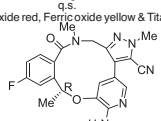
LORLATIZ 25/100
Lorlatinib Tablets 25mg / 100 mg

Rx only
COMPOSITION

LORLATIZ 25
Lorlatinib Tablets 25 mg
Each film coated tablet contains
Lorlatinib 25 mg
Excipients q.s.
Colours: Ferric oxide red, Ferric oxide yellow & Titanium dioxide

LORLATIZ 100
Lorlatinib Tablets 100 mg
Each film coated tablet contains
Lorlatinib 100 mg
Excipients q.s.
Colours: Ferric oxide red, Ferric oxide yellow & Titanium dioxide



DESCRIPTION
LORLATIZ is a kinase inhibitor for oral administration. The molecular formula is $C_{21}H_{19}FN_6O_2$ (anhydrous form) and the molecular weight is 406.41 Daltons. The chemical name is (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-4,8-methenopyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile.

Lorlatinib is a white to off-white powder with a pKa of 4.92. The solubility of lorlatinib in aqueous media decreases over the range pH 2.55 to pH 8.02 from 32.38 mg/mL to 0.17 mg/mL. The log of the distribution coefficient (octanol/water) at pH 9 is 2.45.

LORLATIZ is supplied as tablets containing 25 mg or 100 mg of Lorlatinib with the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate. The film-coating contains hydroxypropyl methylcellulose (HPMC) 2910/hypromellose, lactose monohydrate, macrogol/polyethylene glycol (PEG) 3350, triacetin, ferric oxide red, ferric oxide yellow & Titanium dioxide

CLINICAL PHARMACOLOGY
Mechanism of Action: LORLATIZ is a kinase inhibitor with in vitro activity against ALK and ROS1 as well as TYK1, FER, FPS, TRKA, TRKB, TRKC, FAK, FAK2, and ACK. LORLATIZ demonstrated in vitro activity against multiple mutant forms of the ALK enzyme, including some mutations detected in tumors at the time of disease progression on LORLATIZ and other ALK inhibitors.
In mice subcutaneously implanted with tumors harboring EML4 fusions with either ALK variant 1 or ALK mutations, including the G1202R and I1171T mutations detected in tumors at the time of disease progression on ALK inhibitors, administration of LORLATIZ resulted in antitumor activity. LORLATIZ also demonstrated anti-tumor activity and prolonged survival in mice implanted intracranially with EML4-ALK-driven tumor cell lines. The overall antitumor activity of LORLATIZ in in vivo models was dose-dependent and correlated with inhibition of ALK phosphorylation.

Pharmacodynamics
Cardiac Electrophysiology: In 295 patients who received LORLATIZ at the recommended dosage of 100 mg once daily and had an ECG measurement in Study B7461001, the maximum mean change from baseline for PR interval was 16.4 ms (2-sided 90% upper confidence interval [CI] 19.4 ms). Among the 284 patients with PR interval <200 ms at baseline, 14% had PR interval prolongation ≥200 ms after starting LORLATIZ. The prolongation of PR interval occurred in a concentration-dependent manner. Atrioventricular block occurred in 1% of patients.
In 275 patients who received LORLATIZ at the recommended dosage in the activity-estimation cohort of Study B7461001, no large mean increases from baseline in the QTcF interval (i.e., >20 ms) were detected.
Pharmacokinetics
Steady-state LORLATIZ maximum plasma concentration (Cmax) increases proportionally and AUC increased slightly less than proportionally over the dose range of 1 mg to 200 mg orally once daily (0.1 to 2 times the recommended dosage). At the recommended dosage, the mean (coefficient of variation [CV] %) Cmax was 577 ng/mL (42%) and the $AUC_{ss,24h}$ was 5650 ng.h/mL (39%) in patients with cancer. LORLATIZ oral clearance increased at steady-state compared to single dose, indicating autoinduction.
Absorption: The median LORLATIZ Tmax was 1.2 hours (0.5 to 4 hours) following a single oral 100 mg dose and 2 hours (0.5 to 23 hours) following 100 mg orally once daily at steady state. The mean absolute bio availability is 81% (90% CI 75.7%, 86.2%) after oral administration compared to intravenous administration.
Effect of Food: Administration of LORLATIZ with a high fat, high calorie meal (approximately 1000 calories with 150 calories from protein, 250 calories from carbohydrate, and 500 to 600 calories from fat) had no clinically meaningful effect on LORLATIZ pharmacokinetics.
Distribution: In vitro, LORLATIZ was 66% bound to plasma proteins at a concentration of 2.4 µM. The blood-to-plasma ratio was 0.99. The mean (CV%) steady state volume of distribution (Vss) was 305 L (28%) following a single intravenous dose.
Elimination: The mean plasma half-life (t½) of LORLATIZ was 24 hours (40%) after a single oral 100 mg dose of LORLATIZ. The mean oral clearance (CL/F) was 11 L/h (35%) following a single oral 100 mg dose and increased to 18 L/h (39%) at steady state, suggesting autoinduction.
Metabolism: *In vitro*, LORLATIZ is metabolized primarily by CYP3A4 and UGT1A4, with minor contribution from CYP2C8, CYP2C19, CYP3A5, and UGT1A3.
In plasma, a benzoic acid metabolite (M8) of LORLATIZ resulting from the oxidative cleavage of the amide and aromatic ether bonds of LORLATIZ accounted for 21% of the circulating radioactivity in a human [14C] mass balance study. The oxidative cleavage metabolite, M8, is pharmacologically inactive.
Excretion: Following a single oral 100 mg dose of radiolabeled LORLATIZ, 48% of the radioactivity was recovered in urine (<1% as unchanged) and 41% in feces (about 9% as unchanged).

