Cerixen
Ceritinib INN

Everest

COMPOSITION

CERIXEN capsule: Each capsule contains Ceritinib INN 150 mg.

PHARMACOLOGY

Ceritinib is a kinase inhibitor primarily targeting ALK, with additional activity against IGF-1R, InsR, and ROS1. It blocks ALK autophosphorylation, downstream STAT3 activation, and ALK-dependent cancer cell growth in vitro and in vivo. Ceritinib inhibits proliferation of cells with EML4-ALK and NPM-ALK fusions and shows dose-dependent anti-tumor effects in EML4-ALK-positive NSCLC xenografts, including crizotinib-resistant models, at clinically relevant concentrations.

INDICATION

Ceritinib is indicated for the treatment of anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC).

DOSAGE AND ADMINISTRATION

Patient Selection

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

Recommended Dosage

The recommended dosage of Ceritinib is 450 mg orally once daily with food until disease progression or unacceptable toxicity.

If a dose of Ceritinib is missed, make up that dose unless the next dose is due within 12 hours. If vomiting occurs during the course of treatment, do not administer an additional dose and continue with the next scheduled dose of Ceritinib.

Dosage Modifications for Adverse Reactions

Table 1: Recommended Ceritinib Dose Reductions

Dose Reduction	Recommended Dose
First-dose reduction	300 mg taken orally once daily with food
Second-dose reduction	150 mg taken orally once daily with food

Discontinue Ceritinib for patients unable to tolerate 150 mg taken orally once daily with food.

Dosage modifications for selected adverse reactions of Ceritinib are provided in Table 2. If dose reduction is required due to an adverse reaction not listed in Table 2, then reduce the daily dose of Ceritinib by 150 mg.

Table 2: Recommended Ceritinib Dosage Modifications for Adverse Reactions

Adverse Reaction	Ceritinib Dose Modification
Gastrointestinal Adverse Reactions	
Severe or intolerable nausea, vomiting, or diarrhea despite optimal antiemetic or anti-diarrheal therapy	Withhold until improved, then resume Ceritinib at the next lower dosage.
Hepatotoxicity	
ALT or AST elevation greater than 5 times ULN with total bilirubin elevation less than or equal to 2 times ULN	Withhold until recovery to baseline or less than or equal to 3 times ULN, then resume Ceritinib at the next lower dosage.
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 Ceritinib.
Interstitial Lung Disease/Pneumonitis	
Any Grade treatment-related ILD/pneumonitis	Permanently discontinue Ceritinib.
QT Interval Prolongation	
QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then resume Ceritinib at the next lower dosage.
QTc interval prolongation in combination with torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue Ceritinib .
Hyperglycemia	
Persistent hyperglycemia greater than 250 mg/dL despite optimal anti-hyperglycemic therapy	Withhold until hyperglycemia is adequately controlled, then resume Ceritinib at the next lower dosage. If adequate hyperglycemic control cannot be achieved with optimal medical management, discontinue Ceritinib .
Bradycardia	
Symptomatic bradycardia that is not life-threatening	Withhold until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, evaluate concomitant medications known to cause bradycardia. If bradycardia cannot be attributed to another drug, resume Ceritinib at the next lower dosage.
Clinically significant bradycardia requiring intervention or life-threatening bradycardia in patients taking a concomitant medication also known to cause bradycardia or a medication known to cause hypotension	Withhold until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If the concomitant medication can be adjusted or discontinued, resume Ceritinib at the next lower dosage with frequent monitoring.
Life-threatening bradycardia in patients who are not taking a concomitant medication also known to cause bradycardia or known to cause hypotension	Permanently discontinue Ceritinib .
Pancreatitis	
Lipase or amylase elevation greater than 2 times ULN	Withhold until recovery to less than 1.5 times ULN, then resume Ceritinib at the next lower dosage.

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal; ILD, interstitial lung disease; ECG, electrocardiogram; bpm, beats per minute.

Dosage Modification for Strong CYP3A Inhibitors

Avoid concurrent use of strong CYP3A inhibitors during treatment with Ceritinib.

If concurrent use of a strong CYP3A inhibitor is unavoidable, reduce the Ceritinib dose by approximately one-third, rounded to the nearest multiple of the 150 mg dosage strength. After discontinuation of a strong CYP3A inhibitor, resume the Ceritinib dose that was taken prior to initiating the strong CYP3A inhibitor.

