Crizotinib (krih-zoh-tin-ib)

Classification
Therapeutic: antineoplastics
Pharmacologic: kinase inhibitors

Pregnancy Category D

Indications
Locally advanced/metastatic non-small cell lung cancer (NSCLC) that is positive for anaplastic lymphoma kinase (ALK).

Action
Inhibits receptor tyrosine kinases including anaplastic lymphoma kinase (ALK), Hepatocyte Growth Factor Receptor (HGFR, c-Met), and Recepteur d'Origine Nantais (RON).

Therapeutic Effects:
Decreased spread of lung cancer.

Pharmacokinetics
Absorption:
43% absorbed following oral administration.

Distribution:
Extensively distributed to tissues.

Metabolism and Excretion:
Mostly metabolized by the liver (CYP3A4/5 enzyme system), also acts as an inhibitor of CYP3A. 53% excreted in feces unchanged, 2.3% eliminated unchanged in urine.

Half-life:
42 hr.

TIME/ACTION PROFILE (blood levels)
ROUTE ONSET PEAK DURATION
PO unknown 4–6 hr unknown

Contraindications/Precautions
Contraindicated in:
- Concurrent use of strong inhibitors/inducers of the CYP3A enzyme system; Congenital long QT syndrome; OB: May cause fetal harm; Lactation: Breast feeding should be avoided.

Use Cautiously in:
- Heart failure, bradyarrhythmias, electrolyte abnormalities, concurrent medications that prolong QT interval, risk of arrhythmias; Asian patients (↑ blood levels); Hepatic impairment; Severe renal impairment. Patients with child-bearing potential. Pedi: Safety and effectiveness not established.

Adverse Reactions/Side Effects
CNS:
fatigue, headache, insomnia.

EENT:
visual disturbances.

Resp:
PNEUMONITIS.

CV:
QTC interval prolongation, bradycardia, edema, chest pain.

GI:
HEPATOTOXICITY, constipation, diarrhea, nausea, vomiting, abdominal pain, dysgeusia, ↑ appetite, stomatitis.

Derm:
rash.

Neuro:
neuropathy.

Misc:
fever.

Interactions
Drug-Drug:
- Concurrent use of strong CYP3A inhibitors including atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, methadone, methicillin, ritonavir, saquinavir, telithromycin, and voriconazole may ↓ levels and should be avoided. Concurrent use of strong CYP3A inducers including carbamazepine, phenobarbital, phenytoin, rifampin, and rifabutin may ↑ levels and effectiveness and should be avoided. Antacids, H₂ blockers, and proton pump inhibitors may ↓ levels. Beta-blockers, vasopressor, dilators, digoxin, and cholestyramine may ↑ risk of bradycardia, avoid concurrent use, if possible.

Drug-Natural Products:
- Concurrent use of St. John’s wort may ↓ levels and effectiveness and should be avoided.

Drug-Food:
- Grapefruit or grapefruit juice may ↓ levels and should be avoided.

Route/Dosage
PO (Adults):
- 250 mg twice daily; dose adjusted according to tolerance, toxicity or adverse effects.

PO (Adults): CCr 30 mL/min (not on dialysis)—250 mg once daily.

NURSING IMPLICATIONS
Assessment
● Assess respiratory function (lung sounds, dyspnea, oxygen saturation) periodically during therapy.

Nursing Considerations
- May cause fluid retention (swelling, edema, weight gain) periodically during therapy. If any Grade of pneumonitis occurs, permanently discontinue.
Assess for signs and symptoms of neuropathy (burning, dysesthesia, hyperesthesia, hypoesthesia, neuralgia, paresthesia, peripheral neuropathy sensory and motor) periodically during therapy. Usually Grade 1.

- Monitor ECG periodically during therapy in patients with HF, bradyarrhythmias, electrolyte imbalances, or taking medications that may prolong QT interval. If Grade 3 QTc prolongation occurs, withhold until recovery to Grade 1, then resume at 200 mg twice daily. If Grade 4 QTc prolongation occurs, permanently discontinue. If symptomatic bradycardia occurs, withhold dose until heart rate returns to ≥60 bpm. Evaluate contributing medications; if contributing medication is identified and dose reduced or discontinued, return to previous dose of crizotinib once heart rate ≥60 bpm and/or bradycardia is asymptomatic. If no contributing medication is identified or dose modifications are not made, rechallenge as a reduced dose once heart rate ≥60 bpm and/or bradycardia is asymptomatic. If bradycardia is life-threatening and no contributing medication identified, discontinue crizotinib. If contributing medication is identified and dose is reduced or discontinued, reduce crizotinib dose to 250 mg once daily with frequent monitoring once heart rate ≥60 bpm and/or bradycardia is asymptomatic.

- Lab Test Considerations: Monitor CBC with differential monthly and as clinically indicated; more frequently if Grade 3 or 4 toxicities occur. If Grade 3 hematologic toxicity occurs, withhold dose until recovery to Grade 2, then resume at same dose schedule. If Grade 4 hematologic toxicity occurs, withhold until recovery to Grade 2, then resume at 200 mg twice daily. Max dose: 300 mg twice daily. Thrombocytopenia, thrombocytopathy, and lymphopenia.

- Monitor liver function tests monthly and as clinically indicated; more frequently if Grade 2, 3, or 4 abnormalities occur. If Grade 3 or 4 AST or ALT with Grade 1 total bilirubin occurs, withhold until recovery to Grade 1 or baseline, then resume at 200 mg twice daily. If Grade 2, 3, or 4 AST or ALT with concurrent Grade 2, 3, or 4 total bilirubin (with no cholestasis or hemolysis), permanently discontinue.

Potential Nursing Diagnoses

- Impaired gas exchange (Indications)

Implementation

- PO: Administer twice daily without regard to food. Swallow capsules whole, do not crush, dissolve, or open.

Patient/Family Teaching

- Instruct patient to take crizotinib as directed; do not change dose or stop taking without consulting health care professional. Take missed doses as soon as remembered within 6 hrs of next dose. If >6 hr to next dose, skip dose and return to regular schedule; do not double doses. Advise patient to read Patient Information leaflet before starting and with each Rx refill in case of changes. Advise patient to avoid eating grapefruit or drinking grapefruit juice during therapy.
- Caution patient that dizziness and visual disorders may occur. Advise patient to avoid driving or other activities requiring alertness until response to medication is known. Visual disturbances generally start within 2 wks of therapy. Instruct patient to notify health care professional if flashes of light or new or worse vision-related visual disturbances or ophthalmological evaluation should be considered.
- Advise patient to notify health care professional immediately if symptoms of weakness, fatigue, anorexia, nausea, vomiting, abdominal pain (especially RUQ abdominal pain), jaundice, dark urine, generalized pruritus, and bleeding occur, especially in combination with fever and rash.
- Instruct patient that nausea, diarrhea, constipation, and constipation are common side effects. Standard anti-emetic, antidiarrheal, and laxative medications are usually effective.
- Instruct patient to notify health care professional of all Rx or OTC medications, vitamins, or herbal products being taken and consult health care professional before taking any new medications.
- Instruct women of childbearing age and their partners to use effective contraception during and for at least 90 days following discontinuation of therapy and to avoid breast feeding during therapy.

Evaluation/Desired Outcomes

- Decrease spread of lung cancer.
- Decrease risk of CNS disease.
- Decrease risk of CNS disease.

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