For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

PAZOBRITE

1. Generic Name

Pazopanib Tablets

2. Qualitative and quantitative Composition:

PAZOBRITE 200

Each film coated tablet contains:

Pazopanib Hydrochloride Eq. to Pazopanib……..200 mg

Excipients……..q.s.

Colours: Ferric Oxide USP-NF Red and Titanium Dioxide I.P.

The excipients used are Mannitol, Pregelatinized Starch, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Talc, Hydroxyl Propyl Cellulose, Sepitrap 80, Magnesium Stearate, Croscarmellose Sodium, Opadry Pink 15B24005.

PAZOBRITE 400

Each film coated tablet contains:

Pazopanib Hydrochloride Eq. to Pazopanib……..400 mg

Excipients……..q.s.

Colours: Ferric Oxide USP-NF Red and Titanium Dioxide I.P.

The excipients used are Mannitol, Pregelatinized Starch, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Talc, Hydroxyl Propyl Cellulose, Sepitrap 80, Magnesium Stearate, Croscarmellose Sodium, Opadry Pink 15B24005.

3. Dosage form and strength

Dosage form: Tablets

Strength: Pazopanib 200, 400 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the treatment of patients with advanced renal cell carcinoma and for the treatment of patients with advanced Soft Tissue Sarcoma (STS) who have received prior chemotherapy.

4.2 Posology and method of administration

Posology

Pazopanib treatment should only be initiated by a physician experienced in the administration of anti-cancer medicinal products.

Adults

The recommended dose of pazopanib for the treatment of RCC or STS is 800 mg once daily.

Dose modifications

Dose modification (decrease or increase) should be in 200 mg decrements or increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions. The dose of pazopanib should not exceed 800 mg.

Paediatric population

Pazopanib should not be used in children younger than 2 years of age because of safety concerns with regard to organ growth and maturation.

The safety and efficacy of pazopanib in children aged 2 to 18 years of age have not yet been established.

Currently available reported data but no recommendation on a posology can be made.

Elderly

There are limited data on the use of pazopanib in patients aged 65 years and older. In the reported RCC studies of pazopanib, overall no clinically significant differences in safety of pazopanib were observed between subjects aged at least 65 years and younger subjects. Clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some elderly patients cannot be ruled out.

Renal impairment

Renal impairment is unlikely to have a clinically relevant effect on pazopanib pharmacokinetics given the low renal excretion of pazopanib and metabolites. Therefore, no dose adjustment is required in patients with creatinine clearance above 30 ml/min. Caution is advised in patients with creatinine clearance below 30 ml/min as there is no experience of pazopanib in this patient population.

Hepatic impairment

Dosing recommendations in hepatically impaired patients are based on pharmacokinetic studies of pazopanib in patients with varying degrees of hepatic dysfunction. All patients should have liver function tests to determine whether they have hepatic impairment before starting and during pazopanib therapy. Administration of pazopanib to patients with mild or moderate hepatic impairment should be undertaken with caution and close monitoring of tolerability. 800 mg pazopanib once daily is the recommended dose in patients with mild abnormalities in serum liver tests (defined either as normal bilirubin and any degree of alanine aminotransferase (ALT) elevation or as an elevation of bilirubin (>35% direct) up to 1.5 x upper limit of normal (ULN) regardless of the ALT value). A reduced pazopanib dose of 200 mg once daily is recommended in patients with moderate hepatic impairment (defined as an elevation of bilirubin >1.5 to 3 x ULN regardless of the ALT value).

Pazopanib is not recommended in patients with severe hepatic impairment (defined as total bilirubin >3 x ULN regardless of the ALT value).

Method of administration

- Pazopanib is for oral use.
- It should be taken without food, at least one hour before or two hours after a meal.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Hepatic effects

Cases of hepatic failure (including fatalities) have been reported during use of pazopanib. Administration of pazopanib to patients with mild or moderate hepatic impairment should be undertaken with caution and close monitoring. 800 mg pazopanib once daily is the recommended dose in patients with mild abnormalities in serum liver tests (either normal bilirubin and any degree of ALT elevation or elevation of bilirubin up to 1.5 x ULN regardless of the ALT value). A reduced pazopanib dose of 200 mg once daily is recommended in patients with moderate hepatic impairment (elevation of bilirubin >1.5 to 3 x ULN regardless of the ALT value). Pazopanib is not recommended in patients with severe hepatic impairment (total bilirubin >3 x ULN regardless of the ALT value). Exposure at a 200 mg dose is markedly reduced, though highly variable, in these patients, with values considered insufficient to obtain a clinically relevant effect.

In reported clinical studies 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 mild (>3 x ULN) to severe (>8 x ULN) elevation of ALT. Patients who carry the HLA-B*57:01 allele have an increased risk of pazopanib-associated ALT elevations. Liver function should be monitored in all subjects receiving pazopanib, regardless of genotype or age.

