Crizonix
Crizotinib

COMPOSITION:

Crizonix Capsule: Each capsule contains Crizotinib INN 250 mg.

CLINICAL PHARMACOLOGY:

Crizotinib is an inhibitor of receptor tyrosine kinases including ALK, Hepatocyte Growth Factor Receptor (HGFR, c-Met), ROS 1 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 and c-Met phosphorylation in cell-based assays using tumor cell lines and demonstrated antitumor activity in mice bearing tumor xenografts that expressed EML4- or NPM-ALK fusion proteins or c-Met.

Pharmacokinetics:

Absorption

Following oral single-dose administration, Crizotinib was absorbed with median time to achieve peak concentration of 4 to 6 hours. 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 systemic exposure (C_{min} and AUC) appeared to increase in a greater than dose proportional manner over the dose range of 200-300 mg twice daily.

The mean absolute bioavailability of Crizotinib was 43% (range: 32% to 66%) following the administration of a single 250 mg oral dose.

A high-fat meal reduced Crizotinib AUC_{inf} and C_{max} by approximately 14%. Crizotinib can be administered with or without food.

Distribution

The geometric mean volume of distribution (V_{ss}) of Crizotinib was 1,772 L following intravenous administration of a 50 mg dose, indicating extensive distribution into tissues from the plasma.

Binding of Crizotinib to human plasma proteins in vitro is 91% and is independent of drug concentration. In vitro studies suggested that Crizotinib is a substrate for P-glycoprotein (P-gp). The blood-to-plasma concentration ratio is approximately1.

Metabolism

In vitro studies demonstrated that 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.

In vitro studies in human liver microsomes demonstrated that Crizotinib is a time-dependent inhibitor of CYP3A.

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. Unchanged Crizotinib represented approximately 53% and 2.3% of the administered dose in feces and urine, respectively.

The mean apparent clearance (CL/F) of Crizotinib was lower at steady state (60 L/hr) after 250 mg twice daily than that after a single 250 mg oral dose (100 L/hr), which was likely due to autoinhibition of CYP3A by Crizotinib after multiple dosing.

INDICATION:

Crizotinib is a kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors are

- Anaplastic Lymphoma Kinase (ALK)-positive as detected by an FDA-approved test
- ROS1-positive,gene mutation,detected by an FDA-approved test

These indications are based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with Crizotinib.

DOSAGE AND ADMINISTRATION:

Standard Dosage

The recommended dose and schedule of Crizotinib is 250 mg taken orally twice daily. Continue treatment as long as the patient is deriving clinical benefit from therapy. Capsules should be swallowed whole. Crizotinib may be taken with or without food. If a dose of Crizotinib is missed, then it should be taken as soon as the patient remembers unless it is less than 6 hours until the next dose, in which case the patient should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.

Dose Modification

Reduce dose 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: 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

Use in specific populations:

Pregnancy

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

Lactation

Because of the potential for adverse reactions in breastfed infants, do not breastfeed during treatment with Crizotinib and for 45 days after the final dose.

Females and Males of Reproductive Potential

Contraception

Females: Crizotinib can cause fetal harm when administered to a pregnant woman . Advise females of reproductive potential to use effective contraception during treatment with Crizotinib and for at least 45 days after the final dose.

Males: Because of the potential for genotoxicity, advise males with female partners of reproductive potential 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. It is not known whether these effects on fertility are reversible.

Pediatric Use

The safety and efficacy of Crizotinib in pediatric patients has not been established.

Geriatric Use

No overall differences in safety or effectiveness were observed between these patients and younger patients.

Hepatic Impairment

Crizotinib has not been studied in patients with hepatic impairment.

Renal Impairment

No starting dose adjustment is needed for patients with mild (CL_{cr} 60-89 mL/min) or moderate (CL_{cr} 30-59 mL/min) renal impairment based

OVERDOSAGE:

There have been no known cases of Crizotinib overdose. There is no antidote for Crizotinib.

CONTRAINDICATION:

None

PRECAUTION:

Hepatotoxicity

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

Discontinue Crizotinib in patients with severe visual loss. Perform an ophthalmological evaluation.

Embryo-fetal toxicity

Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception.

ADVERSE REACTION:

The most common adverse reactions (≥ 25%) are vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory infection, dizziness, and neuropathy

DRUG INTERACTION:

Drugs that may increase Crizotinib plasma concentrations

Coadministration of Crizotinib with strong cytochrome P450 (CYP) 3A inhibitors increases Crizotinib plasma concentrations. Avoid concomitant use of strong CYP3A inhibitors, including but not limited to Atazanavir, Clarithromycin, Indinavir, Itraconazole, Ketoconazole, Nefazodone, Nelfinavir, Ritonavir, Saquinavir, Telithromycin, Troleandomycin, and Voriconazole. Avoid grapefruit or grapefruit juice which may also increase plasma concentrations of Crizotinib. Exercise caution 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. Avoid concomitant use of strong CYP3A inducers, including but not limited to Carbamazepine, Phenobarbital, Phenytoin, Rifabutin, Rifampin, and St. John's Wort.

Drugs whose plasma concentrations may be altered by Crizotinib

Crizotinib inhibits CYP3A both in vitro and in vivo. Avoid concomitant use of CYP3A substrates with narrow therapeutic range, 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.

PHARMACEUTICAL INFORMATION:

Storage Conditions

Store in a cool and dry place, away from light. Keep out of the reach of children.

Presentation & Packing

Crizonix Capsule: Each commercial box contains 28 capsules in Alu-Alu blister pack.

LF20701

Manufactured By
BEACON Pharmaceuticals Limited
Mymensingh, Bangladesh

Only for Export