Pazonix

Pazopanib Hydrochloride INN

COMPOSITION

Pazonix 200 Tablet: Each film coated tablet contains Pazopanib Hydrochloride INN equivalent to Pazopanib 200 mg.

Pazonix 400 Tablet: Each film coated tablet contains Pazopanib Hydrochloride INN equivalent to Pazopanib 400 mg.

Therapeutic Class - Anti Cancer

CLINICAL PHARMACOLOGY

Mechanism of Action

Pazopanib is a multi-tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α and -β, fibroblast growth factor receptor (FGFR) -1 and -3, cytokine receptor (Kit), interleukin-2 receptor inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck), and trans membrane glycoprotein receptor tyrosine kinase (c-Fms). *In vitro,* Pazopanib inhibited ligand-induced auto-phosphorylation of VEGFR-2, Kit and PDGFR-β receptors. *In vivo,* Pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in a mouse model, and the growth of some human tumor xenografts in mice.

Pharmacodynamics

Increases in blood pressure have been observed and are related to steady-state trough plasma Pazopanib concentrations. The QT prolongation potential of Pazopanib was assessed in a randomized, blinded, parallel trial (N = 96) using Moxifloxacin as a positive control. Pazopanib 800 mg was dosed under fasting conditions on Days 2 to 8 and 1,600 mg was dosed on Day 9 after a meal in order to increase exposure to Pazopanib and its metabolites. No large changes (i.e., >20 msec) in QTc interval following the treatment of pazopanib were detected in this QT trial. The trial was not able to exclude small changes (<10 msec) in QTc interval, because assay sensitivity below this threshold (<10 msec) was not established in this trial.

Pharmacokinetics

Absorption: Pazopanib is absorbed orally with median time to achieve peak concentrations of 2 to 4 hours after the dose. Daily dosing at 800 mg results in geometric mean AUC and C_{max} of 1,037 hr/microgram /mL and 58.1 microgram/mL (equivalent to 132 MicroM), respectively. There was no consistent increase in AUC or C_{max} at Pazopanib doses above 800 mg. Administration of a single Pazopanib 400 mg crushed tablet increased AUC(0-72) by 46% and C_{max} by approximately 2 fold and decreased t_{max} by approximately 2 hours compared to administration of the whole tablet. These results indicate that the bioavailability and the rate of Pazopanib oral absorption are increased after administration of the crushed tablet relative to administration of the whole tablet. Therefore, due to this potential for increased exposure, tablets of Pazopanib should not be crushed. Systemic exposure to Pazopanib is increased when administered with food. Administration of Pazopanib with a high-fat or low-fat meal results in an approximately 2 fold increase in AUC and C_{max}. Therefore, Pazopanib should be administered at least 1 hour before or 2 hours after a meal.

Distribution: Binding of Pazopanib to human plasma protein *in vivo* was greater than 99% with no concentration dependence over the range of 10 to 100 microgram/mL. *In vitro* studies suggest that Pazopanib is a substrate for P-glycoprotein (Pgp) and breast cancer resistant protein (BCRP).

Metabolism: *In vitro* studies demonstrated that Pazopanib is metabolized by CYP3A4 with a minor contribution from CYP1A2 and CYP2C8.

Elimination: Pazopanib has a mean half-life of 30.9 hours after administration of the recommended dose of 800 mg. Elimination is primarily via feces with renal elimination accounting for <4% of the administered dose.

INDICATIONS AND USAGE

• Pazopanib is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

• Pazopanib is indicated for the treatment of patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy.

DOSAGE AND ADMINISTRATION

Recommended Dosing

The recommended starting dose of Pazopanib is 800 mg orally once daily without food (at least 1 hour before or 2 hours after a meal). The dose of Pazopanib should not exceed 800 mg.

Do not crush tablets due to the potential for increased rate of absorption which may affect systemic exposure.

If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.

