Cerinib

Ceritinib INN 150 mg Capsule

DRUG INTERNATIONAL LTD.

Composition: Each capsule contains Ceritinib INN 150 mg.

Mechanism of Action: Ceritinib is a kinase inhibitor. Targets of Ceritinib inhibition identified in either biochemical or cellular assays at clinically relevant concentrations include ALK, insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and ROS1. Among these, Ceritinib is most active against ALK. Ceritinib inhibited autophosphorylation of ALK, ALK-mediated phosphorylation of the downstream signaling protein STAT3, and proliferation of ALK-dependent cancer cells in in vitro and in vivo assays.

Pharmacokinetics:

Absorption: After a single oral administration of Cerinib in patients, peak plasma levels (C_{max}) of Ceritinib were achieved at approximately 4 to 6 hours, and AUC and C_{max} increased dose proportionally over 50 to 750 mg under fasted conditions. The absolute bioavailability of Cerinib has not been determined.

Distribution: Ceritinib is 97% bound to human plasma proteins, independent of drug concentration. The apparent volume of distribution (V_d/F) is 4230 L following a single 750 mg fasted Cerinib dose in patients. Ceritinib also has a slight preferential distribution to red blood cells, relative to plasma, with a mean in vitro blood-to-plasma ratio of 1.35.

Elimination: Following a single 750 mg fasted Cerinib dose, the geometric mean apparent plasma terminal half-life (t½) of Ceritinib was 41 hours in patients. Ceritinib demonstrates nonlinear PK over time. The geometric mean apparent clearance (CL/F) of Ceritinib was lower at steady-state (33.2 L/h) after 750 mg daily dosing than after a single 750 mg dose (88.5 L/h).

Metabolism: In vitro studies demonstrated that CYP3A was the major enzyme involved in the metabolic clearance of Ceritinib. Following oral administration of a single 750 mg radiolabeled Ceritinib dose under fasted conditions, Ceritinib as the parent compound was the main circulating component (82%) in human plasma.

Excretion: Following oral administration of a single 750 mg radiolabeled Ceritinib dose under fasted conditions, 92.3% of the administered dose was recovered in the feces (with 68% as unchanged parent compound) while 1.3% of the administered dose was recovered in the urine.

Indications: Cerinib 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.

Dosage and Administration:

Patient Selection: Patients should be selected for treatment of metastatic NSCLC with Cerinib based on the presence of ALK positivity in tumor specimens.

The recommended dose of Cerinib is 450 mg orally once daily with food until disease progression or unacceptable toxicity. If a dose of Cerinib is missed, that dose should be made up unless the next dose is due within 12 hours. If vomiting occurs during the course of treatment, an additional dose should not be administered and the next scheduled dose of Cerinib should be continued. Or, as directed by the registered physician.

Dose Modifications for Adverse Reactions: Cerinib should be discontinued for patients unable to tolerate 150 mg daily with food.

Adverse Reaction	Cerinib Dose Modification
Gastrointestinal Adverse Reactions	
Lipase or amylase elevation greater than 2 times ULN	Withhold and monitor serum lipase and amylase. Resume Cerinib with a 150 mg dose reduction after recovery to less than 1.5 times ULN.
Severe or intolerable nausea, vomiting or diarrhea despite optimal antiemetic or antidiarrheal therapy	Withhold until improved, then resume Cerinib with a 150 mg dose reduction.
Hyperglycemia	
Persistent hyperglycemia greater than 250 mg/dL despite optimal antihyperglycemic therapy	Withhold until hyperglycemia is adequately controlled, then resume Cerinib with a 150 mg dose reduction. If adequate hyperglycemic control cannot be achieved with optimal medical management, discontinue Cerinib.
Pneumonitis	
Any Grade treatment-related ILD/pneumonitis	Permanently discontinue Cerinib.
Cardiac Arrhythmias	
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 Cerinib with a 150 mg dose reduction.
QTc interval prolongation in combination with torsadesde pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue Cerinib.
Symptomatic bradycardia that is not life -threatening	Withhold until recovery to asymptomatic bradycardia or to a heart rate of 60 b pm or above, evaluate concomitant medications known to cause bradycardia, and adjust the dose of Cerinib.
Clinically significant bradycardia requiring intervention or life -threatening bradycardia in patients taking a concomitant medication also known to c ause 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 Cerinib with a 150 mg dose reduction, 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 Cerinib.
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 Cerinib with a 150 mg dose reduction.
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 Cerinib.

