PAZITORZ 200 (Pazopanib Film-Coated Tablets 200mg)
PAZITORZ 400 (Pazopanib Film-Coated Tablets 400mg)

1. NAME OF THE MEDICINAL PRODUCT

PAZITORZ 200 (Pazopanib Film-Coated Tablets 200mg)
PAZITORZ 400 (Pazopanib Film-Coated Tablets 400mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PAZITORZ 200: Each tablet contains 216.7mg of Pazopanib hydrochloride equivalent to 200mg Pazopanib.

PAZITORZ 400: Each tablet contains 433.4mg of Pazopanib hydrochloride equivalent to 400mg Pazopanib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

PAZITORZ 200: White to off white, film-coated, modified capsule shaped tablets, debossed with '2' on one side and plain on other side

PAZITORZ 400: White to off white, film-coated, modified capsule shaped tablets, debossed with '4' on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Renal cell carcinoma (RCC)
PAZITORZ is indicated for the treatment of patients with advanced and/or metastatic renal cell carcinoma (RCC).

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

The Phase III trial population excluded patients with gastrointestinal stromal tumor (GIST) or adipocytic STS.

4.2 Posology and Method of Administration

Dosage regimen
General target population
The recommended dose of PAZITORZ is 800 mg orally once daily.

Dose modifications
Dose modification, either an increase or decrease in dose, should be in 200 mg increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions. The daily dose of PAZITORZ should not exceed 800 mg.

Special populations
Renal impairment
Renal impairment is not expected to have a clinically relevant effect on PAZITORZ pharmacokinetics given the low renal excretion of pazopanib and metabolites. Renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary in patients with creatinine clearance ≥30 mL/min. There is no experience of pazopanib in patients with severe renal impairment or in patients undergoing peritoneal dialysis or hemodialysis; therefore, use of PAZITORZ is not recommended in these patients.

Hepatic impairment
The safety and pharmacokinetics of PAZITORZ in patients with pre-existing hepatic impairment have not been fully established. No dose adjustment is required in patients with mild hepatic impairment as defined by alanine aminotransferase (ALT) and bilirubin.

The dose of PAZITORZ should be reduced to 200 mg per day in patients with moderate hepatic impairment.

There are insufficient data in patients with severe hepatic impairment (total bilirubin > 3 times the upper limit of normal [X ULN] regardless of the ALT value); therefore, use of PAZITORZ is not recommended in these patients.

Pediatric patients (below 18 years)
PAZITORZ is not recommended for use in children and adolescents under 18 years.

Geriatric patients (above 65 years)
No alteration of dosage, dosing frequency or route of administration is required in patients over 65 years.

Method of administration
PAZITORZ should be taken without food (at least one hour before or two hours after a meal). PAZITORZ should be taken whole with water and must not be broken or crushed. If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.

4.3 Contraindications

PAZITORZ is contraindicated in patients with hypersensitivity to any of the ingredients.

4.4 Special Warnings and Precautions for Use

Hepatic effects
Cases of hepatic failure (including fatalities) have been reported during use of pazopanib. In a study with pazopanib, increase in serum transaminases (ALT, aspartate aminotransferase [AST]) and bilirubin were observed. In the majority of the cases, isolated increases in ALT and AST have been reported, without concomitant elevations of alkaline phosphatase or bilirubin. Patients over 60 years of age may be at greater risk for ALT >3 X ULN. Patients who carry the *HLA-B**57:01 allele also have an increased risk of pazopanib-associated ALT elevations. Liver function should be monitored in all subjects receiving pazopanib, regardless of genotype or age. The vast majority (over 90%) of all transaminase elevations of any grade occurred in the first 18 weeks. Grades are based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3 (NCI CTCAE).

Serum liver tests should be performed before initiation of treatment with pazopanib, at weeks 3, 5, 7 and 9, then at Months 3 and 4, with additional tests as clinically indicated. Periodic testing should then continue after Month 4.

