TIVOXEN

Tivozanib 1.34 mg capsules

Everest

COMPOSITION

Tivoxen capsule: Each capsule contains 1.34 mg of Tivozanib equivalent to 1.5 mg of tivozanib hydrochloride INN.

PHARMACOLOGY

Mechanism of Action

Tivozanib is a tyrosine kinase inhibitor. In vitro cellular kinase assays demonstrated that Tivozanib inhibits phosphorylation of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2 and VEGFR-3 and inhibits other kinases including c-kit and PDGFR β at clinically relevant concentrations. In tumor xenograft models in mice and rats, Tivozanib inhibited angiogenesis, vascular permeability, and tumor growth of various tumor cell types including human renal cell carcinoma.

Pharmacokinetic properties

Absorption

The median Tmax of Tivozanib is 10 hours with a range of 3 to 24 hours.

Effect of Food

No clinically significant differences in Tivozanib AUC or Cmax were observed following administration of a high fat meal (approximately 500-600 fat calories, 250 carbohydrate calories and 150 protein calories) in healthy subjects.

Distribution

The apparent volume of distribution (V/F) of Tivozanib is 123 L. Protein binding of Tivozanib is ≥ 99%, primarily to albumin in vitro and is independent of concentration. The mean blood-to-plasma concentration ratios ranged from 0.495 to 0.615 in healthy subjects.

Elimination

The apparent clearance (CL/F) of Tivozanib is 0.75 L/h and the half-life is 111 hours.

Metabolism

Tivozanib is metabolized predominantly by CYP3A4. Following oral administration of a single radiolabeled 1.34 mg dose of Tivozanib to healthy subjects, unchanged Tivozanib constituted 90% of the radioactive drug components in serum.

Excretion

Following oral administration of a single radiolabeled 1.34 mg dose of Tivozanib to healthy subjects, 79% of the administered dose was recovered in feces (26% unchanged) and 12% in urine (unchanged Tivozanib not detected).

Specific Populations

No clinically significant differences in the pharmacokinetics of Tivozanib were observed based on age (18 years to 88 years), sex, race (93% Caucasian, 3% African American, 2% Asian, 2% others), body weight (39 kg to 158 kg), mild to severe renal impairment (CLcr 15-89 mL/min as estimated by Cockcroft-Gault) or mild hepatic impairment (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST). The effect of end-stage renal disease or severe hepatic impairment on Tivozanib pharmacokinetics is unknown.

Patients with Hepatic Impairment

Compared to subjects with normal hepatic function, Tivozanib AUCtau increased by 1% in patients with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST) hepatic impairment. Compared to subjects with normal hepatic function, Tivozanib AUCtau increased by 62% in patients with moderate (total bilirubin greater than 1.5 to 3 times ULN with any AST) hepatic impairment. The effect of severe (total bilirubin greater than 3 to 10 times ULN with any AST) hepatic impairment on Tivozanib pharmacokinetics has not been studied.

Drug Interaction Studies

Clinical Studies

Strong CYP3A Inducers: Concomitant use of multiple doses of rifampin (strong CYP3A inducer) did not change Tivozanib Cmax but decreased Tivozanib AUC0-INF by 52%.

Strong CYP3A Inhibitors: No clinically significant differences in the pharmacokinetics of Tivozanib were observed when multiple doses of ketoconazole (strong CYP3A inhibitor) was coadministered with Tivozanib.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Tivozanib does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 at clinically relevant concentrations. Tivozanib does not induce CYP1A, CYP2B6, CYP2C9, CYP2C19, or CYP3A at clinically relevant concentrations.

Uridine Diphosphate (UDP)-glucuronosyl Transferase (UGT) Enzymes

Tivozanib does not inhibit UGT at clinically relevant concentrations.

Transporter Systems

Tivozanib inhibits BCRP but does not inhibit P-gp, OCT1, OATP1B1, OATP1B3, BSEP, OAT1, OAT3, OCT2, MATE1 or MATE2-K at clinically relevant concentrations. Tivozanib is not a substrate for P-gp, MRP2, BCRP, OCT1, OATP1B1, OATP1B3, or BSEP.

INDICATIONS

Tivozanib is indicated for the treatment of adult patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies.

DOSAGE AND ADMINISTRATION

Recommended Dosing

The recommended dosage of Tivozanib is 1.34 mg taken orally once daily for 21 days on treatment followed by 7 days off treatment for a 28-day cycle.

Continue treatment until disease progression or until unacceptable toxicity occurs.

Take Tivozanib with or without food. Swallow the Tivozanib capsule whole with a glass of water. Do not open the capsule.

If a dose is missed, the next dose should be taken at the next scheduled time. Do not take two doses at the same time.

Dose Modifications for Adverse Reactions

Initiate medical management for diarrhea, nausea, or vomiting prior to dose interruption or reduction.

If dose modifications are required for adverse reactions, reduce the dosage of Tivozanib to 0.89 mg for 21 days on treatment followed by 7 days off treatment for a 28-day cycle.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Hypertension and Hypertensive Crisis

Tivozanib can cause severe hypertension and hypertensive crisis. Hypertension occurred in 45% of patients treated with Tivozanib, with 22% of the events ≥ Grade 3. Median time to onset of hypertension was 2 weeks (range: 0 – 192 weeks).

