Alecnib
Alectinib 150 mg

Everest

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

INDICATION AND USAGE
Alectinib (**Alecnib**) as monotherapy is indicated for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

Alectinib (**Alecnib**) as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib.

DOSAGE AND ADMINISTRATION
The recommended dose of Alectinib (**Alecnib**) is 600 mg (four 150 mg capsules) taken twice daily with food (total daily dose of 1200 mg).

Patients with underlying severe hepatic impairment (Child-Pugh C) should receive a starting dose of 450 mg taken twice daily with food (total daily dose of 900 mg).

Duration of treatment
Treatment with Alectinib (**Alecnib**) should be continued until disease progression or unacceptable toxicity.

Delayed or missed doses
If a planned dose of Alectinib (**Alecnib**) is missed, patients can make up that dose unless the next dose is due within 6 hours. Patients should not take two doses at the same time to make up for a missed dose. If vomiting occurs after taking a dose of Alectinib (**Alecnib**), patients should take the next dose at the scheduled time.

Dose adjustments
Management of adverse events may require dose reduction, temporary interruption, or discontinuation of treatment with Alectinib (**Alecnib**). The dose of Alectinib (**Alecnib**) should be reduced in steps of 150 mg twice daily based on tolerability. Alectinib (**Alecnib**) treatment should be permanently discontinued if patients are unable to tolerate the 300 mg twice daily dose.

Special populations
Hepatic impairment
No starting dose adjustment is required in patients with underlying mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Patients with underlying severe hepatic impairment (Child-Pugh C) should receive a starting dose of 450 mg taken twice daily (total dose of 900 mg). For all patients with hepatic impairment, appropriate monitoring (e.g. markers of liver function) is advised.

Renal impairment
No dose adjustment is required in patients with mild or moderate renal impairment. Alectinib (**Alecnib**) has not been studied in patients with severe renal impairment. However, since Alectinib (**Alecnib**) elimination via the kidney is negligible, no dose adjustment is required in patients with severe renal impairment.

Elderly (≥ 65 years)
The limited data on the safety and efficacy of Alectinib (**Alecnib**) in patients aged 65 years and older do not suggest that a dose adjustment is required in elderly patients. There are no available data on patients over 80 years of age.

Paediatric population
The safety and efficacy of Alectinib (**Alecnib**) in children and adolescents below 18 years of age have not been established. No data are available.

Extreme body weight (>130 kg)
Although PK simulations for Alectinib (**Alecnib**) do not indicate a low exposure in patients with extreme body weight (i.e. >130 kg), Alectinib (**Alecnib**) is widely distributed and clinical studies for Alectinib enrolled patients within a range of body weights of 36.9-123 kg. There are no available data on patients with body weight above 130 kg.

Method of administration
Alectinib is for oral use. The hard capsules should be swallowed whole, and must not be opened or dissolved. They must be taken with food.

CONTRAINDICATIONS
Patients with known hypersensitivity to Alectinib or any of the excipients

WARNINGS AND PRECAUTIONS
Interstitial lung disease (ILD)/pneumonitis
Cases of ILD/pneumonitis have been reported in clinical trials with Alectinib. Patients should be monitored for pulmonary symptoms indicative of pneumonitis. Alectinib should be immediately interrupted in patients diagnosed with ILD/pneumonitis and should be permanently discontinued if no other potential causes of ILD/pneumonitis have been identified.

Hepatotoxicity
Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) greater than 5 times the ULN as well as bilirubin elevations of more than 3 times the ULN occurred in patients in pivotal clinical trials with Alectinib. The majority of these events occurred during the first 3 months of treatment. In the pivotal Alectinib clinical trials it was reported that three patients with Grade 3-4 AST/ALT elevations had drug induced liver injury. Concurrent elevations in ALT or AST greater than or equal 3 times the ULN and total bilirubin greater than or equal 2 times the ULN, with normal alkaline phosphatase, occurred in one patient treated in Alectinib clinical trials.