The following guidelines are provided for patients with baseline values of total bilirubin ≤ 1.5 X ULN and AST and ALT ≤ 2 X ULN.

- 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 return to Grade 1 (NCI CTCAE) or baseline.
- Patients with ALT of > 8 X ULN should have pazopanib interrupted until they return to Grade 1 (NCI CTCAE) or baseline. If the potential benefit of reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce pazopanib at a reduced dose of 400 mg once daily and perform 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 return to Grade 1 (NCI CTCAE) or baseline. Pazopanib is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinemia, known or suspected 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.

Beyond recommending that patients with mild hepatic impairment are treated with 800 mg pazopanib once daily and reducing the initial starting dose to 200 mg per day for patients with moderate impairment, no further dose modification guidelines based on results of serum liver tests during therapy have been established for patients with pre-existing hepatic impairment.

Hypertension
In a study with pazopanib, events of hypertension including hypertensive crisis have occurred. Blood pressure should be well controlled prior to initiating pazopanib. Patients should be monitored for hypertension early after

starting treatment (no longer than one week after starting pazopanib) and frequently thereafter to ensure blood pressure control, and treated promptly with a combination of standard anti-hypertensive therapy and pazopanib dose reduction or interruption as clinically warranted. Hypertension (systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥100 mm Hg) occurs early in the course of pazopanib treatment (approximately 40% of cases occurred by Day 9 and approximately 90% of cases occurred in the first 18 weeks). Pazopanib should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persists despite anti-hypertensive therapy and pazopanib dose reduction.

Posterior reversible encephalopathy syndrome (PRES)/Reversible posterior leukoencephalopathy syndrome (RPLS)
PRES/RPLS has been reported in association with pazopanib. PRES/RPLS can present with headache, hypertension, seizure, lethargy, confusion, blindness and other visual and neurological disturbances, and can be fatal. Pazopanib should be permanently discontinued in patients developing PRES/RPLS.

Interstitial lung disease (ILD)/Pneumonitis
ILD, which can be fatal, has been reported in association with pazopanib. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis and pazopanib should be discontinued in patients developing ILD or pneumonitis.

Cardiac dysfunction
In a study with Pazopanib, events of cardiac dysfunction such as congestive heart failure and decreased left ventricular ejection fraction (LVEF) have occurred. In a randomized RCC trial of Pazopanib compared with sunitinib, in subjects who had baseline and follow-up LVEF measurements, myocardial dysfunction was observed in 13% (47/362) of subjects in the Pazopanib arm compared to 11% (42/369) of subjects in the sunitinib arm. Congestive heart failure was observed in 0.5% of subjects in each treatment arm. In the Phase III STS clinical trial, congestive heart failure was reported in 3 out of 240 subjects (1%). In this trial decreases in LVEF in subjects who had post-baseline measurement were detected in 11% (16/142) in the Pazopanib arm compared with 5% (2/40) in the placebo arm. Fourteen of the 16 subjects in the Pazopanib arm had concurrent hypertension which may have exacerbated cardiac dysfunction in patients at risk (e.g., those with prior anthracycline therapy) by increasing cardiac after-load. 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.

QT prolongation and torsade de pointes
In a study with pazopanib, events of QT prolongation or torsade de pointes have occurred. Pazopanib should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medications that may potentially prolong QT interval, or in patients with relevant pre-existing cardiac disease. When using pazopanib, baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (calcium, magnesium, potassium) within normal range is recommended.

Arterial thrombotic events
In a study with pazopanib, myocardial infarctions, angina, ischemic stroke and transient ischemic attack were observed. Fatal events have been observed. Pazopanib should be used with caution in patients who are at increased risk of thrombotic events or who have had a history of thrombotic events. Pazopanib has not been studied in patients who have had an event within the previous 6 months. A treatment decision should be made based on the assessment of individual patient's benefit/risk.