Dose Modification Guidelines

In RCC, the initial dose reduction should be 400 mg, and additional dose decrease or increase should be in 200-mg steps based on individual tolerability.

In STS, a decrease or increase should be in 200-mg steps based on individual tolerability.

Hepatic Impairment: No dose adjustment is required in patients with mild hepatic impairment. In patients with moderate hepatic impairment, alternatives to Pazopanib should be considered. If Pazopanib is used in patients with moderate hepatic impairment, the dose should be reduced to 200 mg per day Pazopanib is not recommended in patients with severe hepatic impairment.

Concomitant Strong CYP3A4 Inhibitors: The concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin) increases Pazopanib concentrations and should be avoided. Consider an alternate concomitant medication with no or minimal potential to inhibit CYP3A4. If co-administration of a strong CYP3A4 inhibitor is warranted, reduce the dose of Pazopanib to 400 mg. Further dose reductions may be needed if adverse effects occur during therapy.

Concomitant Strong CYP3A4 Inducer: The concomitant use of strong CYP3A4 inducers (e.g., Rifampin) may decrease Pazopanib concentrations and should be avoided. Consider an alternate concomitant medication with no or minimal enzyme induction potential. Pazopanib should not be used in patients who cannot avoid chronic use of strong CYP3A4 inducers.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Hepatic Toxicity and Hepatic Impairment

In clinical trials with Pazopanib, hepatotoxicity, manifested as increases in serum transaminases (ALT, AST) and bilirubin, was observed. This hepatotoxicity can be severe and fatal. Patients older than 65 years are at greater risk for hepatotoxicity. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks).

In the randomized RCC trial, ALT >3 X ULN was reported in 18% and 3% of the groups receiving Pazopanib and placebo, respectively. ALT >10 X ULN was reported in 4% of patients who received Pazopanib and in <1% of patients who received placebo. Concurrent elevation in ALT >3 X ULN and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >3 X ULN occurred in 2% (5/290) of patients on Pazopanib and 1% (2/145) on placebo.

In the randomized STS trial, ALT >3 X ULN was reported in 18% and 5% of the groups receiving Pazopanib and placebo, respectively. ALT >8 X ULN was reported in 5% and 2% of the groups receiving Pazopanib and placebo, respectively. Concurrent elevation in ALT >3 X ULN and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >3 X ULN occurred in 2% (4/240) of patients on Pazopanib and <1% (1/123) on placebo.

Two-tenths percent of the patients (2/977) from trials that supported the RCC indication died with disease progression and hepatic failure and 0.4% of patients (1/240) in the randomized STS trial died of hepatic failure.

Monitor serum liver tests before initiation of treatment with Pazopanib and at Weeks 3, 5, 7, and 9. Thereafter, monitor at Month 3 and at Month 4, and as clinically indicated. Periodic monitoring should then continue after Month 4.

Patients with isolated ALT elevations between 3 X ULN and 8 X ULN may be continued on Pazopanib with weekly monitoring of liver function until ALT returns to Grade 1 or baseline.

Patients with isolated ALT elevations of >8 X ULN should have Pazopanib interrupted until they return to Grade 1 or baseline. If the potential benefit for reinitiating treatment with Pazopanib is considered to outweigh the risk for hepatotoxicity, then reintroduce Pazopanib at a reduced dose of no more than 400 mg once daily and measure serum liver tests weekly for 8 weeks. Following reintroduction of Pazopanib, if ALT elevations >3 X ULN recur, then Pazopanib should be permanently discontinued.

If ALT elevations >3 X ULN occur concurrently with bilirubin elevations >2 X ULN, Pazopanib should be permanently discontinued. Patients should be monitored until resolution. Pazopanib is a uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1) inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinemia, known Gilbert's syndrome, and elevation in ALT >3 X ULN should be managed as per the recommendations outlined for isolated ALT elevations.

Concomitant use of Pazopanib and simvastatin increases the risk of ALT elevations and should be undertaken with caution and close monitoring. Insufficient data are available to assess the risk of concomitant administration of alternative statins and Pazopanib.

