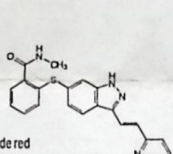
Rx only

COMPOSITION

TIZIAX 1



Axitinib Tablets 1mg

Each film coated tablet contains	
Axitinib	1 mg
Excipients	q.s.

Colours: Titanium dioxide, Iron oxide red

TIZIAX 5

Axitinib Tablets 5mg

Each film coated tablet contains	
Axitinib	5 mg
Excipients	q.s.

Colours: Titanium dioxide, Iron oxide red

DESCRIPTION

TIZIAX is a kinase inhibitor. Axitinib has the chemical name N-methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]-benzamide. The molecular formula is $C_{22}H_{18}N_4OS$ and the molecular weight is 386.47 Daltons. TIZIAX is a white to light-yellow powder with a pKa of 4.8. The solubility of TIZIAX in aqueous media over the range pH 1.1 to pH 7.8 is in excess of 0.2 µg/mL. The partition coefficient (n-octanol/water) is 3.5. TIZIAX is supplied as red, film-coated tablets containing either 1 mg or 5 mg of TIZIAX together with microcrystalline cellulose, lactose monohydrate, Croscarmellose sodium, magnesium stearate, and Titanium dioxide, Iron oxide red as inactive ingredients.

CLINICAL PHARMACOLOGY

Mechanism of Action: TIZIAX has been shown to inhibit receptor tyrosine kinases including vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2, and VEGFR-3 at therapeutic plasma concentrations. These receptors are implicated in pathologic angiogenesis, tumor growth, and cancer progression. VEGF-mediated endothelial cell proliferation and survival were inhibited by TIZIAX in vitro and in mouse models. TIZIAX was shown to inhibit tumor growth and phosphorylation of VEGFR-2 in tumor xenograft mouse models.

Pharmacodynamics: The effect of a single oral dose of TIZIAX (5 mg) in the absence and presence of 400 mg ketoconazole on the QTc interval was evaluated in a randomized, single-blinded, two-way crossover study in 35 healthy subjects. No large changes in mean QTc interval (i.e., >20 ms) from placebo were detected up to 3 hours post-dose. However, small increases in mean QTc interval (i.e., <10 ms) cannot be ruled out.

Pharmacokinetics: The population pharmacokinetic analysis pooled data from 17 trials in healthy subjects and patients with cancer. A two-compartment disposition model with first-order absorption and lag-time adequately describes the TIZIAX concentration-time profile.

Absorption and Distribution: Following single oral 5-mg dose administration, the median Tmax ranged from 2.5 to 4.1 hours. Based on the plasma half-life, steady state is expected within 2 to 3 days of dosing. Dosing of TIZIAX at 5 mg twice daily resulted in approximately 1.4-fold accumulation compared to administration of a single dose. At steady state, TIZIAX exhibits approximately linear pharmacokinetics within the 1-mg to 20-mg dose range. The mean absolute bioavailability of TIZIAX after an oral 5 mg dose is 58%. Compared to overnight fasting, administration of TIZIAX with a moderate fat meal resulted in 10% lower AUC and a high fat, high-calorie meal resulted in 19% higher AUC. TIZIAX can be administered with or without food. TIZIAX is highly bound (>99%) to human plasma proteins with preferential binding to albumin and moderate binding to α1-acid glycoprotein. In patients with advanced RCC (n=20), at the 5 mg twice daily dose in the fed state, the geometric mean (CV%) Cmax and AUC0–24 were 27.8 (79%) ng/mL and 265 (77%) ng h/mL, respectively. The geometric mean (CV%) clearance and apparent volume of distribution were 38 (80%) L/h and 160 (105%) L, respectively.