Venous thromboembolic events
In a study with pazopanib, venous thromboembolic events including venous thrombosis and fatal pulmonary embolus have occurred. The incidence was higher in the STS population than in the RCC population.

Thrombotic microangiopathy (TMA)
Thrombotic microangiopathy (TMA) has been reported in a study of pazopanib as monotherapy, in combination with bevacizumab, and in combination with topotecan. Pazopanib should be permanently discontinued in patients developing TMA. Reversal of effects of TMA has been observed after treatment was discontinued. Pazopanib is not indicated for use in combination with other agents.

Hemorrhagic events
In a study with pazopanib, hemorrhagic events have been reported. Fatal hemorrhagic events have occurred. Pazopanib has not been studied in patients who had a history of hemoptysis, cerebral hemorrhage, or clinically significant gastrointestinal hemorrhage in the past 6 months. Pazopanib should be used with caution in patients with significant risk of hemorrhage.

Aneurysms and artery dissections
Artery dissections and aneurysms have been reported in association with VEGF pathway inhibitors, including pazopanib. The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysm and/or artery dissections. Before initiating pazopanib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Gastrointestinal perforations and fistula
In a study with pazopanib, events of gastrointestinal (GI) perforation or fistula have occurred. Fatal perforation events have occurred. Pazopanib should be used with caution in patients at risk for GI perforation or fistula.

Wound healing
No formal studies of the effect of pazopanib on wound healing have been conducted. Since vascular endothelial growth factor (VEGF) inhibitors may impair wound healing, treatment with pazopanib should be stopped at least 7 days prior to scheduled surgery. The decision to resume pazopanib after surgery should be based on clinical judgement of adequate wound healing. Pazopanib should be discontinued in patients with wound dehiscence.

Hypothyroidism
In a study with pazopanib, events of hypothyroidism have occurred. Proactive monitoring of thyroid function tests is recommended.

Proteinuria
In a study with pazopanib, proteinuria has been reported. Baseline and periodic urinalyses during treatment are recommended and patients should be monitored for worsening proteinuria. Pazopanib should be discontinued if the patient develops nephrotic syndrome.

Tumor lysis syndrome (TLS)
Cases of TLS, including fatal cases, have been reported in patients treated with pazopanib. Patients generally at risk of TLS are those with rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration.
Preventative measures such as treatment of high uric acid levels and intravenous hydration should be considered prior to initiation of pazopanib. Patients at risk should be closely monitored and treated as clinically indicated.

Infections
Cases of serious infections (with or without neutropenia), in some cases with fatal outcome, have been reported.

Combination with other systemic anti-cancer therapies
A study of pazopanib in combination with pemetrexed (non-small cell lung cancer (NSCLC)), lapatinib (cervical cancer) or pembrolizumab (advanced renal cell carcinoma) were terminated early due to concerns over increased toxicity and/or mortality, and a safe and effective combination dose has not been established with these regimens. Pazopanib is not indicated for use in combination with other anti-cancer agents.

Juvenile animal toxicity
Because the mechanism of action of pazopanib can severely affect organ growth and maturation during early post-natal development, pazopanib should not be given to human pediatric patients younger than 2 years of age.

Pregnancy
Studies in animals have shown reproductive toxicity.
Based on animal reproduction studies and its mechanism of action, pazopanib can cause fetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to a fetus. Females of reproductive potential should be advised to avoid becoming pregnant while receiving treatment with pazopanib.

Interactions
Concomitant treatment with strong inhibitors of CYP3A4, P-glycoprotein (P-gp) or breast cancer resistance protein (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 CYP3A4, P-gp or BCRP should be considered.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

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, P-gp, BCRP inhibitors
Pazopanib is a substrate for CYP3A4, P-gp and BCRP.