In patients with pre-existing moderate hepatic impairment, the starting dose of Pazopanib should be reduced or alternatives to Pazopanib should be considered. Treatment with Pazopanib is not recommended in patients with pre-existing severe hepatic impairment, defined as total bilirubin >3 X ULN with any level of ALT.

QT Prolongation and Torsades de Pointes

In the RCC trials of Pazopanib, QT prolongation (≥500 msec) was identified on routine electrocardiogram monitoring in 2% (11/558) of patients. Torsades de pointes occurred in <1% (2/977) of patients who received Pazopanib in the monotherapy trials.

In the randomized RCC and STS trials, 1% (3/290) of patients and 0.4% (1/240) of patients, respectively, who received Pazopanib had post-baseline values between 500 to 549 msec. Post-baseline QT data were only collected in the STS trial if ECG abnormalities were reported as an adverse reaction. None of the 268 patients who received placebo on the two trials had post-baseline QTc values ≥500 msec.

Pazopanib should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. When using Pazopanib, baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g., calcium, magnesium, potassium) within the normal range should be performed.

Cardiac Dysfunction

In clinical trials with Pazopanib, events of cardiac dysfunction such as decreased left ventricular ejection fraction (LVEF) and congestive heart failure have occurred. In the overall safety population for RCC (N = 586), cardiac dysfunction was observed in 0.6% (4/586) of patients without routine on-study LVEF monitoring. In a randomized RCC trial of Pazopanib compared with sunitinib, myocardial dysfunction was defined as symptoms of cardiac dysfunction or ≥15% absolute decline in LVEF compared with baseline or a decline in LVEF of ≥10% compared with baseline that is also below the lower limit of normal. In patients who had baseline and follow up LVEF measurements, myocardial dysfunction occurred in 13% (47/362) of patients on Pazopanib compared with 11% (42/369) of patients on sunitinib. Congestive heart failure occurred in 0.5% of patients on each arm. In the randomized STS trial, myocardial dysfunction occurred in 11% (16/142) of patients on Pazopanib compared with 5% (2/40) of patients on placebo. One percent (3/240) of patients on Pazopanib in the STS trial had congestive heart failure which did not resolve in one patient.

Fourteen of the 16 patients with myocardial dysfunction treated with Pazopanib in the STS trial had concurrent hypertension which may have exacerbated cardiac dysfunction in patients at risk (e.g., those with prior anthracycline therapy) possibly by increasing cardiac afterload. Blood pressure should be monitored and managed promptly using a combination of anti-hypertensive therapy and dose modification of Pazopanib (interruption and re-initiation at a reduced dose based on clinical judgment). Patients should be carefully monitored for clinical signs or symptoms of congestive heart failure. Baseline and periodic evaluation of LVEF is recommended in patients at risk of cardiac dysfunction including previous anthracycline exposure.

Hemorrhagic Events

Fatal hemorrhage occurred in 0.9% (5/586) in the RCC trials; there were no reports of fatal hemorrhage in the STS trials. In the randomized RCC trial, 13% (37/290) of patients treated with Pazopanib and 5% (7/145) of patients on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events in the patients treated with Pazopanib were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). Nine of 37 patients treated with Pazopanib who had hemorrhagic events experienced serious events including pulmonary, gastrointestinal, and genitourinary hemorrhage. One percent (4/290) of patients treated with Pazopanib died from hemorrhage compared with no (0/145) patients on placebo. In the overall safety population in RCC (N = 586), cerebral/intracranial hemorrhage was observed in <1% (2/586) of patients treated with Pazopanib.

In the randomized STS trial, 22% (53/240) of patients treated with Pazopanib compared with 8% (10/123) treated with placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events were epistaxis (8%), mouth hemorrhage (3%), and anal hemorrhage (2%). Grade 4 hemorrhagic events in the STS population occurred in 1% (3/240) of patients and included intracranial hemorrhage, subarachnoid hemorrhage, and peritoneal hemorrhage.