INDICATIONS AND USAGE
LORLATIZ is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on
- LORLATIZ and at least one other ALK inhibitor for metastatic disease; or
- LORLATIZ as the first ALK inhibitor therapy for metastatic disease; or
- LORLATIZ as the first ALK inhibitor therapy for metastatic disease.

This indication is approved under accelerated approval based on tumor response rate and duration of response

DOSAGE AND ADMINISTRATION
The recommended dosage of LORLATIZ is 100 mg orally once daily, with or without food, until disease progression or unacceptable toxicity. Swallow tablets whole. Do not chew, crush or split tablets. Do not ingest if tablets are broken, cracked, or otherwise not intact.
Take LORLATIZ at the same time each day. If a dose is missed, then take the missed dose unless the next dose is due within 4 hours. Do not take 2 doses at the same time to make up for a missed dose. Do not take an additional dose if vomiting occurs after LORLATIZ but continue with the next scheduled dose.
Dosage Modifications for Adverse Reactions
The recommended dose reductions are:
- First dose reduction: LORLATIZ 75 mg orally once daily
- Second dose reduction: LORLATIZ 50 mg orally once daily

Permanently discontinue LORLATIZ in patients who are unable to tolerate 50 mg orally once daily.
Dosage modifications for adverse reactions of LORLATIZ are provided in Table 1.
Abbreviation: AV=atrioventricular.
*Grade based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

ADVERSE REACTIONS
The following adverse reactions are described elsewhere in the labeling:
- Risk of Serious Hepatotoxicity with Concomitant Use of Strong CYP3A Inducers
- Central Nervous System Effects
- Hyperlipidemia
- Atrioventricular Block
- Interstitial Lung Disease/Pneumonitis

The most common (≥20%) adverse reactions were edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight gain, arthralgia, mood effects, and diarrhea. Of the worsening laboratory values occurring in ≥20% of patients, the most common were hypercholesterolemia, hypertriglyceridemia, anemia, hyperglycemia, increased AST, hypoalbuminemia, increased ALT, increased lipase, and increased alkaline phosphatase.

Serious adverse reactions occurred in 32% of the 295 patients; the most frequently reported serious adverse reactions were pneumonia (3.4%), dyspnea (2.7%), pyrexia (2%), mental status changes (1.4%), and respiratory failure (1.4%). Fatal adverse reactions occurred in 2.7% of patients and included pneumonia (0.7%), myocardial infarction (0.7%), acute pulmonary edema (0.3%), embolism (0.3%), peripheral artery occlusion (0.3%), and respiratory distress (0.3%). Permanent discontinuation of lorlatinib for adverse reactions occurred in 8% of patients.