Liver function, including ALT, AST, and total bilirubin should be monitored at baseline and then every 2 weeks during the first 3 months of treatment. Thereafter, monitoring should be performed periodically, since events may occur later than 3 months, with more frequent testing in patients who develop aminotransferase and bilirubin elevations. Based on the severity of the adverse drug reaction, Alectinib should be withheld and resumed at a reduced dose, or permanently discontinued.

Severe myalgia and creatine phosphokinase (CPK) elevation
Myalgia or musculoskeletal pain was reported in patients in pivotal trials with Alectinib, including Grade 3 events.

Elevations of CPK occurred in pivotal trials with Alectinib, including Grade 3 events. Median time to Grade 3 CPK elevation was 14 days across clinical trials (NP28761, NP28673, BO28984).

Patients should be advised to report any unexplained muscle pain, tenderness, or weakness. CPK levels should be assessed every two weeks for the first month of treatment and as clinically indicated in patients reporting symptoms. Based on the severity of the CPK elevation, Alectinib should be withheld, then resumed or dose reduced.

Bradycardia
Symptomatic bradycardia can occur with Alectinib. Heart rate and blood pressure should be monitored as clinically indicated. Dose modification is not required in case of asymptomatic bradycardia. If patients experience symptomatic bradycardia or life-threatening events, concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products should be evaluated and Alectinib treatment should be adjusted.

Photosensitivity
Photosensitivity to sunlight has been reported with Alectinib administration. Patients should be advised to avoid prolonged sun exposure while taking Alectinib, and for at least 7 days after discontinuation of treatment. Patients should also be advised to use a broad-spectrum Ultraviolet A (UVA)/ Ultraviolet B (UVB) sun screen and lip balm (SPF ≥50) to help protect against potential sunburn.

Women of child-bearing potential
Alectinib may cause foetal harm when administered to a pregnant woman. Female patients of child-bearing potential receiving Alectinib, must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of Alectinib.

Lactose intolerance
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, a congenital lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium content
This medicinal product contains 48 mg sodium per daily dose (1200 mg), equivalent to 2.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

ADVERSE REACTIONS
The most common adverse drug reactions (ADRs) (≥ 20%) were constipation (35%), oedema (30%, including oedema peripheral, oedema, generalised oedema, eyelid oedema, periorbital oedema, face oedema and localised oedema), and myalgia (28%, including myalgia and musculoskeletal pain). Interstitial lung disease.

(ILD)/ pneumonitis
Severe ILD/pneumonitis occurred in patients treated with Alectinib. Across clinical trials (NP28761, NP28673, BO28984), 1 out of 405 patients treated with Alectinib (0.2%) had a Grade 3 ILD. This event led to withdrawal from Alectinib treatment. In the phase III clinical trial BO28984, Grade 3 or 4 ILD/pneumonitis was not observed in patients receiving Alectinib versus 2.0% of patients receiving crizotinib. There were no fatal cases of ILD in any of the clinical trials. Patients should be monitored for pulmonary symptoms indicative of pneumonitis.

Hepatotoxicity
Across clinical trials (NP28761, NP28673, BO28984) two patients with Grade 3-4 AST/ALT elevations had documented drug induced liver injury by liver biopsy. In addition, one patient experienced a Grade 4 adverse event of drug-induced liver injury. Two of these cases led to withdrawal from Alectinib treatment. Adverse reactions of increased AST and ALT levels (15% and 14% respectively) were reported in patients treated with Alectinib across clinical trials (NP28761, NP28673, BO28984). The majority of these events were of Grade 1 and 2 intensity, and events of Grade ≥ 3 were reported in 3.7% and 3.7% of the patients, respectively. The events generally occurred during the first 3 months of treatment, were usually transient and resolved upon temporary interruption of Alectinib treatment (reported for 1.5% and 3.0% of the patients, respectively) or dose reduction (2.2% and 1.2%, respectively). In 1.2% and 1.5% of the patients, AST and ALT elevations, respectively, led to withdrawal from Alectinib treatment. Grade 3 or 4 ALT or AST elevations were each observed in 5% of patients receiving Alectinib versus 15% and 11% of patients receiving crizotinib in the phase III clinical trial BO28984.