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.

See Table 1 for dose modification guidance for patients with baseline values of total bilirubin ≤1.5 x ULN and AST and ALT ≤2 x ULN:

Dose modifications for drug-induced hepatotoxicity

Liver test values	Dose modification
Transaminase elevation between 3 and 8 x ULN	Continue on pazopanib with weekly monitoring of liver function until transaminases return to Grade 1 or baseline.
Transaminase elevation of >8 x ULN	Interrupt pazopanib until transaminases return to Grade 1 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 daily and perform serum liver tests weekly for 8 weeks. Following reintroduction of pazopanib, if transaminase elevations >3 x ULN recur, then pazopanib should be permanently discontinued.
Transaminase elevations >3 x ULN concurrently with bilirubin elevations >2 x ULN	Permanently discontinue pazopanib. Patients should be monitored until return to Grade 1 or baseline. Pazopanib is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinaemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinaemia, 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.

Hypertension

In clinical studies with pazopanib, events of hypertension including newly diagnosed symptomatic episodes of elevated blood pressure (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. Elevated blood pressure levels (systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥100 mm Hg) occurred early in the course of treatment (approximately 40% of cases occurred by day 9 and approximately 90% of cases occurred in the first 18 weeks). 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 judgement) 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. Patients developing PRES/RPLS should permanently discontinue treatment with pazopanib.

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/Heart failure

The risks and benefits of pazopanib should be considered before beginning therapy in patients who have pre-existing cardiac dysfunction. The safety and pharmacokinetics of pazopanib in patients with moderate to severe heart failure or those with a below normal left ventricular ejection fraction (LVEF) have not been studied.
In clinical studies with pazopanib, events of cardiac dysfunction such as congestive heart failure and decreased LVEF have occurred. In a reported randomised study comparing pazopanib and sunitinib in RCC (VEG108844), subjects had baseline and follow up LVEF measurements. Myocardial dysfunction occurred 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. Congestive heart failure was reported in 3 out of 240 subjects (1%) in the reported Phase III VEG110727 STS study. Decreases in LVEF in subjects who had post-baseline and follow-up LVEF measurement were detected in 11% (15/140) in the pazopanib arm, compared with 3% (1/39) in the placebo arm.

Risk factors

Thirteen of the 15 subjects in the pazopanib arm of the STS Phase III reported study had concurrent hypertension which may have exacerbated cardiac dysfunction in patients at risk by increasing cardiac after-load. 99% of patients (243/246) enrolled in the STS Phase III study, including the 15 subjects, received anthracycline. Prior anthracycline therapy may be a risk factor for cardiac dysfunction.

Outcome

Four of the 15 subjects had full recovery (within 5% of baseline) and 5 had partial recovery (within the normal range, but >5% below baseline). One subject did not recover and follow-up data were not available for the other 5 subjects.

Management

Interruption of pazopanib and/or dose reduction should be combined with treatment of in patients with significant reductions in LVEF, as clinically indicated.
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 clinical studies with pazopanib, events of QT prolongation and 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 medicinal products that may prolong QT interval and in patients 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 normal range is recommended.

Arterial thrombotic events

In clinical studies with pazopanib, myocardial infarction, myocardial ischaemia, ischaemic stroke and transient ischaemic 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 clinical studies with pazopanib, venous thromboembolic events including venous thrombosis and fatal pulmonary embolus have occurred. While observed in both RCC and STS studies, the incidence was higher in the STS population (5%) than in the RCC population (2%).

Thrombotic microangiopathy (TMA)

TMA has been reported in clinical studies of pazopanib as monotherapy, in combination with bevacizumab, and in combination with topotecan. Patients developing TMA should permanently discontinue treatment with pazopanib. Reversal of effects of TMA has been observed after treatment was discontinued. Pazopanib is not indicated for use in combination with other agents.

Haemorrhagic events

In reported clinical studies with pazopanib haemorrhagic events have been reported. Fatal haemorragic events have occurred. Pazopanib has not been studied in patients who had a history of haemoptysis, cerebral haemorrhage or clinically significant gastrointestinal (GI) haemorrhage in the past 6 months. Pazopanib should be used with caution in patients with significant risk of haemorrhage.

Aneurysms and artery dissections

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 (GI) perforations and fistula

In reported clinical studies with pazopanib, events of 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 reported. 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 reported clinical studies with pazopanib, events of hypothyroidism have occurred. Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism should be treated as per standard medical practice prior to the start of pazopanib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction on pazopanib treatment. Laboratory monitoring of thyroid function should be performed periodically and managed as per standard medical practice.

