AlkiXen
Crizotinib 250 mg capsules

Everest

COMPOSITION
ALKIXEN capsule: Each capsule contains Crizotinib INN 250 mg.

PHARMACOLOGY
Mechanism of Action:
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). Translocations can affect the ALK gene resulting in the expression of oncogenic fusion proteins. The formation of ALK fusion proteins results in activation and dysregulation of the gene's expression and signaling which can contribute to increased cell proliferation and survival in tumors expressing these proteins. Crizotinib demonstrated concentration-dependent inhibition of ALK, ROS1, and c-Met phosphorylation in cell-based assays using tumor cell lines and demonstrated antitumor activity in mice bearing tumor xenografts that expressed echinoderm microtubule-associated protein-like 4 (EML4)-or nucleophosmin (NPM)-ALK fusion proteins or c-Met.

Pharmacokinetic Properties
Following Crizotinib 250 mg twice daily, steady-state was reached within 15 days and remained stable, with a median accumulation ratio of 4.8. Steady-state observed minimum concentration (C_{min}) and AUC increased in a greater than dose-proportional manner over the dose range of 200 mg to 300 mg twice daily (0.8 to 1.2 times the approved recommended dosage).

Absorption
A single Crizotinib dose was absorbed with median time to achieve peak concentration of 4 to 6 hours, and the mean absolute bioavailability of Crizotinib was 43% (range: 32% to 66%).

Effect of food
A high-fat meal reduced Crizotinib $AUC_{0\text{-}INF}$ and maximum observed plasma concentration (C_{max}) by approximately 14%.

Distribution
The geometric mean volume of distribution (V_{ss}) of Crizotinib was 1772L following a single intravenous dose. Protein binding of Crizotinib is 91% and is independent of drug concentration in vitro. Crizotinib is a substrate for P-glycoprotein (P-gp) in vitro. The blood-to-plasma concentration ratio is approximately 1.

Elimination
The mean apparent plasma terminal half-life of Crizotinib was 42 hours following single doses of Crizotinib in patients. The mean apparent clearance (CL/F) of Crizotinib was lower at steady-state (60 L/h) after 250 mg twice daily than after a single 250 mg oral dose (100 L/h).

Metabolism
Crizotinib is predominantly metabolized by CYP3A.

Excretion
Following administration of a single oral 250 mg dose of radiolabeled Crizotinib dose to healthy subjects, 63% (53% as unchanged) of the administered dose was recovered in feces and 22% (2.3% as unchanged) in urine.

INDICATIONS AND USAGE
Crizotinib is a kinase inhibitor indicated for the treatment of
• Patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1
• Positive as detected by an FDA-approved test. 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
• Limitations of Use: The safety and efficacy of Crizotinib have not been established in older adults with relapsed or refractory systemic ALK-positive ALCL.

DOSAGE AND ADMINISTRATION
Patient Selection
Select patients for the treatment of metastatic NSCLC with Crizotinib based on the presence of ALK or ROS1 positivity in tumor specimens.

Recommended Dosage for ALK- or ROS1-Positive Metastatic Non-Small Cell Lung Cancer
The recommended dosage of Crizotinib for patients with NSCLC is 250 mg orally twice daily, with or without food, until disease progression or no longer tolerated by the patient.

Recommended Dosage for Relapsed or Refractory, Systemic ALK-Positive Anaplastic Large Cell Lymphoma
The recommended dosage of Crizotinib for patients with ALCL is 280 mg/m^2 orally twice daily until disease progression or unacceptable toxicity. The recommended dosage of Crizotinib is based on body surface area (BSA) is provided in Table 1. If needed, attain the desired dose by combining different strengths of Crizotinib capsules.

Table 1. Recommended Crizotinib Dosage for Patients with ALCL

Body Surface Area *	Recommended Crizotinib Dosage
0.60 – 0.80 m^2	200 mg orally twice daily
0.81 – 1.16 m^2	250 mg orally twice daily
1.17 – 1.51 m^2	400 mg orally twice daily
1.52 – 1.69 m^2	450 mg orally twice daily
1.70 m^2 or greater	500 mg orally twice daily

* The recommended dosage for patients with a BSA less than 0.60 m2 has not been established.

Concomitant Treatments for Patients with ALCL
Provide standard antiemetic and antidiarrheal agents for gastrointestinal toxicities. Antiemetics are recommended prior to and during treatment with Crizotinib to prevent nausea and vomiting. Consider intravenous or oral hydration for patients at risk of dehydration, and replace electrolytes as clinically indicated.

Dosage Modifications for Adverse Reactions
Recommended Dosage Reductions

ALK- or ROS1-positive metastatic NSCLC
The recommended dose reductions for adverse reactions in patients with metastatic NSCLC are:
• 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.

Systemic ALK-positive ALCL
The recommended dose reductions for adverse reactions in patients with ALCL are provided in Table 2.

Table 2. Recommended Dose Reductions for Crizotinib in Patients with ALCL

Body Surface Area	First Dose Reduction	Second Dose Reduction
0.60 – 0.80 m^2	200 mg orally twice daily	Permanently discontinue
0.81 – 1.16 m^2	250 mg orally twice daily	250 mg Once daily*
1.17 – 1.51 m^2	400 mg orally twice daily	200 mg Twice daily*
1.52 – 1.69 m^2	450 mg orally twice daily	250 mg Twice daily*

* Permanently discontinue in patients who are unable to tolerate Crizotinib after 2 dose reductions.