Adverse reactions of bilirubin elevations were reported in 18% of the patients treated with Alectinib across clinical trials (NP28761, NP28673, BO28984). The majority of the events were of Grade 1 and 2 intensity; Grade 3 events were reported in 3.2% of the patients. The events generally occurred during the first 3 months of treatment, were usually transient and the majority resolved upon dose modification. In 5.2% of patients, bilirubin elevations led to dose modifications and in 1.5% of patients, bilirubin elevations led to withdrawal from Alectinib treatment. In the phase III clinical trial BO28984, Grade 3 or 4 bilirubin elevations occurred in 3.3% of patients receiving Alectinib versus no patient receiving crizotinib.

Concurrent elevations in ALT or AST greater than or equal to three times the ULN and total bilirubin greater than or equal to two times the ULN, with normal alkaline phosphatase, occurred in one patient (0.2%) treated in Alectinib clinical trials.

Patients should be monitored for liver function including ALT, AST, and total bilirubin.

Bradycardia
Cases of bradycardia (8.9%) of Grade 1 or 2 have been reported in patients treated with Alectinib across clinical trials (NP28761, NP28673, BO28984). No patients had events of Grade ≥ 3 severity. There were 66 of 365 patients (18%) treated with Alectinib who had post-dose heart rate values below 50 beats per minutes (bpm). In the phase III clinical trial BO28984 15% of patients treated with Alectinib had post-dose heart rate values below 50 bpm versus 20% of patients treated with crizotinib. Patients who develop symptomatic bradycardia should be managed. No case of bradycardia led to withdrawal from Alectinib treatment.

Severe myalgia and CPK elevations
Cases of myalgia (28%) including myalgia events (22%) and musculoskeletal pain (7.4%) have been reported in patients treated with Alectinib across clinical trials (NP28761, NP28673, BO28984). The majority of events were Grades 1 or 2 and three patients (0.7%) had a Grade 3 event. Dose modifications of Alectinib treatment due to these adverse events were only required for two patients (0.5%); Alectinib treatment was not withdrawn due to these events of myalgia. Elevations of CPK occurred in 43% of 362 patients with CPK laboratory data available across clinical trials (NP28761, NP28673, BO28984) with Alectinib. The incidence of Grade 3 elevations of CPK was 3.7%. Median time to Grade 3 CPK elevation was 14 days across trials (NP28761, NP28673, BO28984). Dose modifications for elevation of CPK occurred in 3.2% of patients; withdrawal from Alectinib treatment did not occur due to CPK elevations. Severe myalgia has not been reported in the clinical trial BO28984. Grade 3 elevation of CPK was reported for 2.6% of patients receiving Alectinib and 1.3% of patients receiving crizotinib; and median time to Grade 3 CPK elevation was 27.5 days and 369 days, respectively, in the pivotal phase III clinical trial BO28984 (ALEX).

Gastrointestinal effects
Constipation (35%), nausea (19%), diarrhoea (16%) and vomiting (11%) were the most commonly reported gastrointestinal (GI) reactions. Most of these events were of mild or moderate severity; Grade 3 events were reported for diarrhea (0.7%), nausea (0.5%), and vomiting (0.2%). These events did not lead to withdrawal from Alectinib treatment. Median time to onset for constipation, nausea, diarrhea, and/or vomiting events across clinical trials (NP28761, NP28673, BO28984) was 21 days. The events declined in frequency after the first month of treatment. In the phase III clinical trial BO28984, one patient (0.2%) experienced a Grade 4 event of nausea in the Alectinib arm and the incidence of Grade 3 and 4 events for nausea, vomiting, and diarrhoea was 3.3%, 3.3%, and 2.0%, respectively, in the crizotinib arm.

