Zopanib

Pazopanib

COMPOSITION:

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

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

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 -ß), 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 transmembrane glycoprotein receptor tyrosine kinase (c-Fms).

INDICATIONS:

Zopanib (Pazopanib) tablet is indicated for the treatment of patients with-

1. advanced renal cell carcinoma (RCC) and
2. advanced soft tissue sarcoma (STS) who have received prior chemotherapy.

DOSAGE AND ADMINISTRATION:

Recommended Dosing

800 mg orally once daily without food (at least 1 hour before or 2 hours after a meal).

Baseline moderate hepatic impairment - 200 mg orally once daily.

Not recommended in patients with severe hepatic impairment.

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 Cmax of 1,037 mcg•hr/mL and 58.1 mcg/mL (equivalent to 132 µM), respectively. There was no consistent increase in AUC or Cmax at Pazopanib doses above 800 mg.

Administration of a single Pazopanib 400 mg crushed tablet increased AUC (0-72) by 46% and Cmax by approximately 2 fold and decreased tmax 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, Pazopanib tablets 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 folds increase in AUC and Cmax. 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 mcg/mL.

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 and small amount via renal (<4% of the administered dose).

Hepatic Impairment:

An analysis of data from a pharmacokinetic trial of Pazopanib in patients with hepatic impairment suggested that, no dose adjustment is required in patients with mild hepatic impairment (either total bilirubin within normal limit [WNL] with ALT greater than ULN or bilirubin greater than 1 X to 1.5 X ULN regardless of the ALT value). The maximum tolerated dose in patients with moderate hepatic impairment (total bilirubin greater than 1.5 X to 3 X ULN regardless of the ALT value) was 200 mg per day. Pazopanib is not recommended in patient with severe hepatic impairment.

CONTRAINDICATIONS:

None

WARNINGS AND PRECAUTION:

In clinical trials with Pazopanib, hepatotoxicity, manifested as increases in serum transaminases (alanine transferase (ALT), aspartate aminotransferase (AST)) and bilirubin, was observed. This hepatotoxicity can be severe and fatal. Patients older than 65 years are at greater risk for hepatotoxicity. Following warnings and precautions should be exercised-

· Use with caution in patients at higher risk of developing QT interval prolongation. Monitoring electrocardiograms and electrolytes should be considered.

· Cardiac dysfunction such as congestive heart failure and decreased left ventricular ejection fraction have occurred. Monitor blood pressure and manage hypertension promptly. Baseline and periodic evaluation of LVEF is recommended in patients at risk of cardiac dysfunction.

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

· Arterial thrombotic events have been observed and can be fatal. Use with caution in patients who are at increased risk for these events.

· Venous thrombotic events (VTE) have been observed, including fatal pulmonary emboli (PE). Monitor for signs and symptoms of VTE and PE.

· Gastrointestinal perforation or fistula has occurred. Fatal perforation events have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula.

· Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been observed. Permanently discontinue Pazopanib if signs or symptoms of RPLS occur.

· Hypertension including hypertensive crisis has been observed. Blood pressure should be well-controlled prior to initiating Pazopanib. Monitor blood pressure within one week after starting Pazopanib and frequently thereafter.

· Interruption of therapy with Pazopanib is recommended in patients undergoing surgical procedures.

· Hypothyroidism may occur. Monitoring of thyroid function tests is recommended.

· Proteinuria: Monitor urine protein. Interrupt treatment for 24-hour urine protein ≥ 3 grams and discontinue for repeat episodes despite dose reductions.

· Infection: Serious infections (with or without neutropenia), some with fatal outcome, have been reported. Monitor for signs and symptoms and treat active infection promptly. Consider discontinuation of Pazopanib.

· Pazopanib can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant while taking Pazopanib.

ADVERSE REACTIONS:

The most common adverse reactions in patients with advanced renal cell carcinoma (≥20%) are diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting.

The most common adverse reactions in patients with advanced soft tissue sarcoma (≥20%) are fatigue, diarrhea, nausea, decreased weight, hypertension, decreased appetite, hair color changes, vomiting, tumor pain, dysgeusia, headache, musculoskeletal pain, myalgia, gastrointestinal pain, and dyspnea.

USE IN SPECIFIC POPULATIONS:

Pregnancy

Pregnancy Category D

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 aged ≥ 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.

Renal Impairment

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 less than 4% of a radiolabeled oral dose was recovered in the urine. 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. If coadministration of a strong CYP3A4 inhibitor is warranted, reduce the dose of Zopanib 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. 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 (Pgp) and breast cancer resistance protein (BCRP). Therefore, absorption and subsequent elimination of Pazopanib may be influenced by products that affect Pgp and BCRP. Concomitant treatment with strong inhibitors of Pgp or breast cancer resistance protein (BCRP) should be avoided due to risk of increased exposure to Pazopanib.

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.

Effect of Concomitant use of Pazopanib and Simvastatin

Concomitant use of Pazopanib and simvastatin increases the incidence of ALT elevations. Across monotherapy studies 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.

OVERDOSAGE:

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 it is not significantly renally excreted and is highly bound to plasma proteins.

STORAGE:

Store below 30°C, dry place and away from light. Keep out of the reach of children.

PACKING AND PRESENTATION:

Zopanib 200 Tablet: Each commercial box contains 30 tablets in Alu-Alu blister pack.

Zopanib 400 Tablet: Each commercial box contains 20 tablets in Alu-Alu blister pack.

Manufactured By
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LF29001