Patients with NSCLC
Modify the dosage for hematologic and non-hematologic adverse reactions for patients with NSCLC.

Patients with ALCL
Modify the dosage for hematologic and non-hematologic adverse reactions for patients with ALCL.

Dosage Modifications for Moderate and Severe Hepatic Impairment

ALK- or ROS1-positive metastatic NSCLC
The recommended dose of Crizotinib in patients with severe hepatic impairment (any AST and total bilirubin greater than 3 times ULN) is 250 mg orally once daily.

Systemic ALK-positive ALCL
The recommended dose of Crizotinib in patients with severe hepatic impairment (any AST and total bilirubin greater than 3 times ULN) is the second dose reduction based on BSA as shown in Table 2.

Dosage Modification for Severe Renal Impairment
ALK- or ROS1-positive metastatic NSCLC
The recommended dosage of Crizotinib in patients with severe renal impairment [creatinine clearance (CLcr) less than 30 mL/min, calculated using the modified Cockcroft-Gault equation] not requiring dialysis is 250 mg orally once daily.

Systemic ALK-positive ALCL
The recommended dosage of Crizotinib in patients with severe renal impairment (CLcr) less than 30 mL/min, calculated using the modified Cockcroft-Gault equation for adult patients and the Schwartz equation for pediatric patient's not requiring dialysis is the second dose reduction based on BSA as shown in Table 2.

Dosage Modification for Concomitant Use of Strong CYP3A Inhibitors
ALK- or ROS1-positive metastatic NSCLC
Avoid concomitant use of strong CYP3A inhibitors. If concomitant use of strong CYP3A inhibitors is unavoidable, reduce the dose of Crizotinib to 250 mg orally once daily.

Systemic ALK-positive ALCL
Avoid concomitant use of strong CYP3A inhibitors. If concomitant use of strong CYP3A inhibitors is unavoidable, reduce the dose of Crizotinib to the second dose reduction based on BSA as shown in Table 2.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Hepatotoxicity
Monitor liver function tests, including ALT, AST, and total bilirubin, every 2 weeks during the first 2 months of treatment, then once a month, and as clinically indicated, with more frequent repeat testing for increased liver transaminases, alkaline phosphatase, or total bilirubin in patients who develop increased transaminases. Withhold, reduce dose, or permanently discontinue Crizotinib for hepatotoxicity as recommended.

Interstitial Lung Disease/Pneumonitis
Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Exclude other potential causes of ILD/pneumonitis, and permanently discontinue Crizotinib in patients diagnosed with drug-related ILD/pneumonitis.

QT Interval Prolongation
Avoid use of Crizotinib in patients with congenital long QT syndrome. Monitor ECGs and electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QT interval. Withhold, reduce dose, or permanently discontinue Crizotinib for QT/QTc interval prolongation as recommended.

Bradycardia
Avoid using Crizotinib in combination with other medications known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Monitor heart rate and blood pressure regularly. If bradycardia occurs, re-evaluate for the use of concomitant medications known to cause bradycardia. Withhold, reduce dose, or permanently discontinue Crizotinib for bradycardia as recommended.

Severe Visual Loss
There is insufficient information to characterize the risks of resumption of Crizotinib in patients who develop visual symptoms or visual loss. A decision to resume Crizotinib should consider the potential benefits versus risks to the patient.

Gastrointestinal Toxicity in Patients with ALCL
Provide standard antiemetic & antidiarrheal agents for gastrointestinal toxicities in patients with ALCL.

Embryo-Fetal Toxicity
Based on its mechanism of action, Crizotinib can cause fetal harm when administered to a pregnant woman.

SIDE EFFECTS
DRUG INTERACTIONS
- Strong CYP3A Inhibitors: Avoid concomitant use.
- Strong CYP3A Inducers: Avoid concomitant use.
- CYP3A Substrates: Avoid concomitant use with CYP3A substrates, where minimal concentration changes may lead to serious adverse reactions.

USE IN SPECIFIC POPULATIONS
Pregnancy
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.

Females and Males of Reproductive Potential
Pregnancy Testing:
Verify the pregnancy status of females of reproductive potential prior to initiating Crizotinib

Contraception:
Crizotinib can cause fetal harm when administered to a pregnant woman.

Females:
Advise females of reproductive potential to use effective contraception during treatment with Crizotinib and for at least 45 days after the final dose.

Males:
Advise males partners to use condoms during treatment with Crizotinib and for at least 90 days after the final dose.

Infertility:
Based on reproductive organ findings in animals, Crizotinib may cause reduced fertility in females and males of reproductive potential.

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.

Geriatric Use
In clinical studies, no overall differences in safety or effectiveness were observed in between older and younger patients.

Hepatic Impairment
Reduce Crizotinib dosage in patients with moderate or severe hepatic impairment.

Renal Impairment
No dose adjustment is recommended in patients with mild to moderate renal impairment.

PHARMACEUTICAL INFORMATION
Storage Condition
Store below 30°C, in a cool and dry place. Keep away from light. Keep out of the reach of children.

HOW SUPPLIED
ALKIXEN capsule: Each HDPE container contains 60 capsules (each capsule contains 250 mg Crizotinib) a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
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