Metabolism and Elimination: The plasma half-life of TIZIAX ranges from 2.5 to 6.1 hours. TIZIAX is metabolized primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1. Following oral administration of a 5-mg radioactive dose of TIZIAX, approximately 41% of the radioactivity was recovered in feces and approximately 23% was recovered in urine. Unchanged TIZIAX accounting for 12% of the dose, was the major component identified in feces. Unchanged TIZIAX was not detected in urine; the carboxylic acid and sulfoxide metabolites accounted for the majority of radioactivity in urine. In plasma, the N-glucuronide metabolite represented the predominant radioactive component (50% of circulating radioactivity) and unchanged TIZIAX and the sulfoxide metabolite each accounted for approximately 20% of the circulating radioactivity. The sulfoxide and N-glucuronide metabolites show approximately ≥400-fold less in vitro potency against VEGFR-2 compared to TIZIAX.

INDICATIONS AND USAGE

First-Line Advanced Renal Cell Carcinoma

TIZIAX in combination with avelumab is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

TIZIAX in combination with pembrolizumab is indicated for the first-line treatment of patients with advanced renal cell carcinoma.

Second-Line Advanced Renal Cell Carcinoma

TIZIAX as a single agent is indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.

DOSAGE AND ADMINISTRATION

The recommended dose of TIZIAX orally taken twice daily (12 hours apart) with or without food.

Advise patients to swallow TIZIAX whole with a full glass of water. If the patient vomits or misses a dose, an additional dose should not be taken. Advise the patient to take the next prescribed dose at the usual time.

ADVERSE REACTIONS

The following risks, including appropriate action to be taken, are discussed in greater detail in other sections of the label: hypertension, arterial thromboembolic events, venous thromboembolic events, hemorrhage, cardiac failure, gastrointestinal perforation and fistula formation, thyroid dysfunction, wound healing complications, RPLS, proteinuria, elevation of liver enzymes, hepatic impairment and fetal development.

Table 1. Adverse Reactions Occurring in ≥10% of Patients Who Received TIZIAX or Sorafenib

Adverse Reaction*	TIZIAX (N=359)		Sorafenib (N=355)	
	All Grades†	Grade 3/4	All Grades†	Grade 3/4
	%	%	%	%
Diarrhea	55	11	53	7
Hypertension	40	16	29	11
Fatigue	39	11	32	5
Decreased appetite	34	5	29	4
Nausea	32	3	22	1
Dysphonia	31	0	14	0
Palmar-plantar erythrodysesthesia syndrome	27	5	51	16
Weight decreased	25	2	21	1
Vomiting	24	3	17	1
Asthenia	21	5	14	3
Constipation	20	1	20	1
Hypothyroidism	19	<1	8	0
Cough	15	1	17	1
Mucosal inflammation	15	1	12	1
Arthralgia	15	2	11	1
Stomatitis	15	1	12	<1
Dyspnea	15	3	12	3
Abdominal pain	14	2	11	1
Headache	14	1	11	0
Pain in extremity	13	1	14	1
Rash	13	<1	32	4
Proteinuria	11	3	7	2
Dysgeusia	11	0	8	0
Dry skin	10	0	11	0
Dyspepsia	10	0	2	0
Pruritus	7	0	12	0
Alopecia	4	0	32	0
Erythymia	2	0	10	<1

Selected adverse reactions (all grades) that were reported in <10% of patients treated with TIZIAX included dizziness (9%), upper abdominal pain (8%), myalgia (7%), dehydration (6%), epistaxis (6%), anemia (4%), hemorrhoids (4%), hematuria (3%), tinnitus (3%), lipase increased (3%), glossodynia (3%), pulmonary embolism (2%), rectal hemorrhage (2%), hemoptysis (2%), deep vein thrombosis (1%), retinal-vein occlusion/thrombosis (1%), polycythemia (1%), and transient ischemic attack (1%).

Table 2 presents the most common laboratory abnormalities reported in ≥10% patients who received TIZIAX or sorafenib.

