Rizonib

Crizotinib INN Capsule

DRUG INTERNATIONAL LTD.

Composition: Each capsule contains Crizotinib INN 250 mg.

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.

Pharmacokinetics:

Absorption: Following a single oral dose, Crizotinib was absorbed with median time to achieve peak concentration of 4 to 6 hours. The mean absolute bioavailability of Crizotinib was 43% (range: 32% to 66%) following a single 250 mg oral dose. A high-fat meal reduced Crizotinib AUC from time zero to infinity (AUCinf) and maximum observed plasma concentration (Cmax) by approximately 14%.

Distribution: The geometric mean volume of distribution (Vss) of Crizotinib was 1772 L following intravenous administration of a 50 mg dose, indicating extensive distribution into tissues from the plasma.

Elimination: Following single doses of Crizotinib, the mean apparent plasma terminal half-life of Crizotinib was 42 hours in patients. Following the administration of a single 250 mg radiolabeled Crizotinib dose to healthy subjects, 63% and 22% of the administered dose was recovered in feces and urine, respectively.

Metabolism: Crizotinib is predominantly metabolized by CYP3A4/5. The primary metabolic pathways in humans were oxidation of the piperidine ring to Crizotinib lactam and O-dealkylation, with subsequent Phase 2 conjugation of O-dealkylated metabolites.

Indications:

ALK-Positive Metastatic NSCLC: Rizonib is indicated for the treatment of patients with metastatic Non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

ROS1-Positive Metastatic NSCLC: Rizonib is indicated for the treatment of patients with metastatic NSCLC whose tumors are ROS1-positive.

Dosage and Administration: The recommended dose of Rizonib is 250 mg orally, twice daily until disease progression or no longer tolerated by the patient. The recommended dose of Rizonib in patients with severe renal impairment [creatinine clearance (CLcr) < 30 mL/min] not requiring dialysis is 250 mg orally, once daily. Rizonib may be taken with or without food. Swallow capsules whole. If a dose of Rizonib is missed, make up that dose unless the next dose is due within 6 hours. If vomiting occurs after taking a dose of Rizonib, take the next dose at the regular time.

Dose Modification: Dose should be reduced as below if 1 or more dose reductions are necessary due to adverse reactions of Grade 3 or 4 severity, as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0:

- First dose reduction: Rizonib 200 mg taken orally twice daily.
- Second dose reduction: Rizonib 250 mg taken orally once daily.
- Permanently discontinue if unable to tolerate Rizonib 250 mg taken orally once daily.

Or, as directed by the registered physicians.

Contraindication: It is contraindicated in patients with known hypersensitivity to Crizotinib or any other components of this product.

Precautions:

Hepatotoxicity: Drug-induced hepatotoxicity with fatal outcome occurred in 2 (0.1%) of the 1719 patients treated with Rizonib across clinical trials. Liver function tests, including ALT, AST, and total bilirubin should be monitored 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 transaminase elevations. Rizonib should be temporarily suspended, dose reduced, or permanently discontinued in this condition.

Interstitial Lung Disease (Pneumonitis): Severe, life-threatening, or fatal interstitial lung disease (ILD)/Pneumonitis can occur in patients treated with Rizonib. Interstitial lung disease generally occurred within 3 months after the initiation of Rizonib. Patients for pulmonary symptoms indicative of ILD/Pneumonitis should be monitored. Other potential causes of ILD/Pneumonitis should be excluded, and Rizonib should be permanently discontinued in patients diagnosed with drug-related ILD/Pneumonitis.

QT Interval Prolongation: QTc prolongation can occur in patients treated with Rizonib. Use of Rizonib in patients with congenital long QT syndrome should be avoided. ECGs and electrolytes should be monitored in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QT interval. Rizonib should be permanently discontinued in patients who develop QTc greater than 500 ms or greater than or equal to 60 ms change from baseline with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. Rizonib should be withheld n patients who develop QTc greater than 500 ms on at least 2 separate ECGs until recovery to a QTc less than or equal to 480 ms, then Rizonib should be resumed at a reduced dose in this condition.