Pazopanib has not been studied in patients who have a history of hemoptysis, cerebral hemorrhage, or clinically significant gastrointestinal hemorrhage in the past 6 months and should not be used in those patients.

Arterial Thromboembolic Events

Fatal arterial thromboembolic events were observed in 0.3% (2/586) of patients in the RCC trials and in no patients in the STS trials. In the randomized RCC trial, 2% (5/290) of patients receiving Pazopanib experienced myocardial infarction or ischemia, 0.3% (1/290) had a cerebrovascular accident, and 1% (4/290) had an event of transient ischemic attack. In the randomized STS trial, 2% (4/240) of patients receiving Pazopanib experienced a myocardial infarction or ischemia, 0.4% (1/240) had a cerebrovascular accident, and there were no incidents of transient ischemic attack. No arterial thromboembolic events were reported in patients who received placebo in either trial. Pazopanib should be used with caution in patients who are at increased risk for these events or who have had a history of these events. Pazopanib has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months and should not be used in those patients.

Venous Thromboembolic Events

In RCC and STS trials of Pazopanib, venous thromboembolic events (VTE) including venous thrombosis and fatal pulmonary embolus (PE) have occurred. In the randomized STS trial, venous thromboembolic events were reported in 5% of patients treated with Pazopanib compared with 2% with placebo. In the randomized RCC trial, the rate was 1% in both arms. Fatal pulmonary embolus occurred in 1% (2/240) of STS patients receiving Pazopanib and in no patients receiving placebo. There were no fatal pulmonary emboli in the RCC trial. Monitor for signs and symptoms of VTE and PE.

Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), has been reported in clinical trials of Pazopanib as monotherapy, in combination with bevacizumab, and in combination with topotecan. Pazopanib is not indicated for use in combination with other agents. Six of the 7 TMA cases occurred within 90 days of the initiation of Pazopanib. Improvement of TMA was observed after treatment was discontinued. Monitor for signs and symptoms of TMA. Permanently discontinue Pazopanib in patients developing TMA. Manage as clinically indicated.

Gastrointestinal Perforation and Fistula

In the RCC and STS trials, gastrointestinal perforation or fistula occurred in 0.9% (5/586) of patients and 1% (4/382) of patients receiving Pazopanib, respectively. Fatal perforations occurred in 0.3% (2/586) of these patients in the RCC trials and in 0.3% (1/382) of these patients in the STS trials. Monitor for signs and symptoms of gastrointestinal perforation or fistula.

Interstitial Lung Disease (ILD)/Pneumonitis

ILD/pneumonitis, which can be fatal, has been reported in association with Pazopanib. In clinical trials, ILD/pneumonitis occurred in 0.1% of patients treated with Pazopanib.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis and discontinue Pazopanib in patients developing ILD or pneumonitis.

Reversible Posterior Leukoencephalopathy Syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported in patients receiving Pazopanib and may be fatal.

RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances. Mild to severe hypertension may be present. The diagnosis of RPLS is optimally confirmed by magnetic resonance imaging. Permanently discontinue Pazopanib in patients developing RPLS.

Hypertension

In clinical trials, hypertension (systolic blood pressure ≥150 or diastolic blood pressure ≥100 mm Hg) and hypertensive crisis were observed in patients treated with Pazopanib. Blood pressure should be well controlled prior to initiating Pazopanib. Hypertension occurs early in the course of treatment (40% of cases occurred by Day 9 and 90% of cases occurred in the first 18 weeks). Blood pressure should be monitored early after starting treatment (no longer than one week) and frequently thereafter to ensure blood pressure control. Approximately 40% of patients who received Pazopanib experienced hypertension. Grade 3 hypertension was reported in 4% to 7% of patients receiving Pazopanib.