Alecnib
Alectinib 150 mg

Everest

DRUG INTERACTION
Based on *in vitro* data, CYP3A4 is the primary enzyme mediating the metabolism of both Alectinib and its major active metabolite M4, and CYP3A contributes to 40% - 50% of total hepatic metabolism. M4 has shown similar *in vitro* potency and activity against ALK.

CYP3A inducers
Co-administration of multiple oral doses of 600 mg rifampicin once daily, a strong CYP3A inducer, with a single oral dose of 600 mg Alectinib reduced Alectinib C_{max}, and AUC_{inf} by 51% and 73% respectively and increased M4 C_{max} and AUC_{inf} 2.20 and 1.79-fold respectively. The effect on the combined exposure of Alectinib and M4 was minor, reducing C_{max} and AUC_{inf} by 4% and 18%, respectively. Based on the effects on the combined exposure of Alectinib and M4, no dose adjustments are required when Alectinib is co-administered with CYP3A inducers. Appropriate monitoring is recommended for patients taking concomitant strong CYP3A inducers (including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's Wort (Hypericum perforatum).

CYP3A inhibitors
Co-administration of multiple oral doses of 400 mg posaconazole twice daily, a strong CYP3A inhibitor, with a single oral dose of 300 mg Alectinib increased Alectinib exposure C_{max} and AUC_{inf} by 1.18 and 1.75-fold respectively, and reduced M4 C_{max} and AUC_{inf} by 71% and 25% respectively. The effect on the combined exposure of Alectinib and M4 was minor, reducing C_{max} by 7% and increasing AUC_{inf} 1.36-fold. Based on the effects on the combined exposure of Alectinib and M4, no dose adjustments are required when Alectinib is co-administered with CYP3A inhibitors. Appropriate monitoring is recommended for patients taking concomitant strong CYP3A inhibitors (including, but not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole nefazodone, grapefruit or Seville oranges).

Medicinal products that increase gastric pH
Multiple doses of esomeprazole, a proton pump inhibitor, 40 mg once daily, demonstrated no clinically relevant effect on the combined exposure of Alectinib and M4. Therefore, no dose adjustments are required when Alectinib is co-administered with proton pump inhibitors or other medicinal products which raise gastric pH (e.g. H2 receptor antagonists or antacids).

Effect of transporters on Alectinib disposition
M4 is a substrate of P-gp. As Alectinib inhibits P-gp, it is not expected that co-medication with P-gp inhibitors has a relevant effect on M4 exposure.

Effects of Alectinib on other medicinal products
P-gp substrates
In vitro, Alectinib and its major active metabolite M4 are inhibitors of the efflux transporter P-glycoprotein (P-gp). Therefore, Alectinib and M4 may have the potential to increase plasma concentrations of co-administered substrates of P-gp. When Alectinib is co-administered with P-gp substrates (e.g., digoxin, dabigatran etexilate, topotecan, sirolimus, everolimus, nilotinib and lapatinib), appropriate monitoring is recommended.

BCRP substrates
In vitro, Alectinib and M4 are inhibitors of the efflux transporter Breast Cancer Resistance Protein (BCRP). Therefore, Alectinib and M4 may have the potential to increase plasma concentrations of co-administered substrates of BCRP. When Alectinib is co-administered with BCRP substrates (e.g., methotrexate, mitoxantrone, topotecan and lapatinib), appropriate monitoring is recommended.

CYP substrates
In vitro, Alectinib and M4 show weak time-dependent inhibition of CYP3A4, and Alectinib exhibits a weak induction potential of CYP3A4 and CYP2B6 at clinical concentrations.

Multiple doses of 600 mg Alectinib had no influence on the exposure of midazolam (2 mg), a sensitive CYP3A substrate. Therefore, no dose adjustment is required for co-administered CYP3A substrates.