Concurrent administration of Pazopanib (400 mg once daily) with the strong CYP3A4 and P- gp inhibitor, ketoconazole (400 mg once daily) for 5 consecutive days, resulted in a 66% and 45% increase in mean Pazopanib AUC(0-24) and C_{max}, respectively, relative to administration of pazopanib alone (400 mg once daily for 7 days). Pazopanib C_{max} and AUC increase in a less than dose proportional fashion with increasing dose over the range of 50 mg to 2000 mg.

Therefore, a dose reduction to 400 mg pazopanib once daily in the presence of strong CYP3A4 inhibitors will, in the majority of patients, result in systemic exposure similar to that observed after administration of 800 mg pazopanib once daily alone. Some patients however may have systemic pazopanib exposure greater than what has been observed after administration of 800 mg pazopanib alone.

Co-administration of pazopanib with other strong inhibitors of the CYP3A4 family (e.g., itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase pazopanib concentrations. Grapefruit juice may also increase plasma concentrations of pazopanib.

Administration of 1500 mg lapatinib a substrate and weak inhibitor of CYP3A4, P-gp and BCRP with 800 mg pazopanib resulted in an approximately 50% to 60% increase in mean pazopanib AUC(0-24) and C_{max} compared to administration of 800 mg pazopanib alone. Co- administration of pazopanib with a CYP3A4, P-gp, and BCRP inhibitor, such as lapatinib, will result in an increase in plasma pazopanib concentrations.

Concomitant use of pazopanib with a strong CYP3A4 inhibitor should be avoided. If no medically acceptable alternative to a strong CYP3A4 inhibitor is available, the dose of pazopanib should be reduced to 400 mg daily during concomitant administration. Further dose reduction may be considered if possible drug-related adverse events are observed.

Combination with strong P-gp or BCRP inhibitors should be avoided, or selection of an alternate concomitant medication with no or minimal potential to inhibit P-gp or BCRP is recommended.

CYP3A4 inducers
CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. Selection of an alternative concomitant medication with no or minimal enzyme induction potential is recommended.

Effects of PAZITORZ on CYP substrates
In vitro studies with human liver microsomes showed that pazopanib inhibited CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, and 2E1. Potential induction of human CYP3A4 was demonstrated in an in vitro human PXR assay. Studies, using pazopanib 800 mg once daily, have demonstrated that pazopanib does not have a clinically relevant effect on the pharmacokinetics of caffeine (CYP1A2 probe substrate), warfarin (CYP2C9 probe substrate), or omeprazole (CYP2C19 probe substrate) in cancer patients. Pazopanib resulted in an increase of approximately 30% in the mean AUC and C_{max} of midazolam (CYP3A4 probe substrate) and increases of 33% to 64% in the ratio of dextromethorphan to dextrorphan concentrations in the urine after oral administration of dextromethorphan (CYP2D6 probe substrate). Co-administration of pazopanib 800 mg once daily and paclitaxel 80 mg/m^2 (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 26% and 31% in paclitaxel AUC and C_{max}, respectively.

Effects of PAZITORZ on other enzymes and transporters
In vitro studies also showed that pazopanib is a potent inhibitor of UGT1A1 and OATP1B1 with IC_{50} of 1.2 and 0.79 microM, respectively. PAZITORZ may increase concentrations of drugs primarily eliminated through UGT1A1 and OATP1B1.

Effect of concomitant use of PAZITORZ and simvastatin
Concomitant use of pazopanib and simvastatin increases the incidence of ALT elevations. Across monotherapy studies with pazopanib, ALT >3X 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 (p=0.038). If a patient receiving concomitant simvastatin develops ALT elevations, follow guidelines for pazopanib posology and discontinue simvastatin. Insufficient data are available to assess the risk of concomitant administration of alternative statins and pazopanib.

Drug-food/drink interactions
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.

Medicines that raise gastric pH
Concomitant administration of pazopanib with esomeprazole decreases the bioavailability of pazopanib by approximately 40% (AUC and C_{max}), and co-administration of pazopanib with medicines that increase gastric pH should be avoided.