Proteinuria

In clinical studies with pazopanib, proteinuria has been reported. Baseline and periodic urinanalysis during treatment is recommended and patients should be monitored for worsening proteinuria. Pazopanib should be discontinued if the patient develops nephrotic syndrome.

Tumour lysis syndrome (TLS)

The occurrence of TLS, including fatal TLS, has been associated with the use of pazopanib. Patients at increased risk of TLS are those with rapidly growing tumours, a high tumour 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.

Pneumothorax

In reported clinical studies with pazopanib in advanced soft tissue sarcoma, events of pneumothorax have occurred. Patients on pazopanib treatment should be observed closely for signs and symptoms of pneumothorax.

Paediatric population

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

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

In reported clinical studies of pazopanib in combination with a number of other anti-cancer therapies (including for example pemetrexed, lapatinib or pembrolizumab) 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.

Pregnancy

Pre-clinical studies in animals have shown reproductive toxicity. If pazopanib is used during pregnancy, or if the patient becomes pregnant whilst receiving pazopanib, the potential hazard to the foetus should be explained to the patient. Women of childbearing 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.

Concomitant treatment with inducers of CYP3A4 should be avoided due to risk of decreased exposure to pazopanib.

Cases of hyperglycaemia have been observed during concomitant treatment with ketoconazole.

Concomitant administration of pazopanib with uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) substrates (e.g. irinotecan) should be undertaken with caution since pazopanib is an inhibitor of UGT1A1.

Grapefruit juice should be avoided during treatment with pazopanib.

4.5 Drugs interactions

Effects of other medicinal products on pazopanib

In reported 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). Pharmacokinetic parameter comparisons of pazopanib C_{max} (range of means 27.5 to 58.1 µg/ml) and AUC(0-24) (range of means 48.7 to 1040 µg*h/ml) after administration of pazopanib 800 mg alone and after administration of pazopanib 400 mg plus ketoconazole 400 mg (mean C_{max} 59.2 µg/ml, mean AUC(0-24)1300 µg*h/ml) indicated that, in the presence of a strong CYP3A4 and P-gp inhibitor a dose reduction to pazopanib 400 mg once daily 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 contains an inhibitor of CYP3A4 and may also increase plasma concentrations of pazopanib.

Administration of 1500 mg lapatinib (a substrate for and weak inhibitor of CYP3A4 and P-gp and a potent inhibitor of 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. Inhibition of P-gp and/or BCRP by lapatinib likely contributed to the increased exposure to pazopanib.

Co-administration of pazopanib with a CYP3A4, P-gp, and BCRP inhibitor, such as lapatinib, will result in an increase in plasma pazopanib concentrations. Co-administration with potent P-gp or BCRP inhibitors may also alter the exposure and distribution of pazopanib, including distribution into the central nervous systems (CNS).

Concomitant use of pazopanib with a strong CYP3A4 inhibitor should be avoided. If no medically acceptable alternative to a strong CYP34A inhibitor is available, the dose of pazopanib should be reduced to 400 mg daily during concomitant administration. In such cases there should be close attention to adverse drug reaction, and 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 medicinal product with no or minimal potential to inhibit P-gp or BCRP is recommended.

CYP3A4, P-gp, BCRP inducers

CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. Co-administration of pazopanib with potent P-gp or BCRP inducers may alter the exposure and distribution of pazopanib, including distribution into the CNS. Selection of an alternative concomitant medication with no or minimal enzyme or transporter induction potential is recommended.

Effects of pazopanib on other medicinal products

In vitro reported 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. Clinical pharmacology 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 dextrometrophan to dextrophan concentrations in the urine after oral administration of dextromethorphan (CYP2D6 probe substrate). Co-administration of pazopanib 800 mg once daily and paclitaxel 80 mg/m2 (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 26% and 31% in paclitaxel AUC and C_{max}, respectively.

Based on in vitro IC50 and in vivo plasma C_{max} values, pazopanib metabolites GSK1268992 and GSK1268997 may contribute to the net inhibitory effect of pazopanib towards BCRP. Furthermore, inhibition of BCRP and P-gp by pazopanib in the gastrointestinal tract cannot be excluded. Care should be taken when pazopanib is co-administered with other oral BCRP and P-gp substrates.

In vitro, pazopanib inhibited human organic anion transporting polypeptide (OATP1B1). It cannot be excluded that pazopanib will affect the pharmacokinetics of substrates of OATP1B1 (e.g. statins, see "Effect of concomitant use of pazopanib and simvastatin" below).

Pazopanib is an inhibitor of the uridine diphosphoglucuronosyl-transferase 1A1 (UGT1A1) enzyme in vitro. The active metabolite of irinotecan, SN-38, is a substrate for OATP1B1 and UGT1A1. Co-administration of pazopanib 400 mg once daily with cetuximab 250 mg/m2 and irinotecan 150 mg/m2 resulted in an approximately 20% increase in systemic exposure to SN-38. Pazopanib may have a greater impact on SN-38 disposition in subjects with the UGT1A1*28 polymorphism relative to subjects with the wild-type allele. However, the UGT1A1 genotype was not always predictive of

the effect of pazopanib on SN-38 disposition. Care should be taken when pazopanib is co-administered with substrates of UGT1A1.

