Crizonil™

Crizotinib INN

Jenphar Bangladesh | جنفار بنغلاديش

Composition:
Crizonil™ 250 Capsule: Each capsule contains Crizotinib INN 250 mg.

Pharmacology:
Crizotinib is an inhibitor of receptor tyrosine kinases including ALK, Hepatocyte Growth Factor Receptor (HGFR, c-Met), ROS1 (c-ros) and Recepteur d'Origine Nantais (RON). Crizotinib demonstrated concentration-dependent inhibition of ALK, ROS1 and c-Met phosphorylation in cell-based assays using tumor cell lines.
Crizotinib induces apoptosis and inhibits proliferation and ALK-mediated signaling in ALCL-derived cell lines (containing NPM-ALK).

Indications:
Crizotinib is a kinase inhibitor indicated for the treatment of-
1. Patients with metastatic non-small cell lung cancer (mNSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive.
2. Pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive.
3. Adult and pediatric patients 1 year of age and older with unresectable, recurrent, or refractory inflammatory myofibroblastic tumor (IMT) that is ALK-positive.

Dose & administration:

Table 1: Recommended Dosage of Crizotinib

Indication	Recommended Dosage of Crizotinib	Duration of Treatment
ALK- or ROS1-Positive mNSCLC	Adults: 250 mg orally twice daily	Until disease progression or unacceptable toxicity
Relapsed or Refractory, Systemic ALK-Positive ALCL	Pediatric Patients and Young Adults: 280 mg/m² orally twice daily	
Unresectable, Recurrent, or Refractory ALK-Positive IMT	Adults: 250 mg orally twice daily	
	Pediatric Patients: 280 mg/m² orally twice daily	

Table 2. Recommended Crizotinib Dosage for Pediatric and Young Adult Patients with ALCL and for Pediatric Patients with IMT

Body Surface Area	Recommended Crizotinib Dosage
0.60 – 0.80 m²	200 mg orally twice daily
0.81 – 1.16 m²	250 mg orally twice daily
1.17 – 1.51 m²	400 mg orally twice daily
1.52 – 1.69 m²	450 mg orally twice daily
1.70 m² or greater	500 mg orally twice daily
The recommended dosage for patients less than 1 year of age or with a BSA less than 0.60 m² has not been established	

Concomitant Treatments for Pediatric and Young Adult Patients with ALCL or Pediatric Patients with IMT: Provide standard antiemetic and antidiarrheal agents for gastrointestinal toxicities. Antiemetics are recommended prior to and during treatment with Crizotinib to prevent nausea and vomiting.

Dosage Modifications for Adverse Reactions:
Adult Patients with ALK- or ROS1-positive Metastatic NSCLC or Adult Patients with ALK-positive IMT:
• First dose reduction: Crizotinib 200 mg taken orally twice daily
• Second dose reduction: Crizotinib 250 mg taken orally once daily
• Permanently discontinue if unable to tolerate Crizotinib 250 mg taken orally once daily

Pediatric and Young Adult Patients with ALK-positive ALCL or Pediatric Patients with ALK-positive IMT:

Table 3. Recommended Dose Reductions for Crizotinib in Pediatric & Young Adult Patients with ALCL or Pediatric Patients with IMT

Body Surface Area	First Dose Reduction	Second Dose Reduction
	Dose	Dose
0.60 – 0.80 m²	250 mg Once daily	Permanently discontinue
0.81 – 1.16 m²	200 mg Twice daily	250 mg Once daily
1.17 – 1.69 m²	250 mg Twice daily	200 mg Twice daily
1.70 m² or greater	400 mg Twice daily	250 mg Twice daily
Permanently discontinue in patients who are unable to tolerate Crizotinib after 2 dose reductions		

Contra-indication:
None

Warnings & precautions:
Hepatotoxicity: Fatal hepatotoxicity has occurred. Monitor with periodic liver testing. Temporarily suspend, dose reduce, or permanently discontinue Crizotinib.
Interstitial Lung Disease (ILD)/Pneumonitis: Permanently discontinue in patients with ILD/pneumonitis.
QT Interval Prolongation: Monitor electrocardiograms and electrolytes in patients who have a history of or predisposition for QTc prolongation, or who are taking medications that prolong QT. Temporarily suspend, dose reduce, or permanently discontinue Crizotinib.
Bradycardia: Crizotinib can cause bradycardia. Monitor heart rate and blood pressure regularly. Temporarily suspend, dose reduce, or permanently discontinue Crizotinib.
Severe Visual Loss: Crizotinib can cause visual changes including severe visual loss. Discontinue Crizotinib in patients with severe visual loss.
Gastrointestinal Toxicity in Pediatric & Young Adult Patients with ALCL or Pediatric Patients with IMT: Crizotinib can cause severe nausea, vomiting, diarrhea, and stomatitis. Provide standard antiemetic and antidiarrheal agents. Temporarily suspend, dose reduce, or permanently discontinue Crizotinib.
Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception.

