Axinix
Axitinib

COMPOSITION

Axinix 1 Tablet: Each film coated tablet contains Axitinib INN 1 mg.

Axinix 5 Tablet: Each film coated tablet contains Axitinib INN 5 mg.

CLINICAL PHARMACOLOGY

Mechanism of Action

Axitinib 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 Axitinib in vitro and in mouse models. Axitinib 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 Axitinib (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 Axitinib concentration-time profile.

Absorption and Distribution: Following single oral 5-mg dose administration, the median T_{max} 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 Axitinib at 5 mg twice daily resulted in approximately 1.4-fold accumulation compared to administration of a single dose. At steady state, Axitinib exhibits approximately linear pharmacokinetics within the 1-mg to 20-mg dose range. The mean absolute bioavailability of Axitinib after an oral 5 mg dose is 58%.

Compared to overnight fasting, administration of Axitinib with a moderate fat meal resulted in 10% lower AUC and a high fat, high-calorie meal resulted in 19% higher AUC. Axitinib can be administered with or without food.

Axitinib 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, at the 5 mg twice daily dose in the fed state, the geometric mean (CV%) C_{max} and $AUC_{0\text{-}24}$ 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.

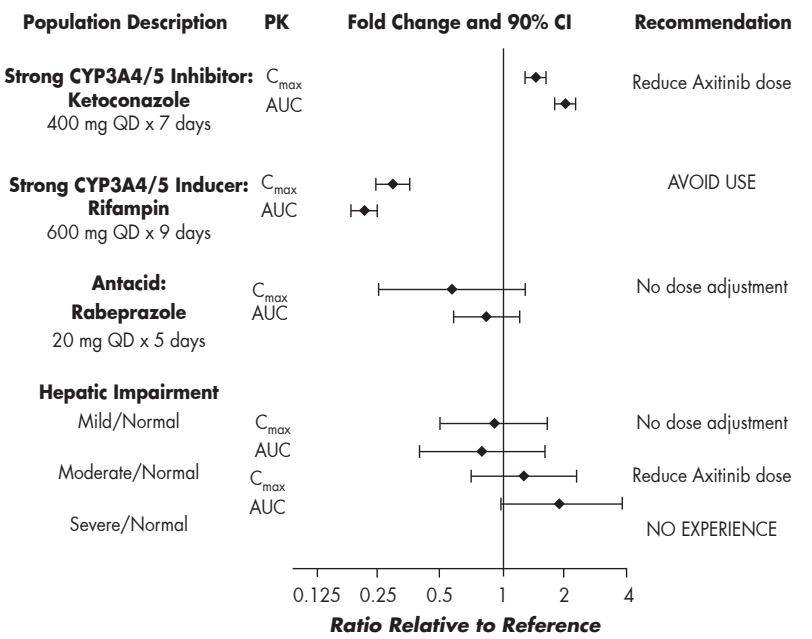
Metabolism and Elimination: The plasma half life of Axitinib ranges from 2.5 to 6.1 hours. Axitinib is metabolized primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1. Following oral administration of a 5-mg radioactive dose of Axitinib, approximately 41% of the radioactivity was recovered in feces and approximately 23% was recovered in urine. Unchanged Axitinib, accounting for 12% of the dose, was the major component identified in feces. Unchanged Axitinib 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 Axitinib 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 Axitinib.

Drug-Drug Interactions

Effects of Other Drugs on Axitinib: Axitinib is metabolized primarily in the liver by CYP3A4/5. Additionally, the aqueous solubility of Axitinib is pH dependent, with higher pH resulting in lower solubility. The effects of a strong CYP3A4/5 inhibitor, a strong CYP3A4/5 inducer, and an antacid on the pharmacokinetics of Axitinib are presented in the below Figure.

Impact of Co-administered Drugs and Hepatic Impairment on Axitinib Pharmacokinetics



AUC: area under the curve; C_{max}: maximum concentration.

Effects of Axitinib on Other Drugs: In vitro studies demonstrated that Axitinib has the potential to inhibit CYP1A2 and CYP2C8. However, co-administration of Axitinib with Paclitaxel, a CYP2C8 substrate, did not increase plasma concentrations of Paclitaxel in patients.

In vitro studies indicated that Axitinib does not inhibit CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or UGT1A1 at therapeutic plasma concentrations. In vitro studies in human hepatocytes indicated that Axitinib does not induce CYP1A1, CYP1A2, or CYP3A4/5.

Axitinib is an inhibitor of the efflux transporter P-glycoprotein (P-gp) in vitro. However, Axitinib is not expected to inhibit P-gp at therapeutic plasma concentrations.

Pharmacokinetics in Specific Populations

Pediatric Use: Axitinib has not been studied in patients <18 years of age.

Hepatic Impairment: The effects of hepatic impairment on the pharmacokinetics of Axitinib are presented in above Figure.

Renal Impairment: Population pharmacokinetic analysis (based on pre-existing renal function) was carried out in 590 healthy volunteers and patients, including five with severe renal impairment (15 mL/min ≤CLcr <29 mL/min), 64 with moderate renal impairment (30 mL/min ≤CLcr <59 mL/min), and 139 with mild renal impairment (60 mL/min ≤CLcr <89 mL/min). Mild to severe renal impairment did not have meaningful effects on the pharmacokinetics of Axitinib. Data from only one patient with end-stage renal disease are available.