Effect of concomitant use of pazopanib and simvastatin

Concomitant use of pazopanib and simvastatin increases the incidence of ALT elevations. Results from a meta-analysis using pooled data from clinical studies with pazopanib show that 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. In addition, concomitant use of pazopanib and other statins should be undertaken with caution as there are insufficient data available to assess their impact on ALT levels. It cannot be excluded that pazopanib will affect the pharmacokinetics of other statins (e.g. atorvastatin, fluvastatin, pravastatin, rosuvastatin).

Effect of food on pazopanib

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.

Medicinal products 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. If the concomitant use of a proton-pump inhibitor (PPI) is medically necessary, it is recommended that the dose of pazopanib be taken without food once daily in the evening concomitantly with the PPI. If the concomitant administration of an H2-receptor antagonist is medically necessary, pazopanib should be taken without food at least 2 hours before or at least 10 hours after a dose of an H2-receptor antagonist. Pazopanib should be administered at least 1 hour before or 2 hours after administration of short-acting antacids. The recommendations for how PPIs and H2-receptor antagonists are co-administered are based on physiological considerations.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

There are no adequate data from the use of pazopanib in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Pazopanib should not be used during pregnancy unless the clinical condition of the woman requires treatment with pazopanib. If pazopanib is used during pregnancy, or if the patient becomes pregnant while receiving pazopanib, the potential hazard to the foetus should be explained to the patient.

Women of childbearing potential should be advised to use adequate contraception during treatment and for at least 2 weeks after the last dose of pazopanib and to avoid becoming pregnant while receiving treatment with pazopanib.

Male patients (including those who have had vasectomies) should use condoms during sexual intercourse while taking pazopanib and for at least 2 weeks after the last dose of pazopanib to avoid potential exposure to the medicinal product for pregnant partners and female partners of reproductive potential.

Breast-feeding

The safe use of pazopanib during breast-feeding has not been established. It is not known whether pazopanib or its metabolites are excreted in human milk. There are no animal data on the excretion of pazopanib in animal milk. A risk to the breast-fed child cannot be excluded. Breast-feeding should be discontinued during treatment with pazopanib.

Fertility

In reported animal studies indicate that male and female fertility may be affected by treatment with pazopanib

4.7 Effects on ability to drive and use machines

Pazopanib 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 reported 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 reported Pooled data from pivotal RCC study (VEG105192, n=290), the extension study (VEG107769, n=71), the supportive Phase II study (VEG102616, n=225) and the reported randomised, open-label, parallel group Phase III non-inferiority study (VEG108844, n=557) were evaluated in the overall evaluation of safety and tolerability of pazopanib (total n=1149) in subjects with RCC.

Pooled data from the reported pivotal STS study (VEG110727, n=369) and the reported supportive Phase II study (VEG20002, n=142) was evaluated in the overall evaluation of safety and tolerability of pazopanib (total safety population n=382) in subjects with STS.

The most important serious adverse reactions identified in the RCC or STS studies were transient ischaemic attack, ischaemic stroke, myocardial ischaemia, myocardial and cerebral infarction, cardiac dysfunction, gastrointestinal perforation and fistula, QT prolongation, Torsade de Pointes and pulmonary, gastrointestinal and cerebral haemorrhage, all adverse reactions being reported in <1% of treated patients. Other important serious adverse reactions identified in STS studies included venous thromboembolic events, left ventricular dysfunction and pneumothorax.

Fatal events that were considered possibly related to pazopanib included gastrointestinal haemorrhage, pulmonary haemorrhage/haemoptysis, abnormal hepatic function, intestinal perforation and ischaemic stroke.

The most common adverse reactions (experienced by at least 10% of the patients) of any grade in the RCC and STS reported trials included: diarrhoea, hair colour change, skin hypopigmentation, exfoliative rash, hypertension, nausea, headache, fatigue, anorexia, vomiting, dysgeusia, stomatitis, weight decreased, pain, elevated alanine aminotransferase and elevated aspartate aminotransferase.

Adverse drug reactions, all grades, which were reported in RCC and STS subjects or during the post-marketing period are listed below by MedDRA body system organ class, frequency and grade of severity. The following convention has been utilised for the classification of frequency: 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); and not known (cannot be estimated from the available data).

Categories have been assigned based on absolute frequencies in the reported clinical trial data. Post-marketing data on safety and tolerability across all pazopanib clinical studies and from spontaneous

reports have also been evaluated. Within each system organ class, adverse reactions with the same frequency are presented in order of decreasing seriousness..

