TIZICER 150
Ceritinib Capsules 150 mg

Rx only

COMPOSITION

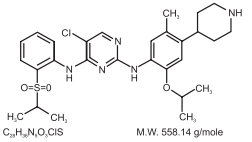
Ceritinib Capsules 150 mg

TIZICER150

Each hard gelatin capsules contains:
Ceritinib 150 mg
Excipients: q.s
Colours: Approved colours used in capsule shell

DESCRIPTION

TIZICER (ceritinib) is a tyrosine kinase inhibitor for oral administration. The molecular formula is $C_{28}H_{36}N_5O_3ClS$. The molecular weight is 558.14 g/mole. It is described chemically as 5-Chloro-N4-[2-[(1-methylethyl) sulfonyl] phenyl]-N2-[5-methyl-2-(1-methylethoxy)-4-(4-piperidinyl) phenyl]-2, 4-pyrimidinediamine.
The structural formula is:



$C_{28}H_{36}N_5O_3ClS$ M.W. 558.14 g/mole

Ceritinib is a white to almost white or light yellow or light brown powder with a pKa of 9. 7 and 4.1.
TIZICER is supplied as hard-gelatin capsules containing 150 mg of ceritinib.

CLINICAL PHARMACOLOGY

Mechanism of Action:

TIZICER is a kinase inhibitor. Targets of TIZICER inhibition identified in either biochemical or cellular assays at clinically relevant concentrations includeAlK, insulin-like growth factor 1 receptor (IGF-1 R), insulin receptor (InsR), and ROS1. Among these, ceritinib is most active against AIK. TIZICER inhibited autophosphorylation of AIK, AIK-mediated phosphorylation of the downstream signaling protein STAT3, and proliferation of AIK-dependent cancer cells in in vitro and in vivo assays.
TIZICER inhibited the in vitro proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins and demonstrated dose-dependent inhibition of EML4-AIK-positive NSCLC xenograft growth in mice and rats. TIZICER exhibited dose-dependent anti-tumor activity in mice bearing EML4-ALK-positive NSCIC xenografts with demonstrated resistance to TIZICER, at concentrations within a clinically relevant range.

Pharmacodynamics

Cardiac Electrophysiology

Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of TIZICER on the QT interval in an open-label, dose-escalation, and expansion study. A total of 304 patients were treated with TIZICER doses ranging from 50 to 750 mg with 255 patients treated with TIZICER 750 mg. One of 304 patients (less than 1%) was found to have a QTcgreater than 500 msec and 10 patients (3%) had an increase from baseline QTc greater than 60 msec. A central tendency analysis of the QTc data at average steady-state concentrations demonstrated that the upper bound of the 2-sided 90% CI for QTc was 16 msec at TIZICER 750 mg. A pharmacokinetic/pharmacodynamic analysis suggested concentration-dependent QTc interval prolongation.

Pharmacokinetics:

Absorption: After single oral administration of TIZICER in patients, peak plasma levels (Cmax) of ceritinib were achieved at approximately 4 to 6 hours, and area under the curve (ALIC) and Cmax increased dose proportionally over 50 to 750 mg. The absolute bio availability of TIZICER has not been determined.

Distribution: TIZICER is 97% bound to human plasma proteins, independent of drug concentration. The apparent volume of distribution (Vd/F) is 4230 L following a single 750 mg TIZICER dose in patients. TIZICER 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 TIZICER dose, the geometric mean apparent plasma terminal half-life (11/2) of ceritinib was 41 hours in patients. TIZICER demonstrates nonlinear PK over time. The geometric mean apparent clearance (CUF) of TIZICER was lower at steady-state (33.2 Uh) after750 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 TIZICER. Following oral administration of a single 750 mg radiolabeled TIZICER dose, TIZICER as the parent compound was the main circulating component (82%) in human plasma.

Excretion: Following oral administration of a single 750 mg radiolabeled TIZICER dose, 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.

Specific Populations:

Age, Gender, Race, and Body Weight: Age, gender, race, and body weight had no clinically important effect on the systemic exposure of TIZICER based on population pharmacokinetic analyses.