4.6 Fertility, pregnancy and lactation
Pregnancy
Risk Summary
Based on animal reproduction studies and its mechanism of action, Pazopanib can cause fetal harm when administered to a pregnant woman. There are no adequate data from the use of Pazopanib in pregnant women. In animal developmental toxicity studies, oral administration of pazopanib to pregnant rats and rabbits throughout organogenesis resulted in teratogenicity and abortion at systemic exposures lower than that observed at the maximum recommended human dose of 800 mg/day (based on AUC). Pazopanib should not be used during pregnancy unless the clinical condition of the woman requires treatment with Pazopanib. Pregnant women or females of reproductive potential should be advised of the potential risk to a fetus.

Animal data
In a female fertility and early embryonic development study in rats, post-implantation loss, embryo lethality and decreased fetal body weights were noted at dosages ≥10 mg/kg/day (approximately 0.2-fold the AUC at the MRHD of 800 mg/day) and increased pre- implantation loss and early resorptions were noted at dosages ≥30 mg/kg/day (approximately 0.4-fold the AUC at the MRHD of 800 mg/day).

In embryo-fetal development toxicity studies, pazopanib produced teratogenic effects (including cardiovascular malformations), delayed ossification, increased post-implantation loss, reduced fetal body weight and embryo lethality in rats at a dose level of ≥3 mg/kg/day (approximately 0.1-fold the AUC at the MRHD of 800 mg/day). In rabbits, maternal toxicity (body weight loss, reduced food consumption), increased post-implantation loss and abortion were observed at doses ≥30 mg/kg/day (approximately 0.007-fold the AUC at the MRHD of 800 mg/day), while fetal weight was reduced at doses ≥3 mg/kg/day (AUC not calculated).

Lactation
Risk Summary
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 pazopanib, a lactating woman should be advised not to breastfeed during treatment with pazopanib.

Fertility
Contraception
Females
Females of reproductive potential should be advised to use effective contraception during treatment with pazopanib and for at least 2 weeks after the last dose.

Males
Male patients (including those who have had vasectomies) with female partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms while taking pazopanib and for at least 2 weeks after the last dose.

Infertility
Based on findings from animal studies, pazopanib may impair fertility in males and females of reproductive potential while receiving treatment.

4.7 Effects on Ability to Drive and Use Machines

PAZITORZ has no or negligible influence on the ability to drive and use machines. A detrimental effect on such activities cannot be predicted from the pharmacology of pazopanib. The clinical status of the patient and the adverse event profile of pazopanib should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills. Patients should avoid driving or using machines if they feel dizzy, tired or weak.

4.8 Undesirable Effects
Summary of the safety profile
The safety and efficacy of Pazopanib in renal cell carcinoma (RCC) were evaluated in a randomized, double-blind, placebo-controlled multi-center study. Patients with locally advanced and/or metastatic RCC were randomized to receive Pazopanib 800 mg once daily (N=290) or placebo (N=145). The median duration of treatment was 7.4

months for the Pazopanib arm and 3.8 months for the placebo arm.

The safety and efficacy of Pazopanib in soft tissue sarcoma (STS) were evaluated in a randomized, double-blind, placebo-controlled multi-center study. Patients (N=369) with advanced STS who had received prior anthracycline treatment, or were unsuited for such therapy, were randomized to receive Pazopanib 800 mg once daily (N=246) or placebo (N=123). The median duration of treatment was 4.5 months for the Pazopanib arm and 1.9 months for the placebo arm. Adverse reactions are listed below by MedDRA body system organ class.