Tabulated list of adverse reactions

Treatment-related adverse reactions reported in RCC studies (n = 1149) or during post-marketing period

System Organ Class	Frequency (all grades)	Adverse reactions	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infections and Infestations	**Common**	Infections (with or without neutropenia)†	not known	not known	not known
	Uncommon	Gingival infection	1 (<1%)	0	0
		Infectious peritonitis	1 (<1%)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Uncommon**	Tumour pain	1 (<1%)	1 (<1%)	0
Blood and lymphatic system disorders	**Common**	Thrombocytopenia	80 (7%)	10 (<1%)	5 (<1%)
		Neutropenia	79 (7%)	20 (2%)	4 (<1%)
		Leukopenia	63 (5%)	5 (<1%)	0
	Uncommon	Polycythaemia	6 (0.03%)	1	0
	Rare	Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome)†	not known	not known	not known
Endocrine disorders	**Common**	Hypothyroidism	83 (7%)	1 (<1%)	0
	Very common	Decreased appetitee	317 (28%)	14 (1%)	0

Metabolism and nutrition disorders	**Common**	Hypophosphataemia	21 (2%)	7 (<1%)	0
		Dehydration	16 (1%)	5 (<1%)	0
	Uncommon	Hypomagnesaemia	10 (<1%)	0	0
	Not known	Tumour lysis syndrome*	not known	not known	not known
Psychiatric disorders	**Common**	Insomnia	30 (3%)	0	0
Nervous system disorders	**Very common**	Dysgeusiac	254 (22%)	1 (<1%)	0
		Headache	122 (11%)	11 (<1%)	0
	Common	Dizziness	55 (5%)	3 (<1%)	1 (<1%)
		Lethargy	30 (3%)	3 (<1%)	0
		Paraesthesia	20 (2%)	2 (<1%)	0
		Peripheral sensory neuropathy	17 (1%)	0	0
	Uncommon	Hypoaesthesia	8 (<1%)	0	0
		Transient ischaemic attack	7 (<1%)	4 (<1%)	0
		Somnolence	3 (<1%)	1 (<1%)	0
		Cerebrovascular accident	2 (<1%)	1 (<1%)	1 (<1%)
		Ischaemic stroke	2 (<1%)	0	1 (<1%)
	Rare	Posterior reversible encephalopathy / reversible posterior leukoencephalopathy syndrome†	not known	not known	not known
Eye disorders	**Common**	Vision blurred	19 (2%)	1 (<1%)	0
	Uncommon	Retinal detachment†	1 (<1%)	1 (<1%)	0

		Retinal tear†	1 (<1%)	1 (<1%)	0
		Eyelash discolouration	4 (<1%)	0	0
Cardiac disorders	**Uncommon**	Bradycardia	6 (<1%)	0	0
		Myocardial infarction	5 (<1%)	1 (<1%)	4 (<1%)
		Cardiac dysfunctionf	4 (<1%)	1 (<1%)	0
		Myocardial ischaemia	3 (<1%)	1 (<1%)	0
Vascular disorders	**Very common**	Hypertension	473 (41%)	115 (10%)	1 (<1%)
	Common	Hot flush	16 (1%)	0	0
		Venous thromboembolic event g	13 (1%)	6 (<1%)	7 (<1%)
		Flushing	12 (1%)	0	0
	Uncommon	Hypertensive crisis	6 (<1%)	0	2 (<1%)
		Haemorrhage	1 (<1%)	0	0
	Not known	Aneurysms and artery dissections	not known	not known	not known
Respiratory, thoracic and mediastinal disorders	**Common**	Epistaxis	50 (4%)	1 (<1%)	0
		Dysphonia	48 (4%)	0	0
		Dyspnoea	42 (4%)	8 (<1%)	1 (<1%)
		Haemoptysis	15 (1%)	1 (<1%)	0
	Uncommon	Rhinorrhoea	8 (<1%)	0	0
		Pulmonary haemorrhage	2 (<1%)	0	0
		Pneumothorax	1 (<1%)	0	0

	Rare	Interstitial lung disease/pneumonitis †	not known	not known	not known
Gastrointestinal disorders	**Very common**	Diarrhoea	614 (53%)	65 (6%)	2 (<1%)
		Nausea	386 (34%)	14 (1%)	0
		Vomiting	225 (20%)	18 (2%)	1 (<1%)
		Abdominal paina	139 (12%)	15 (1%)	0
	Common	Stomatitis	96 (8%)	4 (<1%)	0
		Dyspepsia	83 (7%)	2 (<1%)	0
		Flatulence	43 (4%)	0	0
		Abdominal distension	36 (3%)	2 (<1%)	0
		Mouth ulceration	28 (2%)	3 (<1%)	0
		Dry mouth	27 (2%)	0	0
	Uncommon	Pancreatitis	8 (<1%)	4 (<1%)	0
		Rectal haemorrhage	8 (<1%)	2 (<1%)	0
		Haematochezia	6 (<1%)	0	0
		Gastrointestinal haemorrhage	4 (<1%)	2 (<1%)	0
		Melaena	4 (<1%)	1(<1%)	0
		Frequent bowel movements	3 (<1%)	0	0
		Anal haemorrhage	2 (<1%)	0	0
		Large intestine perforation	2 (<1%)	1 (<1%)	0
		Mouth haemorrhage	2 (<1%)	0	0