Hepatic Impairment: As TIZICER is eliminated primarily via the liver, patients with hepatic impairment may have increased exposure. A pharmacokinetic trial in patients with hepatic impairment has not been conducted. Based on a population pharmacokinetic analysis of 48 patients with mild hepatic impairment (total bilirubin less than or equal to UIN and AST greater than UIN or total bilirubin greater than 1.0 to 1.5 times UIN and any AST) and 254 patients with normal hepatic function (total bilirubin less than or equal to UIN and AST less than or equal to ULN), TIZICER exposures were similar in patients with mild hepatic impairment and normal hepatic function. The pharmacokinetics of TIZICER has not been studied in patients with moderate to severe hepatic impairment.

Renal Impairment: A pharmacokinetic trial in patients with renal impairment has not been conducted as TIZICER elimination via the kidney is low (1.3% of a single oral administered dose). Based on a population pharmacokinetic analysis of 97 patients with mild renal impairment (Cler 60 to less than 90 ml/min), 22 patients with moderate renal impairment (Cler 30 to less than 60 mUmin) and 183 patients with normal renal function (greater than or equal to 90 ml/min), TIZICER exposures were similar in patients with mild and moderate renal impairment and normal renal function, suggesting that no dose adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment (Cler less than 30 mUmin) were not included in the clinical trial.

Pediatrics: No trials have been conducted to evaluate the pharmacokinetics of TIZICER in pediatric patients.

Drug Interactions

Effect of Strong CYP3A Inhibitors on TIZICER: In vitro studies show that TIZICER is a substrate of CYP3A. Co-administration of a single 450 mg TIZICER dose with ketoconazole (a strong CYP3Ainhibitor) 200 mg twice daily for 14 days increased TIZICER AUC (90% CI) by 2.9-fold (2.5, 3.3) and Cmax (90% CI) by 22% (7%, 39%) in 19 healthy subjects. The steady-state ALIC of cTIZICER at reduced doses after co-administration with ketoconazole 200 mg twice daily for 14 days was predicted by simulations to be similar to the steady-state ALIC of TIZICER alone.

INDICATIONS

TIZICER is indicated for the treatment of patients with anaplastic lymphoma kinase (AIK)-positive metastatic non small cell lung cancer (NSCLC) who have progressed on or are intolerant to TIZICER. This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

DOSAGE AND ADMINISTRATION

Dosing and Administration

The recommended dose of TIZICER is 750 mg orally once daily until disease progression or unacceptable toxicity. Administer TIZICER on an empty stomach (i.e., do not administer within 2 hours of a meal).
A recommended dose has not been determined for patients with moderate to severe hepatic impairment.
If a dose of TIZICER 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 TIZICER.

Dose Modifications for Adverse Reactions:

Recommendations for dose modifications of TIZICER for adverse reactions are provided in Table 1. Approximately 58% of patients initiating treatment at the recommended dose required at least one dose reduction and the median time to first dose reduction was 7 weeks. Discontinue TIZICER for patients unable to tolerate 300 mg daily.

Table 1: TIZICER Dose Interruption, Reduction, or Discontinuation Recommendations:

Size: 128x182 mm

Criteria	TIZICER Dosing
ALT or AST elevation greater than 5 times ULN with total bilirubin elevation less than or equal lo 2 times ULN	Withhold until recovery lo baseline or less than or equal lo 3 limes ULN, then resume TIZIICER with a 150 mg dose reduction.
ALT or AST elevation greater than 3 times ULN with total bilirubin elevation greater than 2 limes ULN in the absence of cholestasis or hemolysis	Permanently discontinue TIZICER.
Any Grade treatment-related ILD/pneumonitis	Permanently discontinue TIZICER.
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 TIZICER with a 150 mg dose reduction.
Qtc interval prolongation in combination with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue TIZICER.
Persistent hyperglycemia greater than 250 mg/dLdespite optimal anti-hyperglycemic therapy	Withhold until hyperglycemia is adequately controlled, then resume TIZICER with a 150 mg dose reduction. If adequate hyperglycemic control cannot be achieved with optimal medical management, discontinue TIZICER.
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, and adjust the dose of TIZICER.
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 TIZICER 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 TIZICER.
Lipase or amylase elevation greater than 2 times ULN.	Withhold and monitor serum lipase and amylase. Resume TIZICER with a 150 mg dose reduction after recovery to less than 1.5 times ULN.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; ILD, interstitial lung disease; ECG, electrocardiogram.	

