Pazonib-200

Pazopanib INN 200 mg Tablet

DRUG INTERNATIONAL LTD.

Composition: Each film coated tablet contains Pazopanib 200 mg as Pazopanib HCl INN.

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), lymphocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms). In vitro, Pazopanib inhibited ligand-induced autophosphorylation of VEGFR-2, Kit, and PDGFR-β receptors.

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 mcg•h/mL and 58.1 mcg/mL (equivalent to 132 μM), respectively. There was no consistent increase in AUC or C_{max} at Pazopanib doses above 800 mg.

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. In vitro, studies suggest that Pazopanib is a substrate for P-gp and 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 less than 4% of the administered dose.

Indications:

Pazonib-200 is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

Pazonib-200 is indicated for the treatment of patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy.

Limitations of Use: The efficacy of Pazonib-200 for the treatment of patients with adipocytic STS or gastrointestinal stromal tumors has not been demonstrated.

Dosage and Administration: The recommended starting dose of Pazonib-200 is 800 mg orally once daily without food (at least 1 hour before or 2 hours after a meal). The dose of Pazonib-200 should not exceed 800 mg. Tablets should not be crushed 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. Or, as directed by the registered physicians.

Side Effects:

• Hepatic Toxicity and Hepatic Impairment • QT Prolongation and Torsades de Pointes • Cardiac Dysfunction • Hemorrhagic Events • Arterial and Venous Thromboembolic Events • Thrombotic Microangiopathy • Gastrointestinal Perforation and Fistula • Interstitial Lung Disease/Pneumonitis • Reversible Posterior Leukoencephalopathy Syndrome • Hypertension • Hypothyroidism • Proteinuria • Tumor Lysis Syndrome • Infection • Increased Toxicity with Other Cancer Therapy

Contraindications: It is contraindicated in patients with known hypersensitivity to Pazopanib or any other components of this product.

Use in Pregnancy and Lactation: Pazonib-200 can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform a drug-associated risk. Pregnant women or women should be advised of childbearing potential of the potential risk to a fetus.

Lactation: There is no information regarding the presence of Pazopanib or its metabolites in human milk, or their effects on the breastfed infant, or on milk production. Because of the potential for serious adverse reactions in breastfed infants from Pazonib-200, a lactating woman should be advised not to breastfeed during treatment with Pazonib-200 and for 2 weeks after the final dose.

Females and Males of Reproductive Potential:

Contraception: Females: Pazonib-200 can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should be advised to use effective contraception during treatment and for at least 2 weeks after the last dose of Pazonib-200. **Males:** To avoid potential drug exposure to pregnant partners and female partners of reproductive potential, male patients (including those who have had vasectomies) with female partners of reproductive potential should be advised to use condoms during treatment with Pazonib-200 and for at least 2 weeks after the last dose.

Pediatric Use: The safety and effectiveness of Pazonib-200 in pediatric patients have not been established.

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 coadministration of a strong CYP3A4 inhibitor is warranted, reduce the dose of Pazonib-200 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. Pazonib-200 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 Pazonib-200 with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. Coadministration may result in inhibition of the metabolism of these products and create the potential for serious adverse events.

Effect of Concomitant Use of Pazonib-200 and Simvastatin: Concomitant use of Pazonib-200 and Simvastatin increases the incidence of ALT elevations. Across monotherapy trials with Pazonib-200, ALT greater than 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 Pazonib-200 or consider alternatives to Pazonib-200. Alternatively, consider discontinuing Simvastatin. Insufficient data are available to assess the risk of concomitant administration of alternative statins and Pazonib-200.

Precautions:

Hepatic Toxicity and Hepatic Impairment: In clinical trials with Pazonib-200, 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. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks).

QT Prolongation and Torsades De Pointes: In the RCC trials of Pazonib-200, QT prolongation (greater than or equal to 500 msec) was identified on routine electrocardiogram (ECG) monitoring in 2% (11/558) of patients. Torsades de pointes occurred in less than 1% (2/977) of patients who received Pazonib-200 in the monotherapy trials. Pazonib-200 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 Pazonib-200, baseline and periodic monitoring of ECGs and maintenance of electrolytes (e.g., calcium, magnesium, potassium) within the normal range should be performed.