		Upper gastrointestinal haemorrhage	2 (<1%)	1 (<1%)	0
		Enterocutaneous fistula	1 (<1%)	0	0
		Haematemesis	1 (<1%)	0	0
		Haemorrhoidal haemorrhage	1 (<1%)	0	0
		Ileal perforation	1 (<1%)	0	1 (<1%)
		Oesophageal haemorrhage	1 (<1%)	0	0
		Retroperitoneal haemorrhage	1 (<1%)	0	0
Hepatobiliary disorders	**Common**	Hyperbilirubinaemia	38 (3%)	2 (<1%)	1 (<1%)
		Hepatic function abnormal	29 (3%)	13 (1%)	2 (<1%)
		Hepatotoxicity	18 (2%)	11(<1%)	2 (<1%)
	Uncommon	Jaundice	3 (<1%)	1 (<1%)	0
		Drug induced liver injury	2 (<1%)	2 (<1%)	0
		Hepatic failure†	1 (<1%)	0	1 (<1%)
Skin and subcutaneous disorders	**Very common**	Hair colour change	404 (35%)	1 (<1%)	0
		Palmar-plantar erythrodysaesthesia syndrome	206 (18%)	39 (3%)	0
		Alopecia	130 (11%)	0	0
		Rash	129 (11%)	7 (<1%)	0
	Common	Skin hypopigmentation	52 (5%)	0	0
		Dry skin	50 (4%)	0	0
		Pruritus	29 (3%)	0	0

		Erythema	25 (2%)	0	0
		Skin depigmentation	20 (2%)	0	0
		Hyperhidrosis	17 (1%)	0	0
	Uncommon	Nail disorders	11 (<1%)	0	0
		Skin exfoliation	10 (<1%)	0	0
		Photosensitivity reaction	7 (<1%)	0	0
		Rash erythematous	6 (<1%)	0	0
		Skin disorder	5 (<1%)	0	0
		Rash macular	4 (<1%)	0	0
		Rash pruritic	3 (<1%)	0	0
		Rash vesicular	3 (<1%)	0	0
		Pruritus generalised	2 (<1%)	1 (<1%)	0
		Rash generalised	2 (<1%)	0	0
		Rash papular	2 (<1%)	0	0
		Plantar erythema	1 (<1%)	0	0
Musculoskeletal and connective tissue disorders	**Common**	Arthralgia	48 (4%)	8 (<1%)	0
		Myalgia	35 (3%)	2 (<1%)	0
		Muscle spasms	25 (2%)	0	0
	Uncommon	Musculoskeletal pain	9 (<1%)	1 (<1%)	0
Renal and urinary disorders	**Very Common**	Proteinuria	135 (12%)	32 (3%)	0
	Uncommon	Haemorrhage urinary tract	1 (<1%)	0	0

Reproductive system and breast disorders	**Uncommon**	Menorrhagia	3 (<1%)	0	0
		Vaginal haemorrhage	3 (<1%)	0	0
		Metrorrhagia	1 (<1%)	0	0
General disorders and administration site conditions	**Very common**	Fatigue	415 (36%)	65 (6%)	1 (<1%)
	Common	Mucosal inflammation	86 (7%)	5 (<1%)	0
		Asthenia	82 (7%)	20 (2%)	1 (<1%)
		Oedemab	72 (6%)	1 (<1%)	0
		Chest pain	18 (2%)	2 (<1%)	0
	Uncommon	Chills	4 (<1%)	0	0
		Mucous membrane disorder	1 (<1%)	0	0
Investigations	**Very common**	Alanine aminotransferase increased	246 (21%)	84 (7%)	14 (1%)
		Aspartate aminotransferase increased	211 (18%)	51 (4%)	10 (<1%)
	Common	Weight decreased	96 (8%)	7 (<1%)	0
		Blood bilirubin increased	61 (5%)	6 (<1%)	1 (<1%)
		Blood creatinine increased	55 (5%)	3 (<1%)	0
		Lipase increased	51 (4%)	21 (2%)	7 (<1%)
		White blood cell count decreasedd	51 (4%)	3 (<1%)	0
		Blood thyroid stimulating hormone increased	36 (3%)	0	0
		Amylase increased	35 (3%)	7 (<1%)	0