Bradycardia: Symptomatic bradycardia can occur in patients receiving Rizonib. Using Rizonib in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) should be avoided to the extent possible. Heart rate and blood pressure should be monitored regularly. In cases of symptomatic bradycardia that is not life-threatening, Rizonib should be held until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, re-evaluate the use of concomitant medications, and adjust the dose of Rizonib. It should be permanently discontinue for life-threatening bradycardia due to Rizonib.

Severe Visual Loss: Across all clinical trials, the incidence of Grade 4 visual field defect with vision loss was 0.2% (4/1719). Optic atrophy and optic nerve disorder have been reported as potential causes of vision loss. Rizonib should be discontinued n patients with new onset of severe visual loss (best corrected vision less than 20/200 in one or both eyes). An ophthalmological evaluation should be performed consisting of best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography (OCT) and other evaluations as appropriate for new onset of severe visual loss.

Embryo-Fetal Toxicity: Based on its mechanism of action, Rizonib can cause fetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to a fetus. Females of reproductive potential should be advised to use effective contraception during treatment with Rizonib and for at least 45 days following the final dose. Male patients with female partners of reproductive potential should be advised to use condoms during treatment with Rizonib and for at least 90 days after the final dose.

Side Effects:

- Hepatotoxicity
- Interstitial Lung Disease
- QT Interval Prolongation
- Bradycardia
- Severe Visual Loss

Use in Pregnancy and Lactation: There are no adequate and well-controlled studies in pregnant women using Crizotinib. Females of reproductive potential should be advised of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy. Females of reproductive potential should be advised to use effective contraception during treatment with Rizonib and for at least 45 days after the final dose.

Females and Males of Reproductive Potential: Females and males of reproductive potential should be advised of the potential for reduced fertility from Rizonib. Male patients with female partners of reproductive potential should be advised to use condoms during treatment with Rizonib and for at least 90 days after the final dose.

Lactation: Females should be advised not to breastfeed during treatment with Rizonib and for 45 days after the final dose.

Infertility: Females and males of reproductive potential should be advised of the potential for reduced fertility from Rizonib.

Drug Interction:

Drugs that may increase Crizotinib Plasma Concentrations: Coadministration of Crizotinib with strong cytochrome P450 (CYP) 3A inhibitors increases Crizotinib plasma concentrations. Concomitant use of strong CYP3A inhibitors should be avoided, including but not limited to Atazanavir, Clarithromycin, Indinavir, Itraconazole, Ketoconazole, Nefazodone, Nelfinavir, Ritonavir, Saquinavir, Telithromycin, Troleandomycin, and Voriconazole. Grapefruit or grapefruit juice should be avoided which may also increase plasma concentrations of Crizotinib. Caution should be exercised with concomitant use of moderate CYP3A inhibitors.

Drugs that may decrease Crizotinib Plasma Concentrations: Coadministration of Crizotinib with strong CYP3A inducers decreases Crizotinib plasma concentrations. Concomitant use of strong CYP3A inducers should be avoided, including but not limited to Carbamazepine, Phenobarbital, Phenytoin, Rifabutin, Rifampin, and St. John's Wort.

Drugs whose Plasma Concentrations that may be altered by Crizotinib: Crizotinib inhibits CYP3A both in vitro and in vivo. Concomitant use of CYP3A substrates with narrow therapeutic range should be avoided, including but not limited to Alfentanil, Cyclosporine, Dihydroergotamine, Ergotamine, Fentanyl, Pimozide, Quinidine, Sirolimus, and Tacrolimus in patients taking Crizotinib. If concomitant use of these CYP3A substrates with narrow therapeutic range is required in patients taking Crizotinib, dose reductions of the CYP3A substrates may be required due to adverse reactions.

Overdose: There have been no known cases of Rizonib overdose. There is no antidote for Rizonib.

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

Packing: Each box contains 30 capsules in blister pack.