Dosage Modification for Patients With Severe Hepatic Impairment

For patients with severe hepatic impairment (Child-Pugh C), reduce the Ceritinib dose by approximately one-third, rounded to the nearest multiple of the 150 mg dosage strength

CONTRAINDICATION

None.

SIDE EFFECTS

The most common side effects of Ceritinib are:

- Gastrointestinal Adverse Reactions
- Hepatotoxicity
- Interstitial Lung Disease/Pneumonitis

- QT Interval Prolongation
- Hyperglycemia
- Bradycardia
- Pancreatitis
- Embryo-Fetal Toxicity

WARNINGS AND PRECAUTION

Gastrointestinal Adverse Reactions

Ceritinib can cause severe gastrointestinal effects including diarrhea, nausea, vomiting, and abdominal pain, especially at 750 mg under fasting conditions. These reactions led to dose adjustments in up to 36% of patients. Incidence and severity were lower with 450 mg taken with food. Supportive care and dose modification are recommended based on severity.

Hepatotoxicity

Liver toxicity, including elevated ALT and AST levels, has been observed with Ceritinib. In some cases, liver enzyme increases led to treatment discontinuation. Monthly liver function monitoring is recommended, with dose adjustments or discontinuation for significant elevations.

Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, or fatal ILD/pneumonitis occurred in Ceritinib-treated patients. Symptoms require prompt evaluation to exclude other causes. If ILD/pneumonitis is confirmed, permanently discontinue treatment.

QT Interval Prolongation

Ceritinib can prolong the QT interval, increasing the risk of arrhythmia or sudden death. QTc > 500 msec and dose-dependent effects have been observed. Periodic ECG and electrolyte monitoring is advised, especially in high-risk patients. Adjust or stop treatment as needed.

Hyperglycemia

Grade 3 or 4 hyperglycemia occurred in 13% of Ceritinib-treated patients. Blood glucose should be monitored before and during treatment, and antihyperglycemic therapy initiated or adjusted as needed. Severe cases may require dose changes or discontinuation.

Bradycardia

Ceritinib may cause sinus bradycardia (heart rate < 50 bpm), with 1% of patients affected. Regular monitoring of heart rate and blood pressure is recommended. Avoid combining with other bradycardia-inducing drugs. Adjust dose or discontinue based on severity.

Pancreatitis

Elevated lipase and amylase levels and rare cases of pancreatitis, including one fatality, were reported with Ceritinib. Monitor pancreatic enzymes regularly and withhold treatment if elevations are severe, resuming at a reduced dose upon improvement.

Embryo-Fetal Toxicity

Ceritinib may cause fetal harm based on animal studies and its mechanism of action. Advise pregnant women of the risk and ensure effective contraception during treatment and for 6 months after (females) or 3 months after (males) treatment ends.

USE IN SPECIFIC POPULATIONS

Pregnancy:

Ceritinib poses a risk of fetal harm based on animal studies and its mechanism of action. Limited human data are available, but animal studies with rats and rabbits showed dose-related skeletal anomalies and, in rabbits, some visceral anomalies when ceritinib was administered during organogenesis. Skeletal effects appeared at doses below human exposure levels, with higher doses causing maternal toxicity and embryolethality in rabbits. Pregnant women should be informed of the potential fetal risk

Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating Ceritinib.

Contraception

Ceritinib can cause fetal harm when administered to a pregnant woman

Females

Advise females of reproductive potential to use effective contraception during treatment with Ceritinib and for 6 months following completion of therapy.

Males

Based on the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with Ceritinib and for 3 months following completion of therapy.

Lactation:

Advise not to breastfeed.

Pediatric Use:

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

Hepatic Impairment

For patients with severe hepatic impairment (Child-Pugh C), reduce the dose of. No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child- Pugh B) hepatic impairment.

OVERDOSE

In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

DRUG INTERACTIONS

• CYP3A Inhibitors and Inducers: Avoid concurrent use of Ceritinib with strong CYP3A inhibitors or inducers. If concurrent use of a strong CYP3A inhibitor is unavoidable, dose reduce Ceritinib.

• CYP3A Substrates: Avoid coadministration of Ceritinib with sensitive CYP3A substrates.

• CYP2C9 Substrates: Avoid coadministration of Ceritinib with CYP2C9 substrates for which minimal concentration changes may lead to serious toxicities.

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

CERIXEN capsule: Each HDPE container contains 90 capsules (each capsule contains Ceritinib INN 150 mg) a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
Everest Pharmaceuticals Ltd.
BSCIC I/A, Kanchpur, Narayanganj, Bangladesh
www.everestpharmabd.com

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