Cardiac Failure

Tivozanib can cause serious, sometimes fatal, cardiac failure. Cardiac failure in Tivozanib treated patients occurred in 1.6%, with 1% of events ≥ Grade 3, and 0.6% events were fatal.

Periodically monitor patients for symptoms of cardiac failure throughout treatment with Tivozanib.

Discontinue Tivozanib in patients who develop any severe or life-threatening arterial thromboembolic event.

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Venous Thromboembolic Events
Closely monitor patients who are at risk for, or who have a history of these events during treatment with Tivozanib. Discontinue Tivozanib in patients who develop any severe or life-threatening venous thromboembolic event.

Hemorrhagic Events
Discontinue Tivozanib in patients who develop severe or life-threatening hemorrhagic events.

Proteinuria
Monitor patients for proteinuria before initiation of, and periodically throughout, treatment with Tivozanib.

Thyroid Dysfunction
Treat hypothyroidism and hyperthyroidism to maintain euthyroid state before and during treatment with Tivozanib.

Risk of Impaired Wound Healing
Withhold Tivozanib for at least 24 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Tivozanib after resolution of wound healing complications has not been established.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) Perform an evaluation for RPLS in any patient presenting with seizures, headaches, visual disturbances, confusion, or altered mental function. Discontinue Tivozanib in patients who develop RPLS.

Embryo-Fetal Toxicity
Advise females of reproductive potential to use effective contraception during treatment with Tivozanib and for one month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Tivozanib and for one month after the last dose.

SIDE EFFECTS
The following clinically significant adverse reactions are also described elsewhere in the labeling:
- Hypertension and Hypertensive Crisis
- Cardiac Failure
- Cardiac Ischemia and Arterial Thromboembolic Events
- Venous Thromboembolic Events
- Hemorrhagic Events
- Proteinuria
- Thyroid Dysfunction
- Risk of Impaired Wound Healing
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
Based on findings in animal studies and its mechanism of action, Tivozanib can cause fetal harm when administered to a pregnant woman. There are no available data on Tivozanib use in pregnant woman to inform the drug-associated risk. In embryo-fetal developmental studies, oral administration of Tivozanib to pregnant animals during the period of organogenesis caused maternal toxicity, fetal malformations and embryo-fetal death at doses below the maximum recommended clinical dose on a mg/m2 basis. Advise pregnant woman of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically-recognized pregnancies is 2% to 4% and 15% to 20% respectively.

Lactation
There are no data on the presence of Tivozanib in human milk, or the effects of Tivozanib on the breastfed child, or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise a lactating woman not to breastfeed during treatment with Tivozanib and for one month after the last dose.

Females and Males of Reproductive Potential
Tivozanib can cause fetal harm when administered to a pregnant woman.

Pregnancy Testing
Verify pregnancy status of females of reproductive potential prior to starting treatment with Tivozanib.

Contraception
Females
Advise females of reproductive potential to use effective contraception during treatment with Tivozanib and for one month after the last dose.

Males
Advise males with female partners of reproductive potential to use effective contraception during treatment with Tivozanib and for one month after the last dose.

Infertility
Based on findings in animal studies, Tivozanib can impair fertility in females and males of reproductive potential.

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

Geriatric Use
Of the 1008 patients with advanced RCC treated with Tivozanib, 29% were ≥ 65 years of age and 4% were ≥ 75 of age. No overall differences in safety were observed between patients ≥ 65 versus < 65 years of age.

Of the 175 patients with advanced RCC following two or more prior systemic therapies randomized to Tivozanib, 44% were ≥ 65 years of age and 9% were ≥ 75 of age. No overall differences in effectiveness were observed between patients ≥ 65 versus < 65 years of age.

Renal Impairment
No dosage modification is recommended for patients with mild to severe renal impairment (creatinine clearance [CLcr] 15-89 mL/min, estimated by Cockcroft-Gault). The recommended dosage for patients with end-stage renal disease has not been established.

Hepatic Impairment
Reduce the dosage when administering Tivozanib in patients with moderate (total bilirubin greater than 1.5 to 3 times ULN with any AST) hepatic impairment. No dosage modification is recommended for patients with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST) hepatic impairment. The recommended dosage of Tivozanib in patients with severe (total bilirubin greater than 3 to 10 times ULN with any AST) hepatic impairment has not been established.

OVERDOSE
Overdosage with Tivozanib can cause severe hypertension and hypertensive crisis that may result in death.

There is no specific treatment or antidote for Tivozanib overdose.

In cases of suspected overdose, withhold Tivozanib, closely monitor patients for hypertension and hypertensive crisis and other potential adverse reactions. Immediately manage signs or symptoms of hypertension and provide other supportive care as clinically indicated.

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
Tivoxen capsule: Each HDPE container contains 21 capsules (each capsule contains 1.34 mg Tivozanib), a silica gel desiccant and polyester coil with a child-resistant closure.

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