A risk for induction of CYP2B6 and PXR regulated enzymes apart from CYP3A4 cannot be completely excluded. The effectiveness of concomitant administration of oral contraceptives may be reduced.

USE IN SPECIFIC POPULATION
Pregnancy
There are no or limited amount of data from the use of Alectinib in pregnant women. Based on its mechanism of action, Alectinib may cause foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity.

Female patients, who become pregnant while taking Alectinib or during the 3 months following the last dose of Alectinib must contact their doctor and should be advised of the potential harm to the foetus.

Breast-feeding
It is unknown whether Alectinib and its metabolites are excreted in human milk. A risk to the newborn/infant cannot be excluded. Mothers should be advised against breast-feeding while receiving Alectinib.

Fertility
No fertility studies in animals have been performed to evaluate the effect of Alectinib. No adverse effects on male and female reproductive organs were observed in general toxicology studies.

OVERDOSAGE
Patients who experience overdose should be closely supervised and general supportive care instituted. There is no specific antidote for overdose with Alectinib.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: anti-neoplastic agents, protein kinase inhibitor; ATC code: L01XE36.

Mechanism of action
Alectinib is a highly selective and potent ALK and RET tyrosine kinase inhibitor. In preclinical studies, inhibition of ALK tyrosine kinase activity led to blockage of downstream signalling pathways including STAT 3 and PI3K/AKT and induction of tumour cell death (apoptosis).

Alectinib demonstrated *in vitro* and *in vivo* activity against mutant forms of the ALK enzyme, including mutations responsible for resistance to crizotinib. The major metabolite of Alectinib (M4) has shown similar *in vitro* potency and activity.

Based on preclinical data, Alectinib is not a substrate of p-glycoprotein or BCRP, which are both efflux transporters in the blood brain barrier, and is therefore able to distribute into and be retained within the central nervous system.

PHARMACOKINETIC PROPERTIES
The pharmacokinetic parameters for Alectinib and its major active metabolite (M4) have been characterised in ALK-positive NSCLC patients and healthy subjects. Based on population pharmacokinetic analysis, the geometric mean (coefficient of variation %) steady-state C_{max}, C_{min} and $AUC_{0\text{-}12hr}$ for Alectinib were approximately 665 ng/mL (44.3%), 572 ng/mL (47.8%) and 7430 ng*h/mL (45.7%), respectively. The geometric mean steady-state C_{max}, C_{min} and $AUC_{0\text{-}12hr}$ for M4 were approximately 246 ng/mL (45.4%), 222 ng/mL (46.6%) and 2810 ng*h/mL (45.9%), respectively.

Absorption
Following oral administration of 600 mg twice daily under fed conditions in ALK-positive NSCLC patients, Alectinib was absorbed reaching T_{max} after approximately 4 to 6 hours.

Alectinib steady-state is reached within 7 days with continuous 600 mg twice daily dosing. The accumulation ratio for the twice-daily 600 mg regimen was approximately 6-fold. Population PK analysis supports dose proportionality for Alectinib across the dose range of 300 to 900 mg under fed conditions.

The absolute bioavailability of Alectinib capsules was 36.9% (90% CI: 33.9%, 40.3%) under fed conditions in healthy subjects.

Following a single oral administration of 600 mg with a high-fat, high-calorie meal, Alectinib and M4 exposure was increased by around 3-fold relative to fasted conditions.

Distribution
Alectinib and its major metabolite M4 are highly bound to human plasma proteins (>99%), independent of active substance concentration. The mean *in vitro* human blood-to-plasma concentration ratios of Alectinib and M4 are 2.64 and 2.50, respectively, at clinically relevant concentrations.

The geometric mean volume of distribution at steady state (Vss) of Alectinib following IV administration was 475 L, indicating extensive distribution into tissues.

Based on *in vitro* data, Alectinib is not a substrate of P-gp. Alectinib and M4 are not substrates of BCRP or organic anion-transporting polypeptide (OATP) 1B1/B3.