Adverse Reaction*	Dosage Modifications
Central Nervous System Effects	
Grade 1	Continue at the same dose or withhold the dose until recovery to baseline. Resume LORLATIZ at the same dose or at a reduced dose.
Grade 2 OR Grade 3	Withhold dose until Grade 0 or 1. Resume LORLATIZ at a reduced dose.
Grade 4	Permanently discontinue LORLATIZ
Hyperlipidemia	
Grade 4 hypercholesterolemia OR Grade 4 hypertriglyceridemia	Withhold LORLATIZ until recovery of hypercholesterolemia and/or hypertriglyceridemia to less than or equal to Grade 2. Resume LORLATIZ at the same dose. If severe hypercholesterolemia and/or hypertriglyceridemia recurs, resume LORLATIZ at a reduced dose.
Atrioventricular (AV) Block	
Grade 4 hypercholesterolemia OR Grade 4 hypertriglyceridemia	Withhold LORLATIZ until recovery of hypercholesterolemia and/or hypertriglyceridemia to less than or equal to Grade 2. Resume lorlatinib at the same dose. If severe hypercholesterolemia and/or hypertriglyceridemia recurs, resume LORLATIZ at a reduced dose.
Second-degree AV block	Withhold LORLATIZ until PR interval is less than 200 ms. Resume LORLATIZ at a reduced dose.
First occurrence of complete AV block	Withhold LORLATIZ until • pacemaker placed OR • PR interval less than 200 ms. If a pacemaker is placed, resume lorlatinib at the same dose. If no pacemaker is placed, resume lorlatinib at a reduced dose.
Recurrent complete AV block	Place pacemaker or permanently discontinue LORLATIZ.
Interstitial Lung Disease (ILD)/Pneumonitis	
Any Grade treatment–related ILD/Pneumonitis	Permanently discontinue lorlatinib.

Size : 100 x 182 mm

Adverse Reaction*	Dosage Modifications
Other Adverse Reactions	
Grade 1 OR Grade 2	Continue LORLATIZ at same dose or reduced dose.
Grade 3 OR Grade 4	Withhold LORLATIZ until symptoms resolve to less than or equal to Grade 2 or baseline. Resume lorlatinib at reduced dose.

Table 1 Recommended LORLATIZ Dosage Modifications for Adverse Reactions

Tables 2 summarize common adverse reactions and laboratory abnormalities, respectively, in patients treated with lorlatinib

Abbreviations: NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; SOC=System organ class.

*Adverse reactions were graded using NCI CTCAE version 4.0.

†Mood effects (including affective disorder, affect lability, aggression, agitation, anxiety, depressed mood, depression, euphoric mood, irritability, mania, mood altered, mood swings, personality change, stress, suicidal ideation).

‡Peripheral neuropathy (including burning sensation, carpal tunnel syndrome, dysesthesia, formication, gait disturbance, hypoesthesia, muscular weakness, neuralgia, neuropathy peripheral, neurotoxicity, paresthesia, peripheral sensory neuropathy, sensory disturbance).

§Cognitive effects (including events from SOC Nervous system disorders: amnesia, cognitive disorder, dementia, disturbance in attention, memory impairment, mental impairment; and also including events from SOC Psychiatric disorders: attention deficit/hyperactivity disorder, confusional state, delirium, disorientation, reading disorder).

¶Speech effects (including aphasia, dysarthria, slow speech, speech disorder)

#Sleep effects (including abnormal dreams, insomnia, nightmare, sleep disorder, sleep talking, somnambulism)

ÞVision disorder (including blindness, diplopia, photophobia, photopsia, vision blurred, visual acuity reduced, visual impairment, vitreous floaters).

ßMyalgia (including musculoskeletal pain, myalgia).

ÀEdema (including edema, edema peripheral, eyelid edema, face edema, generalized edema, localized edema, periorbital edema, peripheral swelling, swelling).

ÉFatigue (including asthenia, fatigue).

ÐUpper respiratory infection (including fungal upper respiratory infection, upper respiratory infection, viral upper respiratory infection).