Laboratory Abnormality	N	TIZIAX		N	Sorafenib	
		All Grades* %	Grade 3/4 %		All Grades* %	Grade 3/4 %
Hematology						
Hemoglobin decreased	320	35	<1	316	52	4
Lymphocytes (absolute) decreased	317	33	3	309	36	4
Platelets decreased	312	15	<1	310	14	0
White blood cells decreased	320	11	0	315	16	<1
Chemistry						
Creatinine increased	336	55	0	318	41	<1
Bicarbonate decreased	314	44	<1	291	43	0
Hypocalcemia	336	39	1	319	59	2
ALP increased	336	30	1	319	34	1
Hyperglycemia	336	28	2	319	23	2
Lipase increased	338	27	5	319	46	15
Amylase increased	338	25	2	319	33	2
ALT increased	331	22	<1	313	22	2
AST increased	331	20	<1	311	25	1
Hypernatremia	338	17	1	319	13	1
Hypoalbuminemia	337	15	<1	319	18	1
Hyperkalemia	333	15	3	314	10	3
Hypoglycemia	336	11	<1	319	8	<1
Hyponatremia	338	13	4	319	11	2
Hypophosphatemia	336	13	2	318	49	16

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase

* National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0

CONTRAINDICATIONS

None.

DRUG INTERACTIONS:

In vitro data indicate that TIZIAX is metabolized primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase (UGT) 1A1.

CYP3A4/5 Inhibitors

Co-administration of ketoconazole, a strong inhibitor of CYP3A4/5, increased the plasma exposure of TIZIAX in healthy volunteers. Co-administration of TIZIAX with strong CYP3A4/5 inhibitors should be avoided. Grapefruit or grapefruit juice may also increase TIZIAX plasma concentrations and should be avoided. Selection of concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be co-administered, the TIZIAX dose should be reduced.

CYP3A4/5 Inducers

Co-administration of rifampin, a strong inducer of CYP3A4/5, reduced the plasma exposure of TIZIAX in healthy volunteers. Co-administration of TIZIAX with strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and St. John's wort) should be avoided. Selection of concomitant medication with no or minimal CYP3A4/5 induction potential is recommended. Moderate CYP3A4/5 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) may also reduce the plasma exposure of TIZIAX and should be avoided if possible.

WARNINGS AND PRECAUTIONS

Hypertension: In a controlled clinical study with TIZIAX for the treatment of patients with RCC, hypertension was reported in 145/359 patients (40%) receiving TIZIAX and 103/355 patients (29%) receiving sorafenib. Grade 3/4 hypertension was observed in 56/359 patients (16%) receiving TIZIAX and 39/355 patients (11%) receiving sorafenib. Hypertensive crisis was reported in 2/359 patients (<1%) receiving TIZIAX and none of the patients receiving sorafenib

Discontinue TIZIAX if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of TIZIAX, and discontinuation should be considered if there is evidence of hypertensive crisis. If TIZIAX is interrupted, patients receiving antihypertensive medications should be monitored for hypotension.

Arterial Thromboembolic Events: In clinical trials, arterial thromboembolic events have been reported, including deaths. In a controlled clinical study with TIZIAX for the treatment of patients with RCC, Grade 3/4 arterial thromboembolic events were reported in 4/359 patients (1%) receiving TIZIAX and 4/355 patients (1%) receiving sorafenib.

Use TIZIAX with caution in patients who are at risk for, or who have a history of, these events. TIZIAX has not been studied in patients who had an arterial thromboembolic event within the previous 12 months.

Venous Thromboembolic Events: In clinical trials, venous thromboembolic events have been reported, including deaths. In a controlled clinical study with TIZIAX for the treatment of patients with RCC, venous thromboembolic events were reported in 11/359 patients (3%) receiving TIZIAX and 2/355 patients (1%) receiving sorafenib. Grade 3/4 venous thromboembolic events were reported in 9/359 patients (3%) receiving TIZIAX

Use TIZIAX with caution in patients who are at risk for, or who have a history of, these events. TIZIAX has not been studied in patients who had a venous thromboembolic event within the previous 6 months.

Hemorrhage: In a controlled clinical study with TIZIAX for the treatment of patients with RCC, hemorrhagic events were reported in 58/359 patients (16%) receiving TIZIAX and 64/355 patients (18%) receiving sorafenib. Grade 3/4 hemorrhagic events were reported in 5/359 (1%) patients receiving TIZIAX.