Side effects:
The most common adverse reactions (≥25%) in patients with NSCLC are vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory infection, dizziness and neuropathy.
The most common adverse reactions (≥35%) in patients with ALCL, excluding laboratory abnormalities are diarrhea, vomiting, nausea, vision disorder, headache, musculoskeletal pain, stomatitis, fatigue, decreased appetite, pyrexia, abdominal pain, cough and pruritus. Grade 3-4 laboratory abnormalities (≥15%) are neutropenia, lymphopenia and thrombocytopenia.
The most common adverse reactions (≥35%) in adult patients with IMT are vision disorders, nausea and edema. The most common adverse reactions (≥35%) in pediatric patients with IMT are vomiting, nausea, diarrhea, abdominal pain, rash, vision disorder, upper respiratory tract infection, cough, pyrexia, musculoskeletal pain, fatigue, edema, constipation and headache.

Use in Special Population:
Pregnancy: Based on findings from animal studies and its mechanism of action, Crizotinib can cause fetal harm when administered to a pregnant woman. There are no available data on the use of Crizotinib during pregnancy.
Lactation: There is no information regarding the presence of Crizotinib or its metabolites in human milk or the effects on the breastfed child or on milk production. Because of the potential for adverse reactions in breastfeed children, advise women not to breastfeed during treatment with Crizotinib and for 45 days after the final dose.
Females and Males of Reproductive Potential: Advise females of reproductive potential to use effective contraception during treatment with Crizotinib and for at least 45 days after the final dose.
Pediatric Use: The safety and effectiveness of Crizotinib have been established in pediatric patients 12 months of age and older with relapsed or refractory, systemic ALK-positive ALCL or with unresectable, recurrent or refractory ALK positive IMT. The safety and effectiveness have not been established in pediatric patients younger than 12 months of age with ALCL or with IMTor in any pediatric patients with NSCLC.
The safety and effectiveness of Crizotinib in combination with chemotherapy have not been established in patients with newly diagnosed ALCL.
Geriatric Use: No overall differences in safety or effectiveness were observed between these patients and younger patients.
Hepatic Impairment: Crizotinib concentrations increased in patients with pre-existing moderate (any AST and total bilirubin greater than 1.5 times ULN and less than or equal to 3 times ULN) or severe (any AST and total bilirubin greater than 3 times ULN) hepatic impairment. Reduce Crizotinib dosage in patients with moderate or severe hepatic impairment. No dose adjustment is recommended in patients with pre-existing mild hepatic impairment (AST > ULN and total bilirubin less than or equal to 1 times ULN or any AST and total bilirubin greater than 1 times ULN but less than or equal to1.5 times ULN)
Renal Impairment: No dose adjustment is recommended in patients with mild to moderate renal impairment (CLcr 30 to 89 mL/min).

Drug interactions:
Strong CYP3A Inhibitors: Concomitant use of Crizotinib with strong CYP3A inhibitors increases Crizotinib plasma concentrations, which may increase the risk of adverse reactions of Crizotinib. Avoid concomitant use or reduce the dose of Crizotinib. Avoid grapefruit or grapefruit juice which may also increase plasma concentrations of crizotinib. Use caution with concomitant use of moderate CYP3A inhibitors.
Strong CYP3A Inducers: Concomitant use of Crizotinib with strong CYP3A inducers decreases Crizotinib plasma concentrations which may decrease the efficacy of Crizotinib. Avoid concomitant use.
CYP3A Substrates: Concomitant use of crizotinib increases plasma concentrations of CYP3A substrates which may increase the risk of adverse reactions of these substrates. Avoid concomitant use or decrease the CYP3A substrate dosage.

Overdose:
There have been no known cases of Crizotinib overdose. There is no antidote for Crizotinib. However, if overdose is suspected, seek emergency medical attention.

Storage:
Store in a cool and dry place below 30° C, protect from light. Keep out of the reach of children.

Packing:
Crizonil™ 250 Capsule: Each box contains 30 capsules and one packet silica gel in a sealed HDPE container.

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Manufactured by:
Jenphar Bangladesh Ltd.
Sreepur, Gazipur, Bangladesh.