Tabulated summary of adverse drug reactions from clinical trials
Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1 Adverse drug reactions, by organ class and frequency, reported in RCC (VEG105192) and STS (VEG110727) studies

Adverse drug reactions	**Frequency classification**	
	RCC N=290	**STS N=240**
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		
Tumour pain	♦	Very common
Blood and lymphatic system disorders		
Neutropenia	Common	♦
Thrombocytopenia	Common	♦
Endocrine disorders		
Hypothyroidism*	Common	Common
Metabolism and nutrition disorders		
Decreased appetite	Very common	Very common
Nervous system disorders		
Dizziness	♦	Very common
Dysgeusia	Common	Very common
Headache	Very common	Very common
Ischaemic stroke*	Uncommon	Uncommon
Transient ischaemic attack*	Common	♦
Cerebral haemorrhage*	Uncommon	Uncommon
Psychiatric disorders		
Insomnia	♦	Common
Cardiac disorders		
Cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure)*	Uncommon	Common
Bradycardia (asymptomatic)	Very common†	Very common†
Myocardial infarction*	Uncommon	Common
Myocardial ischaemia*	Common	♦
Torsade de Pointes*	Uncommon	♦
Vascular disorders		
Hypertension*	Very common	Very common
Venous embolism*	Common	Common
Respiratory, thoracic and mediastinal disorders		
Cough	♦	Very common
Dysphonia	Common	Common
Dyspnoea	♦	Very common
Pneumothorax	♦	Common

Epistaxis	Common	Common
Pulmonary haemorrhage*	Uncommon	Common
Gastrointestinal disorders		
Abdominal pain	Very common	Very common
Diarrhoea	Very common	Very common
Dyspepsia	Common	Common
Gastrointestinal perforation*	Uncommon	♦
Gastrointestinal fistula*	Uncommon	Uncommon
Gastrointestinal haemorrhage*	Common	Common
Nausea	Very common	Very common
Stomatitis	♦	Very common
Vomiting	Very common	Very common
Hepatobiliary disorders		
Hepatic function abnormal*	Common	♦
Hyperbilirubinaemia*	Common	Uncommon
Skin and subcutaneous tissue disorders		
Alopecia	Common	Very common
Dry skin	♦	Common
Exfoliative rash	♦	Very common
Hair color changes	Very common	Very common
Nail disorder	♦	Common
Palmar-plantar erythrodysaesthesia syndrome	Common	Very common
Rash	Common	Uncommon
Skin depigmentation	Common	Very common
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	♦	Very common
Myalgia	♦	Very common
Renal and urinary disorders		
Proteinuria*	Common	Uncommon
Haematuria	Common	Uncommon
Eye disorders		
Vision blurred	♦	Common
General disorders and administration site conditions		
Asthenia	Very common	Uncommon
Chest pain*	Common	Very common
Chills	♦	Common
Fatigue	Very common	Very common
Oedema peripheral	♦	Very common
Investigations		
Weight decreased	Common	Very common
Electrocardiogram QT prolonged*	Common	Common
Lipase increased	Common‡	♦
Alanine aminotransferase increased*	Very common	Common
Aspartate aminotransferase increased*	Very common	Common

* See Warnings and precautions for additional information.

♦ - Adverse event was not considered causally related to Pazopanib in the pivotal clinical trial for this indication.

Note: Laboratory findings which met the CTC-AE criteria were recorded as adverse events at the discretion of the Investigator

† - Frequency based on heart rate measurement (< 60 beats per minute) rather than adverse event reports. Symptomatic bradycardia has been identified rarely based on a review of the Pazopanib safety database.

‡ - For RCC, the frequency category is based on data from the supportive single-arm study VEG102616.

Neutropenia, thrombocytopenia and palmar-plantar erythrodysaesthesia syndrome were observed more frequently in patients of East Asian descent.

Table 2 presents laboratory abnormalities occurring in ≥ 15% of patients who received Pazopanib in the pivotal RCC study. Grades are based on the NCI CTCAE.