Other Intrinsic Factors: Population pharmacokinetic analyses indicate that there are no clinically relevant effects of age, gender, race, body weight, body surface area, UGT1A1 genotype, or CYP2C19 genotype on the clearance of Axitinib.

INDICATION

Axitinib is indicated for the treatment of advanced Renal Cell Carcinoma (RCC) after failure of one prior systemic therapy.

DOSAGE AND ADMINISTRATION

Recommended Dosing

The recommended starting oral dose of Axitinib is 5 mg twice daily. Administer Axitinib doses approximately 12 hours apart with or without food. Axitinib should be swallowed whole with a glass of water.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

Dose Modification Guidelines

Dose increase or reduction is recommended based on individual safety and tolerability.

Over the course of treatment, patients who tolerate Axitinib for at least two consecutive weeks with no adverse reactions >Grade 2 (according to the Common Toxicity Criteria for Adverse Events [CTCAE]), are normotensive, and are not receiving anti-hypertension medication, may have their dose increased. When a dose increase from 5 mg twice daily is recommended, the Axitinib dose may be increased to 7 mg twice daily, and further to 10 mg twice daily using the same criteria.

Over the course of treatment, management of some adverse drug reactions may require temporary interruption or permanent discontinuation and/or dose reduction of Axitinib therapy. If dose reduction from 5 mg twice daily is required, the recommended dose is 3 mg twice daily. If additional dose reduction is required, the recommended dose is 2 mg twice daily.

Strong CYP3A4/5 Inhibitors: The concomitant use of strong CYP3A4/5 inhibitors should be avoided (e.g., Ketoconazole, Itraconazole, Clarithromycin, Atazanavir, Indinavir, Nefazodone, Nelfinavir, Ritonavir, Saquinavir, Telithromycin, and Voriconazole). Selection of an alternate concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. Although Axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co-administered, a dose decrease of Axitinib by approximately half is recommended, as this dose reduction is predicted to adjust the Axitinib area under the plasma concentration vs time curve (AUC) to the range observed without inhibitors. The subsequent doses can be increased or decreased based on individual safety and tolerability. If co-administration of the strong inhibitor is discontinued, the Axitinib dose should be returned (after 3 – 5 half-lives of the inhibitor) to that used prior to initiation of the strong CYP3A4/5 inhibitor.

Hepatic Impairment: No starting dose adjustment is required when administering Axitinib to patients with mild hepatic impairment (Child-Pugh class A). Based on the pharmacokinetic data, the Axitinib starting dose should be reduced by approximately half in patients with baseline moderate hepatic impairment (Child Pugh class B). The subsequent doses can be increased or decreased based on individual safety and tolerability. Axitinib has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Hypertension including hypertensive crisis has been observed. Blood pressure should be well-controlled prior to initiating Axitinib. Monitor for hypertension and treat as needed. For persistent hypertension despite use of anti-hypertensive medications, reduce the Axitinib dose.
- Arterial and venous thrombotic events have been observed and can be fatal. Use with caution in patients who are at increased risk for these events.
- Hemorrhagic events, including fatal events, have been reported. Axitinib has not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients.
- Cardiac failure has been observed and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with Axitinib.
- Gastrointestinal perforation and fistula, including death, have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula.
- Hypothyroidism requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment with Axitinib.
- Stop Axitinib at least 24 hours prior to scheduled surgery.
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been observed. Permanently discontinue Axitinib if signs or symptoms of RPLS occur.
- Monitor for proteinuria before initiation of, and periodically throughout, treatment with Axitinib. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment with Axitinib.
- Liver enzyme elevation has been observed during treatment with Axitinib. Monitor ALT, AST and bilirubin before initiation of, and periodically throughout, treatment with Axitinib.
- The starting dose of Axitinib should be decreased if used in patients with moderate hepatic impairment. Axitinib has not been studied in patients with severe hepatic impairment.
- Axitinib can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant while receiving Axitinib.

ADVERSE REACTIONS

The most common (≥20%) adverse reactions are diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, asthenia and constipation.

DRUG INTERACTIONS

In vitro data indicate that Axitinib 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 Axitinib in healthy volunteers. Co-administration of Axitinib with strong CYP3A4/5 inhibitors should be avoided. Grapefruit or grapefruit juice may also increase Axitinib 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 coadministered, the Axitinib dose should be reduced.

CYP3A4/5 Inducers

Co-administration of Rifampin, a strong inducer of CYP3A4/5, reduced the plasma exposure of Axitinib in healthy volunteers. Co-administration of Axitinib 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 Axitinib and should be avoided if possible.

PHARMACEUTICAL INFORMATION

Storage Conditions

Store in a cool and dry place, away from light. Keep out of the reach of children.

Presentation & Packaging

Axinix 1 Tablet: Each commercial box contains 180 tablets in a bottle.

Axinix 5 Tablet: Each commercial box contains 60 tablets in a bottle.

For more info:

Manufactured By
BEACON®
Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

Only for Export

LF22601