Alecinix
Alectinib

COMPOSITION

Alecinix Capsule: Each capsule contains Alectinib Hydrochloride INN equivalent to Alectinib 150 mg.

THERAPEUTIC CLASS: Anti Cancer

CLINICAL PHARMACOLOGY

Mechanism of Action

Alectinib is a tyrosine kinase inhibitor that targets ALK and RET. In nonclinical studies, Alectinib inhibited ALK phosphorylation and ALK-mediated activation of the downstream signaling proteins STAT3 and AKT, and decreased tumor cell viability in multiple cell lines harboring ALK fusions, amplifications, or activating mutations. The major active metabolite of Alectinib, M4, showed similar in vitro potency and activity.

Alectinib and M4 demonstrated *in vitro and in vivo* activity against multiple mutant forms of the ALK enzyme, including some mutations identified in NSCLC tumors in patients who have progressed on Crizotinib.

In mouse models implanted with tumors carrying ALK fusions, administration of Alectinib resulted in antitumor activity and prolonged survival, including in mouse models implanted intracranially with ALK-driven tumor cell lines.

Pharmacodynamics

Cardiac Electrophysiology

The ability of Alectinib to prolong the QT interval was assessed in 221 patients administered Alectinib 600 mg twice daily in clinical studies. Alectinib did not prolong the QTc (QT corrected for heart rate) interval to any clinically relevant extent. One patient had a maximum post-baseline QTcF value of greater than 500 msec, and one patient had a maximum QTcF change from baseline of greater than 60 msec.

Pharmacokinetics

The pharmacokinetics of Alectinib and its major active metabolite M4 have been characterized in patients with ALK-positive NSCLC and healthy subjects.

In patients with ALK-positive NSCLC, the geometric mean (coefficient of variation %) steady-state maximal concentration ($C_{max,ss}$) for Alectinib was 665 ng/mL (44%) and for M4 was 246 ng/mL (45%) with peak to trough concentration ratio of 1.2. The geometric mean steady-state area under the curve from 0 to 12 hours ($AUC_{0\text{-}12h,ss}$) for Alectinib was 7,430 ng*h/mL (46%) and for M4 was 2,810 ng*h/mL (46%). Alectinib exposure is dose proportional across the dose range of 460 mg to 900 mg (i.e., 0.75 to 1.5 times the approved recommended dosage) under fed conditions. Alectinib and M4 reached steady-state concentrations by day 7. The geometric mean accumulation was approximately 6-fold for both Alectinib and M4.

Absorption

Alectinib reached maximal concentrations at 4 hours following administration of Alectinib 600 mg twice daily under fed conditions in patients with ALK-positive NSCLC.

The absolute bioavailability of Alectinib was 37% (90% CI: 34%, 40%) under fed conditions.

A high-fat, high-calorie meal increased the combined exposure ($AUC_{0\text{-}inf}$) of Alectinib plus M4 by 3.1-fold (90% CI: 2.7, 3.6) following oral administration of a single 600 mg dose of Alectinib.

Distribution

The apparent volume of distribution is 4,016 L for Alectinib and 10,093 L for M4.

Alectinib and M4 are bound to human plasma proteins greater than 99%, independent of drug concentration.

Alectinib concentrations in the cerebrospinal fluid in patients with ALK-positive NSCLC approximate estimated Alectinib free concentrations in the plasma.

In vitro studies suggest that Alectinib is not a substrate of P-glycoprotein (P-gp), but M4 is a substrate of P-gp. Alectinib and M4 are not substrates of breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP) 1B1, or OATP1B3.

Elimination

The apparent clearance (CL/F) is 81.9 L/hour for Alectinib and 217 L/hour for M4. The geometric mean elimination half-life is 33 hours for Alectinib and 31 hours for M4 in patients with ALK-positive NSCLC.

Metabolism

Alectinib is metabolized by CYP3A4 to its major active metabolite M4. The geometric mean metabolite/parent exposure ratio at steady-state is 0.40. M4 is subsequently metabolized by CYP3A4. Alectinib and M4 were the main circulating moieties in plasma, constituting 76% of the total radioactivity.

Excretion

Ninety-eight percent of the radioactivity was excreted in feces following oral administration of a single radiolabeled dose of Alectinib under fed conditions. Eighty-four percent of the dose was excreted in the feces as unchanged Alectinib, and 6% of the dose was excreted as M4. Excretion of radioactivity in urine was less than 0.5% of administered radiolabeled dose of Alectinib.

INDICATIONS

Alectinib is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.

DOSAGE AND ADMINISTRATION

Patient Selection

Select patients for the treatment of metastatic NSCLC with Alectinib based on the presence of ALK positivity in tumor specimens.

Dosing and Administration

The recommended dose of Alectinib is 600 mg orally twice daily. Administer Alectinib until disease progression or unacceptable toxicity.

The recommended dose of Alectiib in patients with severe hepatic impairment (Child-Pugh C) is 450 mg orally twice daily.

Alectinib should be taken with food. Do not open or dissolve the contents of the capsule. If a dose of Alectinib is missed or vomiting occurs after taking a dose of Alectinib, take the next dose at the scheduled time.

Dose Modifications for Adverse Reactions

The dose reduction schedule for Alectinib is provided in Table 1.

Table 1: Alectinib Dose Reduction Schedule

Dose reduction schedule	Dose level
Starting dose	600 mg taken orally twice daily
First dose reduction	450 mg taken orally twice daily
Second dose reduction	300 mg taken orally twice daily

Discontinue if patients are unable to tolerate the 300 mg twice daily dose.