Table 2 Selected Laboratory Abnormalities in ≥ 15% of Patients who Received Pazopanib and with a frequency greater than Placebo (VEG105192)

Parameters	Pazopanib (N=290)			Placebo (N=145)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Haematological						
Leukopenia	37	0	0	6	0	0
Neutropenia	34	1	<1	6	0	0
Thrombocytopenia	32	<1	<1	5	0	<1
Lymphocytopenia	31	4	<1	24	1	0
Chemistry						
ALT increased	53	10	2	22	1	0
AST increased	53	7	<1	19	<1	0
Glucose increased	41	<1	0	33	1	0
Total bilirubin increased	36	3	<1	10	1	<1
Phosphorus decreased	34	4	0	11	0	0
Calcium decreased	33	1	1	26	1	<1
Sodium decreased	31	4	1	24	4	1
Potassium increased	27	4	<1	23	5	0
Creatinine increased	26	0	<1	25	<1	0
Magnesium decreased	26	<1	1	14	0	0
Glucose decreased	17	0	<1	3	0	0

Table 3 presents laboratory abnormalities occurring in ≥ 15% of patients who received Pazopanib in the pivotal STS study. Grades are based on the NCI CTCAE.

Table 3 Selected Laboratory Abnormalities in ≥ 15% of Patients who Received Pazopanib and with a frequency greater than Placebo (VEG110727)

Parameters	Pazopanib (N=240)			Placebo (N=123)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Haematological						
Leukopenia	44	1	0	15	0	0
Neutropenia	33	4	0	7	0	0
Thrombocytopenia	36	3	<1	6	0	0
Lymphocytopenia	43	10	0	36	9	2
Anaemia	27	5	2	23	<1	<1
Chemistry						
ALKP increased	32	3	0	23	<1	0

ALT increased	46	8	2	18	2	<1
AST increased	51	5	3	22	2	0
Albumin decreased	34	<1	0	21	0	0
Glucose increased	45	<1	0	35	2	0
Total bilirubin increased	29	1	0	7	2	0
Sodium decreased	31	4	0	20	3	0
Potassium increased	16	1	0	11	0	0

The following adverse drug reactions have been identified during post-approval use of Pazopanib. This includes spontaneous case reports as well as serious adverse events from ongoing studies, clinical pharmacology studies and exploratory studies in unapproved indications.

Table 4 Adverse drug reactions identified during post-approval use

Infections and infestations	
Common	Infections (with or without neutropenia); see section WARNINGS AND PRECAUTIONS
Blood and lymphatic system disorders	
Uncommon	Polycythaemia
Uncommon	Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome); see section WARNINGS AND PRECAUTIONS
Eye disorders	
Uncommon	Retinal detachment Retinal tear
Metabolism and nutrition disorders	
Not known	Tumour lysis syndrome (including fatal cases); see section WARNINGS AND PRECAUTIONS
Nervous system disorders	
Rare	Posterior reversible encephalopathy syndrome (see section WARNINGS AND PRECAUTIONS)
Respiratory, thoracic and mediastinal disorders	
Rare	Interstitial lung disease (ILD)/pneumonitis (see section WARNINGS AND PRECAUTIONS)
Gastrointestinal disorders	
Common	Flatulence
Uncommon	Pancreatitis
Hepatobiliary disorders	
Not known	Hepatic failure
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia
Common	Muscle spasms
Vascular Disorders	
Not known	Aneurysms and artery dissections
Skin and subcutaneous tissue disorders	
Uncommon	Skin ulcer
Investigations	
Common	Gamma-glutamyl transpeptidase increased

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

Symptoms and signs
There is currently limited experience with overdosage in pazopanib.

Treatment
Further management should be as clinically indicated or as recommended by the national poisons center, where available. Hemodialysis is not expected to enhance the elimination of pazopanib because pazopanib is not significantly renally excreted and is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group, ATC
Pharmacotherapeutic group: Antineoplastic agents – Protein kinase inhibitor, ATC Code: L01XE11.

Mechanism of action (MOA)
Pazopanib is an orally administered, potent multi-target tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3, platelet-derived growth factor (PDGFR)-alpha and –beta, and stem cell factor receptor (c-KIT), with IC_{50} values of 10, 30, 47, 71, 84 and 74 nM, respectively. In preclinical experiments, pazopanib dose- dependently inhibited ligand-induced auto-phosphorylation of VEGFR-2, c-Kit and PDGFR- beta receptors in cells. *In vivo*, pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in various animal models, and the growth of multiple human tumor xenografts in mice.