ØRash (including dermatitis acneiform, maculopapular rash, pruritic rash, rash

Adverse Reaction*	LORLATIZ (N=295)	
	All Grades (%)	Grade 3 or 4 (%)
Psychiatric		
Mood effects† 23	1.7	
Nervous system		
Peripheral neuropathy‡	47	2.7
Cognitive effects§ 27	2.0	
Headache	18	0.7
Dizziness	16	0.7
Speech effects¶ 12	0.3	
Sleep effects# 10	0	
Respiratory		
Dyspnea	27	5.4
Cough	18	0
Ocular		
Vision disorderÞ 15	0.3	
Gastrointestinal		
Diarrhea	22	0.7
Nausea	18	0.7
Constipation	15	0
Vomiting	12	1
Musculoskeletal and connective tissue		
Arthralgia	23	0.7
Myalgiaß 17	0	
Back pain	13	0.7
Pain in extremity	13	0.3
General		
Edemaà 57	3.1	
Fatigueá 26	0.3	
Weight gain	24	4.4
Pyrexia	12	0.7
Infections		
Upper respiratory tract infectionð	12	0
Skin		
Rashø 14	0.3	

CONTRAINDICATIONS

LORLATIZ is contraindicated in patients taking strong CYP3A inducers, due to the potential for serious hepatotoxicity

DRUG INTERACTIONS

Effect of CYP3A Inducers on LORLATIZ: Concomitant use of LORLATIZ with a strong CYP3A inducer decreased LORLATIZ plasma concentrations, which may decrease the efficacy of LORLATIZ. The effect of concomitant use of LORLATIZ with a moderate CYP3A inducer on LORLATIZ plasma concentrations has not been studied.

Effect of LORLATIZ on CYP3A Substrates: Concomitant use of LORLATIZ decreases the concentration of CYP3A substrates, which may reduce the efficacy of these substrates. LORLATIZ is considered a moderate CYP3A inducer. Avoid concomitant use of LORLATIZ with CYP3A substrates, for which minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the CYP3A substrate dosage in accordance with approved product labeling.

WARNINGS AND PRECAUTIONS

Risk of Serious Hepatotoxicity with Concomitant Use of Strong CYP3A Inducers

Severe hepatotoxicity occurred in 10 of 12 healthy subjects receiving a single dose of LORLATIZ with multiple daily doses of rifampin, a strong CYP3A inducer. Grade 4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations occurred in 50% of subjects, Grade 3 ALT or AST elevations occurred in 33% and Grade 2 ALT or AST elevations occurred in 8%. ALT or AST elevations occurred within 3 days and returned to within normal limits after a median of 15 days (7 to 34 days); the median time to recovery was 18 days in subjects with Grade 3 or 4 ALT or AST elevations and 7 days in subjects with Grade 2 ALT or AST elevations.

Central Nervous System Effects: A broad spectrum of central nervous system (CNS) effects can occur in patients receiving LORLATIZ. These include seizures, hallucinations, and changes in cognitive function, mood (including suicidal ideation), speech, mental status, and sleep.

Hyperlipidemia: Increases in serum cholesterol and triglycerides can occur in patients receiving LORLATIZ. Grade 3 or 4 elevations in total cholesterol occurred in 17% and Grade 3 or 4 elevations in triglycerides occurred in 17% of the 332 patients who received LORLATIZ. The median time to onset was 15 days for both hypercholesterolemia and hypertriglyceridemia.

Embryo-Fetal Toxicity: Based on findings from animal studies and its mechanism of action, LORLATIZ can cause fetal harm when administered to a pregnant woman. Administration of LORLATIZ to pregnant rats and rabbits by oral gavage during the period of organogenesis resulted in malformations, increased post-implantation loss, and abortion at maternal exposures that were equal to or less than the human exposure at the recommended dose of 100 mg once daily based on area under the curve (AUC).

OVERDOSAGE

Treatment of overdose with the medicinal product consists of general supportive measures. Given the dose-dependent effect on PR interval, ECG monitoring is recommended. There is no antidote for LORLATIZ.

HOW SUPPLIED

LORLATIZ 25 mg & 100 mg supplied in a bottle of 30 tablets packed in a HDPE container.

STORAGE

Store at 25°C (77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F).

SHELF LIFE

24 months

MANUFACTURED & MARKETED BY:

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