TIZIAX has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the TIZIAX dose.

Cardiac Failure: In a controlled clinical study with TIZIAX for the treatment of patients with RCC, cardiac failure was reported in 6/359 patients (2%) receiving TIZIAX and 3/355 patients (1%) receiving sorafenib. Grade 3/4 cardiac failure was observed in 2/359 patients (1%) receiving TIZIAX and 1/355 patients (<1%) receiving sorafenib. Fatal cardiac failure was reported in 2/359 patients (1%) receiving TIZIAX and 1/355 patients (<1%) receiving sorafenib. Monitor for signs or symptoms of cardiac failure throughout treatment with TIZIAX Management of cardiac failure may require permanent discontinuation of TIZIAX.

Gastrointestinal Perforation and Fistula Formation: In a controlled clinical study with for the treatment of patients with RCC, gastrointestinal perforation was reported in 1/359 patients (<1%) receiving TIZIAX and none of the patients receiving sorafenib. In clinical trials with TIZIAX gastrointestinal perforation was reported in 5/715 patients (1%), including one death. In addition to cases of gastrointestinal perforation, fistulas were reported in 4/715 patients (1%).

Monitor for TIZIAX symptoms of gastrointestinal perforation or fistula periodically throughout treatment with TIZIAX.

Thyroid Dysfunction: In a controlled clinical study with TIZIAX for the treatment of patients with RCC, hypothyroidism was reported in 69/359 patients (19%) receiving TIZIAX and 29/355 patients (8%) receiving sorafenib. Hyperthyroidism was reported in 4/359 patients (1%) receiving TIZIAX and 4/355 patients (1%) receiving sorafenib. In patients who had thyroid stimulating hormone (TSH) <5 µU/mL before treatment, elevations of TSH to ≥10 µU/mL occurred in 79/245 patients (32%) receiving TIZIAX and 25/232 patients (11%) receiving sorafenib.

Monitor thyroid function before initiation of, and periodically throughout, treatment with TIZIAX. Treat hypothyroidism and hyperthyroidism according to standard medical practice to maintain euthyroid state.

Elevation of Liver Enzymes: In a controlled clinical study with TIZIAX for the treatment of patients with RCC, alanine aminotransferase (ALT) elevations of all grades occurred in 22% of patients on both arms, with Grade 3/4 events in <1% of patients on the TIZIAX arm and 2% of patients on the sorafenib arm.

Monitor ALT, aspartate aminotransferase (AST) and bilirubin before initiation of and periodically throughout treatment with TIZIAX.

Hepatic Impairment: The systemic exposure to TIZIAX was higher in subjects with moderate hepatic impairment (Child-Pugh class B) compared to subjects with normal hepatic function. A dose decrease is recommended when administering TIZIAX to patients with moderate hepatic impairment (Child-Pugh class B). TIZIAX has not been studied in patients with severe hepatic impairment (Child-Pugh class C)

Pregnancy: TIZIAX can cause fetal harm when administered to a pregnant woman based on its mechanism of action. There are no adequate and well-controlled studies in pregnant women using TIZIAX. In developmental toxicity studies in mice, TIZIAX was teratogenic, embryotoxic and fetotoxic at maternal exposures that were lower than human exposures at the recommended clinical dose.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving TIZIAX. If this drug is used during pregnancy, or if a patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

OVER DOSAGE

There is no specific treatment for TIZIAX overdose. In a controlled clinical study with TIZIAX for the treatment of patients with RCC, 1 patient inadvertently received a dose of 20 mg twice daily for 4 days and experienced dizziness (Grade 1).

In a clinical dose finding study with TIZIAX, subjects who received starting doses of 10 mg twice daily or 20 mg twice daily experienced adverse reactions which included hypertension, seizures associated with hypertension, and fatal hemoptysis.

In cases of suspected overdose, TIZIAX should be withheld and supportive care instituted.

HOW SUPPLIED

TIZIAX supplied in a bottle of 28 tablets packed in a HDPE container.

STORAGE

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