Increased blood pressure should be treated promptly with standard anti-hypertensive therapy and dose reduction or interruption of Pazopanib as clinically warranted. Pazopanib should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction. Approximately 1% of patients required permanent discontinuation of Pazopanib because of hypertension.

5.12 Wound Healing

No formal trials on the effect of Pazopanib on wound healing have been conducted. Since vascular endothelial growth factor receptor (VEGFR) inhibitors such as Pazopanib may impair wound healing, treatment with Pazopanib should be stopped at least 7 days prior to scheduled surgery. The decision to resume Pazopanib fter surgery should be based on clinical judgment of adequate wound healing. Pazopanib should be discontinued in patients with wound dehiscence.

Hypothyroidism

Hypothyroidism, confirmed based on a simultaneous rise of TSH and decline of T4, was reported in 7% (19/290) of patients treated with Pazopanib in the randomized RCC trial and in 5% (11/240) of patients treated with Pazopanib in the randomized STS trial. No patients on the placebo arm of either trial had hypothyroidism. In RCC and STS trials of Pazopanib, hypothyroidism was reported as an adverse reaction in 4% (26/586) and 5% (20/382) of patients, respectively. Proactive monitoring of thyroid function tests is recommended.

Proteinuria

In the randomized RCC trial, proteinuria was reported as an adverse reaction in 9% (27/290) of patients receiving Pazopanib and in no patients receiving placebo. In 2 patients, proteinuria led to discontinuation of treatment with Pazopanib. In the randomized STS trial, proteinuria was reported as an adverse reaction in 1% (2/240) of patients, and nephrotic syndrome was reported in 1 patient treated with Pazopanib compared with none in patients receiving placebo. Treatment was withdrawn in the patient with nephrotic syndrome.

Baseline and periodic urinalysis during treatment is recommended with follow up measurement of 24-hour urine protein as clinically indicated. Interrupt Pazopanib and dose reduce for 24-hour urine protein ≥3 grams; discontinue Pazopanib for repeat episodes despite dose reductions.

Infection

Serious infections (with or without neutropenia), including some with fatal outcome, have been reported. Monitor patients for signs and symptoms of infection. Institute appropriate anti-infective therapy promptly and consider interruption or discontinuation of Pazopanib for serious infections.

Increased Toxicity with Other Cancer Therapy

Pazopanib is not indicated for use in combination with other agents. Clinical trials of Pazopanib in combination with pemetrexed and lapatinib were terminated early due to concerns over increased toxicity and mortality. The fatal toxicities observed included pulmonary hemorrhage, gastrointestinal hemorrhage, and sudden death. A safe and effective combination dose has not been established with these regimens.

Increased Toxicity in Developing Organs

The safety and effectiveness of Pazopanib in pediatric patients have not been established. Pazopanib is not indicated for use in pediatric patients. Based on its mechanism of action, Pazopanib may have severe effects on organ growth and maturation during early post-natal development. Administration of Pazopanib to juvenile rats less than 21 days old resulted in toxicity to the lungs, liver, heart, and kidney and in death at doses significantly lower than the clinically recommended dose or doses tolerated in older animals. Pazopanib may potentially cause serious adverse effects on organ development in pediatric patients, particularly in patients younger than 2 years of age.

Pregnancy

Pazopanib can cause fetal harm when administered to a pregnant woman. Based on its mechanism of action, Pazopanib is expected to result in adverse reproductive effects. In pre-clinical studies in rats and rabbits, Pazopanib was teratogenic, embryotoxic, fetotoxic, and abortifacient.

There are no adequate and well-controlled studies of Pazopanib in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while taking Pazopanib.

SIDE EFFECTS

Potentially serious adverse reactions with Pazopanib included:

Hepatotoxicity.

QT prolongation and torsades de pointes.

Cardiac dysfunction.

Hemorrhagic events.

Arterial and venous thromboembolic events.

Thrombotic microangiopathy.