Side Effects:

• Gastrointestinal Adverse Reactions • Hepatotoxicity • Interstitial Lung Disease/Pneumonitis
• QT Interval Prolongation • Hyperglycemia • Bradycardia • Pancreatitis

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

Use in Pregnancy and Lactation: Cerinib can cause fetal harm when administered to a pregnant woman. If it is used during pregnancy or if the patient becomes pregnant while taking it, the patient should be apprised of the potential hazard to the fetus.

Lactation: There are no data regarding the presence of Ceritinib or its metabolites in human milk, the effects of Ceritinib on the breastfed infant, or its effects on milk production. Because of the potential for serious adverse reactions including gastrointestinal adverse reactions, hepatotoxicity, pneumonitis, bradycardia and pancreatitis, a woman should be advised not to breastfeed during treatment with Cerinib and for 2 weeks following completion of therapy.

Females and Males of Reproductive Potential:

Females: Cerinib can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should be advised to use effective contraception during treatment with Cerinib and for 6 months following completion of therapy. **Males:** Based on the potential for genotoxicity, males with female partners of reproductive potential should be advised to use condoms during treatment with Cerinib and for 3 months following completion of therapy.

Pediatric Use: The safety and effectiveness of Cerinib in pediatric patients have not been established.

Geriatric Use: Of the 925 patients in clinical studies of Cerinib, 18% were 65 years or older, while 5% were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Hepatic Impairment: For patients with severe hepatic impairment (Child-Pugh C), the dose of Cerinib should be reduced by approximately one-third, rounded to the nearest multiple of the 150 mg dosage strength. No dose adjustment is recommended in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

Drug Interactions:

Effect of Other Drugs on Ceritinib: Strong CYP3A Inhibitors: A strong CYP3A4/P-gp inhibitor (ketoconazole) increased the systemic exposure of Ceritinib so it should be avoided. If concomitant use of strong CYP3A inhibitors including certain antivirals (e.g., ritonavir), macrolide antibiotics (e.g., telithromycin), antifungals (e.g., ketoconazole), and nefazodone is unavoidable, the Cerinib dose should be reduced by approximately one-third, rounded to the nearest multiple of the 150 mg dosage strength. After discontinuation of a strong CYP3A inhibitor, the Cerinib dose should be resumed that was taken prior to initiating the strong CYP3A inhibitor. Grapefruit and grapefruit juice should not be consumed as they may inhibit CYP3A.

Strong CYP3A Inducers: A strong CYP3A4/P-gp inducer (Rifampin) decreased the systemic exposure of Ceritinib. Concurrent use of strong CYP3A inducers (e.g., Carbamazepine, Phenytoin, Rifampin, and St. John's Wort) should be avoided during treatment with Cerinib.

Effect of Ceritinib on Other Drugs: CYP3A Substrates: Ceritinib increased the systemic exposure of a sensitive CYP3A substrate (Midazolam) so it should be avoided. If concomitant use is unavoidable, dose reduction of the sensitive CYP3A substrates should be considered. If Cerinib is coadministered with other CYP3A substrates, it should be referred to the CYP3A substrate labeling for dosage recommendation with strong CYP3A inhibitors.

CYP2C9 Substrates: Ceritinib increased the systemic exposure of a CYP2C9 substrate (Warfarin). The frequency of INR monitoring should be increased if coadministration with warfarin is unavoidable as the anti-coagulant effect of Warfarin may be enhanced. Coadministration of Cerinib should be avoided with CYP2C9 substrates for which minimal concentration changes may lead to serious toxicities. If concomitant use of such CYP2C9 substrates is unavoidable, dose reduction should be considered for the coadministered CYP2C9 substrates.

Precautions:

Gastrointestinal Adverse Reactions: Severe gastrointestinal toxicity occurred in patients treated with Cerinib 750 mg under fasted conditions. Diarrhea, nausea, vomiting, or abdominal pain occurred in 95% of 925 patients, including severe cases (Grade 3 or 4) in 14% of patients treated with Cerinib across clinical studies. Diarrhea, nausea, vomiting, or abdominal pain leading to dose interruptions or reductions occurred in 36% of patients and leading to treatment discontinuation occurred in 1.6% of patients. Patients should be monitored and managed using standards of care, including antidiarrheals, antiemetics, or fluid replacement, as indicated. Based on the severity of the adverse drug reaction, Cerinib should be withheld with resumption at a reduced dose.