		Gamma-glutamyltransferase increased	31 (3%)	9 (<1%)	4 (<1%)
		Blood pressure increased	15 (1%)	2 (<1%)	0
		Blood urea increased	12 (1%)	1 (<1%)	0
		Liver function test abnormal	12 (1%)	6 (<1%)	1 (<1%)
	Uncommon	Hepatic enzyme increased	11 (<1%)	4 (<1%)	3 (<1%)
		Blood glucose decreased	7 (<1%)	0	1 (<1%)
		Electrocardiogram QT prolonged	7 (<1%)	2 (<1%)	0
		Transaminase increased	7 (<1%)	1 (<1%)	0
		Thyroid function test abnormal	3 (<1%)	0	0
		Blood pressure diastolic increased	2 (<1%)	0	0
		Blood pressure systolic increased	1 (<1%)	0	0

†Treatment-related adverse reaction reported during post-marketing period (spontaneous case reports and serious adverse reactions from all pazopanib clinical studies).
*Treatment-related adverse reaction reported only during the post-marketing period. Frequency cannot be estimated from the available data.
The following terms have been combined:

a) Abdominal pain, abdominal pain upper and abdominal pain lower
b) Oedema, oedema peripheral, eye oedema, localised oedema and face oedema
c) Dysgeusia, ageusia and hypogeusia
d) White cell count decreased, neutrophil count decreased and leukocyte count decreased
e) Decreased appetite and anorexia
f) Cardiac dysfunction, left ventricular dysfunction, cardiac failure and restrictive cardiomyopathy
g) Venous thromboembolic event, deep vein thrombosis, pulmonary embolism and thrombosis

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

Treatment-related adverse reactions reported in STS studies (n=382) or during post-marketing period

System Organ Class	Frequency (all grades)	Adverse reactions	All grades	Grade 3 n (%)	Grade 4 n (%)

			n (%)		
Infections and infestations	**Common**	Gingival infection	4 (1%)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Very common**	Tumour pain	121 (32%)	32 (8%)	0
Blood and lymphatic system disorders[f]	**Very common**	Leukopenia	106 (44%)	3 (1%)	0
		Thrombocytopenia	86 (36%	7 (3%)	2 (<1%)
		Neutropenia	79 (33%)	10 (4%)	0
	Uncommon	Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome)	1 (<1%)	1 (<1%)	0
Endocrine disorders	**Common**	Hypothyroidism	18 (5%)	0	0
Metabolism and nutrition disorders	**Very common**	Decreased appetite	108 (28%)	12 (3%)	0
		Hypoalbuminemia[f]	81 (34%)	2 (<1%)	0
	Common	Dehydration	4 (1%)	2 (1%)	0
	Uncommon	Hypomagnesaemia	1 (<1%)	0	0
	Not known	Tumour lysis syndrome*	not known	not know n	not know n
Psychiatric disorders	**Common**	Insomnia	5 (1%)	1 (<1%)	0
Nervous system disorders	**Very common**	Dysgeusia[c]	79 (21%)	0	0

		Headache	54 (14%)	2 (<1%)	0
	Common	Peripheral sensory neuropathy	30 (8%)	1 (<1%)	0
		Dizziness	15 (4%)	0	0
	Uncommon	Somnolence	3 (<1%)	0	0
		Paresthesia	1 (<1%)	0	0
		Cerebral infarction	1 (<1%)	0	1 (<1%)
Eye disorders	**Common**	Vision blurred	15 (4%)	0	0
Cardiac disorders		Cardiac dysfunction[g]	21 (5%)	3 (<1%)	1 (<1%)
		Left ventricular dysfunction	13 (3%)	3 (<1%)	0
		Bradycardia	4 (1%)	0	0
	Uncommon	Myocardial infarction	1 (<1%)	0	0
Vascular disorders	**Very common**	Hypertension	152 (40%)	26 (7%)	0
	Common	Venous thromboembolic event[d]	13 (3%)	4 (1%)	5 (1%)
		Hot flush	12 (3%)	0	0
		Flushing	4 (1%)	0	0
	Uncommon	Haemorrhage	2 (<1%)	1 (<1%)	0
	Not known	Aneurysms and artery dissections	not known	not known	not known
Respiratory, thoracic and mediastinal disorders	**Common**	Epistaxis	22 (6%)	0	0
		Dysphonia	20 (5%)	0	0
		Dyspnoea	14 (4%)	3 (<1%)	0
		Cough	12 (3%)	0	0