Gastrointestinal perforation and fistula.

Interstitial Lung Disease (ILD)/Pneumonitis.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS).

Hypertension.

Infection.

Increased toxicity with other cancer therapies

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D.

Pazopanib can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of Pazopanib in pregnant women.

In developmental toxicity studies in rats and rabbits, Pazopanib was teratogenic, embryotoxic, fetotoxic, and abortifacient. Administration of Pazopanib to pregnant rats during organogenesis at a dose level of ≥3 mg/kg/day (approximately 0.1 times the human clinical exposure based on AUC) resulted in teratogenic effects including cardiovascular malformations (retroesophageal subclavian artery, missing innominate artery, changes in the aortic arch) and incomplete or absent ossification. In addition, there was reduced fetal body weight, and pre- and post-implantation embryolethality in rats administered Pazopanib at doses ≥3 mg/kg/day. In rabbits, maternal toxicity (reduced food consumption, increased post-implantation loss, and abortion) was observed at doses ≥30 mg/kg/day (approximately 0.007 times the human clinical exposure). In addition, severe maternal body weight loss and 100% litter loss were observed at doses ≥100 mg/kg/day (0.02 times the human clinical exposure), while fetal weight was reduced at doses ≥3 mg/kg/day (AUC not calculated).

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 2 weeks after the last dose of Pazopanib.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Pazopanib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of Pazopanib in pediatric patients have not been established.

Geriatric Use

In clinical trials with Pazopanib for the treatment of RCC, 33% (196/582) of patients were aged ≥ 65 years. No overall differences in safety or effectiveness of Pazopanib were observed between these patients and younger patients. However, patients >60 years of age may be at greater risk for an ALT >3 X ULN. In the STS trials, 24% (93/382) of patients were age ≥ 65 years. Patients ≥ 65 years had increased Grade 3 or 4 fatigue (19% versus 12% for <65), hypertension (10% versus 6%), decreased appetite (11% versus 2%) and ALT (3% versus 2 %) or AST elevations (4% versus 1%). Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment

In clinical trials for Pazopanib, patients with total bilirubin ≤1.5 X ULN and AST and ALT ≤ 2 X ULN were included.

An analysis of data from a pharmacokinetic trial of Pazopanib in patients with varying degrees of hepatic dysfunction suggested that no dose adjustment is required in patients with mild hepatic impairment (either total bilirubin within normal limit [WNL] with ALT >ULN or bilirubin >1 X to 1.5 X ULN regardless of the ALT value). The maximum tolerated dose in patients with moderate hepatic impairment (total bilirubin >1.5 X to 3 X ULN regardless of the ALT value) was 200 mg per day (N = 11). The median steady-state C_{max} and AUC(0-24) achieved at this dose was approximately 40% and 29%, respectively, of that seen in patients with normal hepatic function at the recommended daily dose of 800 mg. The maximum dose explored in patients with severe hepatic impairment (total bilirubin >3 X ULN regardless of the ALT value) was 200 mg per day (N = 14). This dose was not well tolerated. Median exposures achieved at this dose were approximately 18% and 15% of those seen in patients with normal liver function at the recommended daily dose of 800 mg. Therefore, Pazopanib is not recommended in these patients.

Renal Impairment

Patients with renal cell cancer and mild/moderate renal impairment (Creatinine clearance ≥30 mL/min) were included in clinical trials for Pazopanib.

There are no clinical or pharmacokinetic data in patients with severe renal impairment or in patients undergoing peritoneal dialysis or hemodialysis. However, renal impairment is unlikely to significantly affect the pharmacokinetics of Pazopanib since <4% of a radiolabeled oral dose was recovered in the urine. In a population pharmacokinetic analysis using 408 patients with various cancers, creatinine clearance (30 to 150 mL/min) did not influence clearance of Pazopanib. Therefore, renal impairment is not expected to influence Pazopanib exposure, and dose adjustment is not necessary.