Recommendations for dose modifications of Alectinib in case of adverse reactions are provided in Table 2.

Table 2: Alectinib Dose Modifications for Adverse Reactions

Criteria[a]	Alectinib Dose Modification
ALT or AST elevation of greater than 5 times upper limit of normal (ULN) with total bilirubin less than or equal to 2 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 3 times ULN, then resume at reduced dose as per Table 1.
ALT or AST elevation greater than 3 times ULN with total bilirubin elevation greater than 2 times ULN in the absence of cholestasis or hemolysis	Permanently discontinue Alectinib.
Total bilirubin elevation of greater than 3 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 1.5 times ULN, then resume at reduced dose as per Table 1.
Any grade treatment-related interstitial lung disease (ILD)/pneumonitis	Permanently discontinue Alectinib.
Grade 3 renal impairment	Temporarily withhold until serum creatinine recovers to less than or equal to 1.5 times ULN, then resume at reduced dose.
Grade 4 renal impairment	Permanently discontinue Alectinib.
Symptomatic bradycardia	Withhold Alectinib until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume Alectinib at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume Alectinib at reduced dose (see Table 1) upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above.
Bradycardia[b] (life-threatening consequences, urgent intervention indicated)	Permanently discontinue Alectinib if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume Alectinib at reduced dose (see Table 1) upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. Permanently discontinue Alectinib in case of recurrence.
CPK elevation greater than 5 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 2.5 times ULN, then resume at same dose.
CPK elevation greater than 10 times ULN or second occurrence of CPK elevation of greater than 5 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 2.5 times ULN, then resume at reduced dose as per Table 1.

[a] ALT = Alanine transaminase; AST = Aspartate transaminase; ULN = Upper limit of normal; ILD = Interstitial lung disease; CPK = Blood creatine phosphokinase

[b] Heart rate less than 60 beats per minute (bpm)

USE IN SPECIFIC POPULATIONS

Pregnancy

Based on animal studies and its mechanism of action, Alectinib can cause fetal harm when administered to a pregnant woman. There are no available data on Alectinib use in pregnant women.

Administration of Alectinib to pregnant rats and rabbits by oral gavage during the period of organogenesis resulted in embryo-fetal toxicity and abortion at maternally toxic doses with exposures approximately 2.7 times those observed in humans treated with Alectinib at 600 mg twice daily. Advise pregnant women of the potential risk to a fetus.

Lactation

There are no data on the presence of Alectinib or its metabolites in human milk, the effects of Alectinib on the breastfed infant, or its effects on milk production. Because of the potential for serious adverse reactions in breastfed infants from Alectinib, advise a lactating woman not to breastfeed during treatment with Alectinib and for 1 week after the final dose.

Females and Males of Reproductive Potential

Contraception

Females

Alectinib can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with Alectinib and for 1 week after the final dose.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with Alectinib and for 3 months following the final dose.

Pediatric Use

The safety and effectiveness of Alectinib in pediatric patients have not been established.

Geriatric Use

Clinical studies of Alectinib did not include sufficient number of subjects aged 65 and older to determine whether they respond differently from younger subjects.

Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment. The safety of Alectinib in patients with severe renal impairment (creatinine clearance less than 30 mL/min) or end-stage renal disease has not been studied.

Hepatic Impairment

No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Increased exposure of Alectinib occurred in patients with severe hepatic impairment (Child-Pugh C). The recommended dose of Alectinib in patients with severe hepatic impairment (Child-Pugh C) is 450 mg orally twice daily.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- ***Hepatotoxicity:*** Monitor liver laboratory tests every 2 weeks during the first 3 months of treatment, then once a month and as clinically indicated, with more frequent testing in patients who develop transaminase and bilirubin elevations. In case of severe ALT, AST, or bilirubin elevations, withhold, then reduce dose, or permanently discontinue Alectinib.
- ***Interstitial Lung Disease (ILD)/Pneumonitis:*** Immediately withhold Alectinib in patients diagnosed with ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis have been identified.
- ***Renal Impairment:*** Withhold Alectinib for severe renal impairment, then resume Alectinib at reduced dose upon recovery or permanently discontinue.
- ***Bradycardia:*** Monitor heart rate and blood pressure regularly. If symptomatic, withhold Alectinib then reduce dose, or permanently discontinue.
- ***Severe Myalgia and Creatine Phosphokinase (CPK) Elevation:*** Assess CPK every 2 weeks during the first month of treatment and in patients reporting unexplained muscle pain, tenderness, or weakness. In case of severe CPK elevations, withhold, then resume or reduce dose.
- ***Embryo-Fetal Toxicity:*** Alectinib can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

• Hepatotoxicity • Interstitial Lung Disease (ILD)/Pneumonitis • Renal Impairment • Bradycardia

• Severe Myalgia and Creatine Phosphokinase (CPK) Elevation • Embryo-Fetal Toxicity

DRUG INTERACTIONS

No pharmacokinetic interactions with Alectinib requiring dosage adjustment have been identified.

PHARMACEUTICAL INFORMATION

Storage Conditions

Store at below 30°C and dry place, away from light and moisture. Keep out of the reach of children.

Presentation & Packaging

Alecinix Capsule: Each commercial box contains 120 Capsules in a HDPE bottle.

Only for Export

Manufactured By
Beacon Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

Marketed By
BEACON®
Medicare Limited
Dhaka, Bangladesh

LF25401