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 Pazonib-200 and 5% (7/145) of patients on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events in the patients treated with Pazonib-200 were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). Nine of 37 patients treated with Pazonib-200, who had hemorrhagic events, experienced serious events including pulmonary, gastrointestinal, and genitourinary hemorrhage. One percent (4/290) of patients treated with Pazonib-200 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 less than 1% (2/586) of patients treated with Pazonib-200.

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 Pazonib-200 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 Pazonib-200 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. Pazonib-200 should be used with caution in patients who are at increased risk for these events or who have had a history of these events. Pazonib-200 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 Pazonib-200, venous thromboembolic events (VTEs), including venous thrombosis and fatal pulmonary embolus (PE), have occurred. In the randomized STS trial, VTEs were reported in 5% of patients treated with Pazonib-200 compared with 2% with placebo. In the randomized RCC trial, the rate was 1% in both arms. Fatal PE occurred in 1% (2/240) of STS patients receiving Pazonib-200 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 Pazonib-200 as monotherapy, in combination with Bevacizumab, and in combination with Topotecan. Pazonib-200 is not indicated for use in combination with other agents. Six of the 7 TMA cases occurred within 90 days of the initiation of Pazonib-200. Improvement of TMA was observed after treatment was discontinued. Monitor for signs and symptoms of TMA. Permanently discontinue Pazonib-200 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 Pazonib-200, 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/Pneumonitis: Interstitial lung disease (ILD)/pneumonitis, which can be fatal, has been reported in association with Pazonib-200. In clinical trials, ILD/pneumonitis occurred in 0.1% of patients treated with Pazonib-200.Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis and discontinue Pazonib-200 in patients developing ILD or pneumonitis.

Reversible Posterior Leukoencephalopathy Syndrome: Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported in patients receiving Pazonib-200 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 Pazonib-200 in patients developing RPLS.

Wound Healing: No formal trials on the effect of Pazonib-200 on wound healing have been conducted. Since vascular endothelial growth factor receptor (VEGFR) inhibitors such as Pazopanib may impair wound healing, treatment with Pazonib-200 should be stopped at least 7 days prior to scheduled surgery. The decision to resume Pazonib-200 after surgery should be based on clinical judgment of adequate wound healing. Pazonib-200 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 Pazonib-200 in the randomized RCC trial and in 5% (11/240) of patients treated with Pazonib-200 in the randomized STS trial. No patients on the placebo arm of either trial had hypothyroidism. In RCC and STS trials of Pazonib-200, 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.

Tumor Lysis Syndrome: Cases of tumor lysis syndrome (TLS), including fatal cases, have been reported in RCC and STS patients treated with Pazonib-200. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis, and treat as clinically indicated.

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 Pazonib-200 for serious infections.

Increased Toxicity with other Cancer Therapy: Pazonib-200 is not indicated for use in combination with other agents. Clinical trials of Pazonib-200 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.

Embryo-Fetal Toxicity: Based on findings from animal studies and its mechanism of action, Pazonib-200 can cause fetal harm when administered to a pregnant woman. Administration of Pazonib-200 to pregnant rats and rabbits during the period of organogenesis resulted in maternal toxicity, teratogenicity, and abortion at systemic exposures lower than that observed at the maximum recommended human dose (MRHD) of 800 mg (based on area under the curve [AUC]). Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Pazonib-200 and for at least 2 weeks following the final dose.

Overdose: Pazopanib doses up to 2000 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 2000 mg daily and 1000 mg daily, respectively. Treatment of overdose with Pazonib-200 should consist of general supportive measures. There is no specific antidote for overdosage of Pazonib-200. Hemodialysis is not expected to enhance the elimination of Pazonib-200 because Pazopanib is not significantly renally excreted and is highly bound to plasma proteins.

Storage: Store below 30° C in a cool and dry place, away from sunlight. Keep out of reach of children.

Packing: Each box contains 28 tablets in a blister pack.