Biotransformation
In vitro metabolism studies showed that CYP3A4 is the main CYP isozyme mediating Alectinib and its major metabolite M4 metabolism, and is estimated to contribute 40-50% of Alectinib metabolism. Results from the human mass balance study demonstrated that Alectinib and M4 were the main circulating moieties in plasma with 76% of the total radioactivity in plasma. The geometric mean Metabolite/ Parent ratio at steady state is 0.399.

Metabolite M1b was detected as a minor metabolite from *in vitro* and in human plasma in healthy subjects. Formation of metabolite M1b and its minor isomer M1a is likely to be catalyzed by a combination of CYP isozymes (including isozymes other than CYP3A) and aldehyde dehydrogenase (ALDH) enzymes.

In vitro studies indicate that neither Alectinib nor its major active metabolite (M4) inhibits CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations. Alectinib did not inhibit OATP1B1/OATP1B3, OAT1, OAT3 or OCT2 at clinically relevant concentrations *in vitro*.

Elimination
Following administration of a single dose of 14C-labeled Alectinib administered orally to healthy subjects the majority of radioactivity was excreted in faeces (mean recovery 97.8%) with minimal excretion in urine (mean recovery 0.46%). In faeces, 84% and 5.8% of the dose was excreted as unchanged Alectinib or M4, respectively.

Based on a population PK analysis, the apparent clearance (CL/F) of Alectinib was 81.9 L/hour. The geometric mean of the individual elimination half-life estimates for Alectinib was 32.5 hours. The corresponding values for M4 were 217 L/hour and 30.7 hours, respectively.

Pharmacokinetics in special populations
Renal impairment
Negligible amounts of alectinib and the active metabolite M4 are excreted unchanged in urine (< 0.2% of the dose). Based on a population pharmacokinetic analysis Alectinib and M4 exposures were similar in patients with mild and moderate renal impairment and normal renal function. The pharmacokinetics of Alectinib has not been studied in patients with severe renal impairment.

Hepatic impairment
As elimination of Alectinib is predominantly through metabolism in the liver, hepatic impairment may increase the plasma concentration of Alectinib and/or its major metabolite M4. Based on a population pharmacokinetic analysis, Alectinib and M4 exposures were similar in patients with mild hepatic impairment and normal hepatic function.

Following administration of a single oral dose of 300 mg Alectinib in subjects with severe (Child-Pugh C) hepatic impairment, Alectinib C_{max} was the same and AUC_{inf} was 2.2-fold higher compared with the same parameters in matched healthy subjects. M4 C_{max} and AUC_{inf} was 39% and 34% lower respectively, resulting in a combined exposure of Alectinib and M4 (AUC_{inf}) 1.8-fold higher in patients with severe hepatic impairment compared with matched healthy subjects.

The hepatic impairment study also included a group with moderate (Child-Pugh B) hepatic impairment, and a modestly higher Alectinib exposure was observed in this group compared with matched healthy subjects. The subjects in the Child Pugh B group however did in general not suffer from abnormal bilirubin, albumin or prothrombin time, indicating that they may not be fully representative of moderately hepatically impaired subjects with decreased metabolic capacity.

Effects of age, body weight, race and gender
Age, body weight, race and gender had no clinically meaningful effect on the systemic exposure of Alectinib and M4. The range of body weights for patients enrolled in clinical studies is 36.9-123 kg. There are no available data on patients with extreme body weight (>130 kg).

PHARMACEUTICAL INFORMATION
How Supplied
Alecnib Capsule: Each HDPE bottle of **Alecnib** contains 56 capsules, a silica gel desiccant and polyester coil with a child-resistant closure.

Storage
Do not store above 30°C. Keep out of the sight & reach of children. Protect from moisture & light.

Do not remove desiccant. Dispense in original bottle.

Manufactured by
Everest Pharmaceuticals Ltd.
BSCIC, Kanchpur, Narayanganj, Bangladesh
www.everestpharmabd.com
1902000014