5.2 Pharmacokinetic Properties

Absorption
Pazopanib is absorbed orally with median time to achieve peak concentrations of 2.0 to 4.0 hours after the dose. Daily dosing results in 1.23- to 4-fold increase in AUC. There was no consistent increase in AUC and C_{max} when the pazopanib dose increased above 800 mg once daily.

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.

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 1.5 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 should not be crushed.

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 studies suggest that Pazopanib is a substrate for P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP).

Biotransformation/metabolism
Results from studies demonstrated that the metabolism of pazopanib is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8.

Elimination
Pazopanib is eliminated slowly with 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.

Special populations
Renal impairment
In a population pharmacokinetic analysis using 408 subjects with various cancers, creatinine clearance (30 to 150 mL/min) did not influence clearance of pazopanib. Renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary in patients with creatinine clearance ≥30 mL/min.

Hepatic impairment
The median steady-state pazopanib C_{max} and $AUC_{(0-24)}$ in patients with mild hepatic impairment (defined as either

normal bilirubin and any degree of ALT elevations or as an elevation of bilirubin up to 1.5 X ULN regardless of the ALT value) after a once daily dose of 800 mg/day (30.9 microgram/mL, range 12.5 to 47.3 and 841.8 microgram.hr/mL, range 600.4 to 1,078) are similar to the median in patients with no hepatic impairment (49.4 microgram/mL, range 17.1 to 85.7 and 888.2 microgram.hr/mL, range 345.5 to 1,482).

The maximally tolerated pazopanib dose (MTD) in patients with moderate hepatic impairment (defined as an elevation of bilirubin > 1.5 X to 3 X ULN regardless of the ALT values) was 200 mg once daily. The median steady-state values of C_{max} (22.4 microgram/mL, range 6.4 to 32.9) and $AUC_{(0-24)}$ (350.0 microgram.hr/mL, range 131.8 to 487.7) after administration of 200 mg pazopanib once daily in subjects with moderate hepatic impairment were approximately 45% and 39%, respectively, that of the corresponding median values after administration of 800 mg once daily in subjects with normal hepatic function.

There are insufficient data in patients with severe hepatic impairment (total bilirubin > 3 X ULN regardless of the ALT value); therefore, use of pazopanib is not recommended in these patients.

Pharmacogenomics
In a pharmacogenetic meta-analysis of data from 31 clinical studies of pazopanib administered either as monotherapy or in combination with other agents, ALT > 5 X ULN (NCI CTC Grade 3) occurred in 19% of HLA-B*57:01 allele carriers and in 10% of non-carriers. In this dataset, 133/2235 (6%) of the patients carried the HLA-B*57:01 allele.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core:
Microcrystalline cellulose, Sodium Starch Glycolate Type A, Povidone, Silicified Microcrystalline Cellulose, Magnesium stearate

Film coat:
Polysorbate 80, Kollicoat IR

6.2 Incompatibilities

Not applicable

6.3 Special Precautions for Storage

Store below 30°C in the original container

6.4 Nature and Content of Container

PAZITORZ 200:
Blister of OPA/Alu/PVC with Alu Foil containing 10 tablets, such 3 or 9 blisters are packed in an outer carton with a pack insert.

PAZITORZ 400:
Blister of OPA/Alu/PVC with Alu Foil containing 10 tablets, such 3 or 6 blisters are packed in an outer carton with a pack insert.

6.5 Special precautions for disposal and other handling

No special requirements.

7 MANUFACTURER

Dr. Reddy`s Laboratories Limited,
FTO-VII : Plot No. P1 to P9,
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Visakhapatnam District,
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8 PRODUCT REGISTRATION HOLDER

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9. DATE OF REVISION

April 2026