DRUG INTERACTIONS

Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes

In vitro studies suggested that the oxidative metabolism of Pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib.

CYP3A4 Inhibitors: Coadministration of Pazopanib with strong inhibitors of CYP3A4 (e.g., Ketoconazole, ritonavir, clarithromycin) increases Pazopanib concentrations and should be avoided. Consider an alternate concomitant medication with no or minimal potential to inhibit CYP3A4. If co-administration of a strong CYP3A4 inhibitor is warranted, reduce the dose of Pazopanib to 400 mg. Grapefruit or grapefruit juice should be avoided as it inhibits CYP3A4 activity and may also increase plasma concentrations of Pazopanib.

CYP3A4 Inducers: CYP3A4 inducers such as rifampin may decrease plasma Pazopanib concentrations. Consider an alternate concomitant medication with no or minimal enzyme induction potential. Pazopanib should not be used if chronic use of strong CYP3A4 inducers cannot be avoided.

Drugs that Inhibit Transporters

In vitro studies suggested that Pazopanib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Therefore, absorption and subsequent elimination of Pazopanib may be influenced by products that affect P-gp and BCRP.

Concomitant treatment with strong inhibitors of P-gp or BCRP should be avoided due to risk of increased exposure to Pazopanib. Selection of alternative concomitant medicinal products with no or minimal potential to inhibit P-gp or BCRP should be considered.

Effects of Pazopanib on CYP Substrates

Results from drug-drug interaction trials conducted in cancer patients suggest that Pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 in vivo, but had no effect on CYP1A2, CYP2C9, or CYP2C19.

Concomitant use of Pazopanib with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. Co-administration may result in inhibition of the metabolism of these products and create the potential for serious adverse events

Effect of Concomitant Use of Pazopanib and Simvastatin

Concomitant use of Pazopanib and simvastatin increases the incidence of ALT elevations. Across monotherapy trials with Pazopanib, ALT >3 X ULN was reported in 126/895 (14%) of patients who did not use statins, compared with 11/41 (27%) of patients who had concomitant use of simvastatin. If a patient receiving concomitant simvastatin develops ALT elevations, follow dosing guidelines for Pazopanib or consider alternatives to Pazopanib. Alternatively, consider discontinuing simvastatin. Insufficient data are available to assess the risk of concomitant administration of alternative statins and Pazopanib.

Drugs that Raise Gastric pH

In a drug interaction trial in patients with solid tumors, concomitant administration of Pazopanib with esomeprazole, a proton pump inhibitor (PPI), decreased the exposure of Pazopanib by approximately 40% (AUC and Cmax). Therefore, concomitant use of Pazopanib with drugs that raise gastric pH should be avoided. If such drugs are needed, short-acting antacids should be considered in place of PPIs and H2 receptor antagonists. Separate antacid and Pazopanib dosing by several hours to avoid a reduction in Pazopanib exposure.

OVERDOSAGE

Pazopanib doses up to 2,000 mg have been evaluated in clinical trials. Dose-limiting toxicity (Grade 3 fatigue) and Grade 3 hypertension were each observed in 1 of 3 patients dosed at 2,000 mg daily and 1,000 mg daily, respectively.

Treatment of overdose with Pazopanib should consist of general supportive measures. There is no specific antidote for overdosage of Pazopanib. Hemodialysis is not expected to enhance the elimination of Pazopanib because pazopanib is not significantly renally excreted and is highly bound to plasma proteins.

PHARMACEUTICALS INFORMATION

Storage Conditions

Store below 30^{0}C and dry place, away from light and moisture. Keep out of the reach of children.

Presentation and Packaging

Pazonix 200 Tablet: Each commercial box contains 30 tablets in a HPDE pot.

Pazonix 400 Tablet: Each commercial box contains 60 tablets in a HPDE pot.

Only for Export

Manufactured By
Beacon Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

Marketed By
BEACON®
Medicare Limited
Dhaka, Bangladesh

LF28601