expressing the genetic alteration. Ceritinib also inhibits insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and ROS1. Ceritinib has

demonstrated activity in crizotinib-resistant tumors in NSCLC xenograft models.

Pharmacodynamics/Kinetics

Absorption: AUC and C_{max} increased 73% and 41%, respectively, when administered with a high-fat meal, and 58% and 43%, respectively when taken with a low-fat meal (when compared to fasting)

Distribution: 4,230 L (following a single dose), with a small preferential distribution to red blood cells versus plasma

Protein binding: 97% to human plasma proteins

Metabolism: Primarily hepatic via CYP3A

Half-life elimination: 41 hours

Time to peak: ~4 to 6 hours

Excretion: Feces (~92% with 68% as unchanged drug); urine (~1%)

Pricing: US

Capsules (Zykadia Oral)

150 mg (70): $8444.58

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

Zykadia (AR, AT, AU, CZ, DE, DK, EE, FI, FR, HK, HR, HU, IL, JP, KR, LT, NO, PT, SE, SG, SI, SK); Zykadiia (GB)

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