Hepatotoxicity: Drug-induced hepatotoxicity occurred in patients treated with Cerinib. Elevations in alanine aminotransferase (ALT) greater than 5 times the upper limit of normal (ULN) occurred in 28% and elevations in aspartate aminotransferase (AST) greater than 5 times ULN occurred in 16% of 925 patients across clinical studies. Concurrent elevations in ALT greater than 3 times the ULN and total bilirubin greater than 2 times the ULN, with alkaline phosphatase less than 2 times the ULN occurred in 0.3% of patients across clinical studies. Approximately 1.0% of patients required permanent discontinuation due to hepatotoxicity. It should be monitor with liver laboratory tests including ALT, AST, and total bilirubin once a month and as clinically indicated, with more frequent testing in patients who develop transaminase elevations. Based on the severity of the adverse drug reaction, Cerinib should be withheld with resumption at a reduced dose, or permanently discontinue Cerinib.

Interstitial Lung Disease (ILD)/Pneumonitis: Severe, life-threatening, or fatal ILD/pneumonitis occurred in patients treated with Cerinib. Across clinical studies, ILD/pneumonitis was reported in 2.4% of 925 patients treated with Cerinib. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 3 or 4 ILD/pneumonitis was reported in 1.3% of patients, with fatal events reported in 0.2% of patients. Ten patients (1.1%) discontinued Cerinib across clinical studies due to ILD/pneumonitis. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis.

QT Interval Prolongation: QTc interval prolongation, which may lead to an increased risk for ventricular tachyarrhythmia (e.g., torsades de pointes) or sudden death, occurred in patients treated with Cerinib. Across clinical studies, 6% of 919 patients with at least one post-baseline ECG assessment experienced a QTc interval increase over baseline of greater than 60 msec. Approximately 1.3% of patients taking Cerinib 750 mg fasted were found to have a QTc greater than 500 msec. When possible, use of Cerinib should be avoided in patients with congenital long QT syndrome. Periodic monitoring should be conducted with electrocardiograms (ECGs) and electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or those who are taking medications that are known to prolong the QTc interval.

Hyperglycemia: Hyperglycemia occurred in patients receiving Cerinib. Across clinical studies, CTCAE Grade 3 or 4 hyperglycemia, based on laboratory values, occurred in 13% of 925 patients. Fasting serum glucose should be monitored prior to the start of Cerinib treatment and periodically thereafter as clinically indicated. Based on the severity of the adverse drug reaction, Cerinib should be withheld until hyperglycemia is adequately controlled, then resume Cerinib at a reduced dose.

Bradycardia: Bradycardia occurred in patients receiving Cerinib. Across clinical studies, sinus bradycardia, defined as a heart rate of less than 50 beats per minute (bpm), was noted as a new finding in 1% of 925 patients. Bradycardia was reported as an adverse drug reaction in 1% of patients. No patient required discontinuation and 0.1% required interruption with subsequent dose reduction for bradycardia. Using Cerinib should be avoided in combination with other agents known to cause bradycardia (e.g., beta-blockers, nondihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Heart rate and blood pressure should be regularly monitored. In cases of symptomatic bradycardia that is not life-threatening, Cerinib should be withheld until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, evaluate the use of concomitant medications, and adjust the dose of Cerinib.

Pancreatitis: Pancreatitis occurred in patients receiving Cerinib. Pancreatitis, including one fatality, occurred in less than 1% of patients receiving Cerinib in clinical studies. CTCAE Grade 3 or 4 elevations of amylase occurred in 7% of patients receiving Cerinib across clinical studies, while CTCAE Grade 3 or 4 elevations of lipase occurred in 14% of patients. Lipase and amylase should be monitored prior to the start of Cerinib treatment and periodically thereafter as clinically indicated. Based on the severity of the laboratory abnormalities, Cerinib should be withheld with resumption at a reduced dose.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animal studies, Cerinib 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 Cerinib and for 6 months following completion of therapy. Based on the potential for genotoxicity, males with female partners of reproductive potential should be advised to use condoms during treatment with Cerinib and for 3 months following completion of therapy.

Overdose: There is no data available.

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

Packing: Each box contains 30 capsules in blister pack.