CONTRAINDICATIONS
None.

ADVERSE REACTIONS:
The following adverse reactions are discussed in greater detail in other sections of the labeling:
- Severe or Persistent Gastrointestinal Toxicity
- Hepatotoxicity
- Interstitial Lung Disease/Pneumonitis
- QT Interval Prolongation
- Hyperglycemia
- Bradycardia

WARNINGS AND PRECAUTIONS

Severe or Persistent Gastrointestinal Toxicity:
Diarrhea, nausea, vomiting, or abdominal pain occurred in 96% of 255 patients including severe cases in 14% of patients treated with TIZICER in Study 1. Dose modification due to diarrhea, nausea, vomiting, or abdominal pain occurred in 38% of patients.

Hepatotoxicity:
Drug-induced hepatotoxicily occurred in patients treated with TIZICER. Elevations in alanine aminotransferase (ALT) greater than 5 times the upper limit of normal (ULN) occurred in 27% of 255 patients in Study 1. One patient (0.4%) required permanent discontinuation due lo elevated Iransaminases, and jaundice. Concurrent elevations in ALT greater than 3 limes the ULN and total bilirubin greater than 2 times the ULN, with normal alkaline phosphatase, occurred in less than 1 % of patients in clinical studies.

Interstitial Lung Disease (ILD)/Pneumonitis
Severe, life-threatening, or fatal ILD/pneumonitis can occur in patients treated with TIZICER. In Study 1, pneumonitis was reported in 4% of 255 patients treated with TIZICER. CTCAE Grade 3 or 4 ILD/pneumonitis was reported in 3% of patients, and fatal ILD/pneumonitis was reported in 1 patient(0.4%) in Study 1. One percent (1 %) of patients discontinued TIZICER in Study 1 due to ILD/pneumonitis.

QT Interval Prolongation
Qtc interval prolongation, which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de pointes) or sudden death, occurred in patients treated with TIZICER in clinical trials. Three percent (3%) of 255 patients experienced a QTc interval increase over baseline greater than 60 msec in Study 1. Across the development program of TIZICER, one of 304 patients (less than 1 %) treated with TIZICER doses ranging from 50 to 750 mg was found to have a QTc greater than 500 msec and 3% of patients had an increase from baseline QTc greater than 60 msec. A pharmacokinetic analysis suggested that TIZICER causes concentration-dependent increases in the QTc interval.

Hyperglycemia
Hyperglycemia can occur in patients receiving TIZICER. In Study 1, CTCAE Grade 3-4 hyperglycemia, based on laboratory values, occurred in 13% of 255 patients. There was a 6-fold increase in the risk of CTCAE Grade 3-4 hyperglycemia in patients with diabetes or glucose intolerance and a 2-fold increase in patients taking corticosteroids.

Bradycardia
Bradycardia can occur in patients receiving TIZICER. In Study 1, sinus bradycardia, defined as a heart rate ofless than 50 beats per minute, was noted as a new finding in 1 % of 255 patients.
Avoid using TIZICER in combination with other agents known to cause bradycardia (e.g., beta-blockers, nondihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Monitor heart rate and blood pressure regularly. In cases of symptomatic bradycardia that is not life-threatening, withhold TIZICER 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 TIZICER.

Embryofetal Toxicity
Based on its mechanism of action, TIZICER may cause fetal harm when administered to a pregnant woman. In animal studies, administration of TIZICER to rats and rabbits during organogenesis at maternal plasma exposures below the recommended human dose of 750 mg daily caused increases in skeletal anomalies in rats and rabbits. Apprise women of reproductive potential of the potential hazard to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TIZICER and for at least 2 weeks following completion of therapy.

HOW SUPPLIED
TIZICER 150 supplied in a bottle of 50 capsules packed in a HDPE container.

STORAGE
Store at 25°C (77° F); excursions permitted between 15°C to 30°C (59° F to 86° F)
Protect from light.

SHELF LIFE
24 months

MANUFACTURED & MARKETED BY:
Tizig Pharma Private Limited
Factory: Tukucha, Nala-1, Banepa, Nepal.
Regd. Office: Maligaun-5, Kathmandu, Nepal.