		Pneumothorax	7 (2%)	2 (<1%)	1 (<1%)
		Hiccups	4 (1%)	0	0
		Pulmonary haemorrhage	4 (1%)	1 (<1%)	0
	Uncommon	Oropharyngeal pain	3 (<1%)	0	0
		Bronchial haemorrhage	2 (<1%)	0	0
		Rhinorrhoea	1 (<1%)	0	0
		Haemoptysis	1 (<1%)	0	0
	Rare	Interstitial lung disease/pneumonitis†	not known	not known	not known
Gastrointestinal disorders	**Very common**	Diarrhoea	174 (46%)	17 (4%)	0
		Nausea	167 (44%)	8 (2%)	0
		Vomiting	96 (25%)	7 (2%)	0
		Abdominal pain[a]	55 (14%)	4 (1%)	0
		Stomatitis	41 (11%)	1 (<1%)	0
	Common	Abdominal distension	16 (4%)	2 (1%)	0
		Dry mouth	14 (4%)	0	0
		Dyspepsia	12 (3%)	0	0
		Mouth haemorrhage	5 (1%)	0	0
		Flatulence	5 (1%)	0	0
		Anal haemorrhage	4 (1%)	0	0
	Uncommon	Gastrointestinal haemorrhage	2 (<1%)	0	0
		Rectal haemorrhage	2 (<1%)	0	0
		Enterocutaneous fistula	1 (<1%)	1 (<1%)	0

		Gastric haemorrhage	1 (<1%)	0	0
		Melaena	2 (<1%)	0	0
		Oesophageal haemorrhage	1 (<1%)	0	1 (<1%)
		Peritonitis	1 (<1%)	0	0
		Retroperitoneal haemorrhage	1 (<1%)	0	0
		Upper gastrointestinal haemorrhage	1 (<1%)	1 (<1%)	0
		Ileal perforation	1 (<1%)	0	1 (<1%)
Hepatobiliary disorders	**Uncommon**	Hepatic function abnormal	2 (<1%)	0	1 (<1%)
	Not known	Hepatic failure*	not known	not known	not known
Skin and subcutaneous disorders	**Very common**	Hair colour change	93 (24%)	0	0
		Skin hypopigmentation	80 (21%)	0	0
		Exfoliative rash	52 (14%)	2 (<1%)	0
	Common	Alopecia	30 (8%)	0	0
		Skin disorder[c]	26 (7%)	4 (1%)	0
		Dry skin	21 (5%)	0	0
		Hyperhydrosis	18 (5%)	0	0
		Nail disorder	13 (3%)	0	0
		Pruritus	11 (3%)	0	0
		Erythema	4 (1%)	0	0
	Uncommon	Skin ulcer	3 (<1%)	1 (<1%)	0

		Rash	1 (<1%)	0	0
		Rash papular	1 (<1%)	0	0
		Photosensitivity reaction	1 (<1%)	0	0
		Palmar-plantar erythrodysaesthesia syndrome	2 (<1%)	0	0
Musculoskeletal and connective tissue disorders	**Common**	Musculoskeletal pain	35 (9%)	2 (<1%)	0
		Myalgia	28 (7%)	2 (<1%)	0
		Muscle spasms	8 (2%)	0	0
	Uncommon	Arthralgia	2 (<1%)	0	0
Renal and urinary disorders	**Uncommon**	Proteinuria	2 (<1%)	0	0
Reproductive system and breast disorder	**Uncommon**	Vaginal haemorrhage	3 (<1%)	0	0
		Menorrhagia	1 (<1%)	0	0
General disorders and administration site conditions	**Very common**	Fatigue	178 (47%)	34 (9%)	1 (<1%)
	Common	Oedema[b]	18 (5%)	1 (<1%)	0
		Chest pain	12 (3%)	4 (1%)	0
		Chills	10 (3%)	0	0
	Uncommon	Mucosal inflammation[e]	1 (<1%)	0	0
		Asthenia	1 (<1%	0	0
Investigations[h]	**Very common**	Weight decreased	86 (23%)	5 (1%)	0
	Common	Ear, nose and throat examination abnormal[e]	29 (8%)	4 (1%)	0
		Alanine aminotransferase increased	8 (2%)	4 (1%)	2 (<1%)

		Blood cholesterol abnormal	6 (2%)	0	0
		Aspartate aminotransferase increased	5 (1%)	2 (<1%)	2 (<1%)
		Gamma glutamyltransferase increased	4 (1%)	0	3 (<1%)
	Uncommon	Blood bilirubin increased	2 (<1%)	0	0
		Aspartate aminotransferase	2 (<1%)	0	2 (<1%)
		Alanine aminotransferase	1 (<1%)	0	1 (<1%)
		Platelet count decreased	1 (<1%)	0	1 (<1%)
		Electrocardiogram QT prolonged	2 (<1%)	1 (<1%)	0

†Treatment-related adverse reaction reported during post-marketing period (spontaneous case reports and serious adverse reactions from all pazopanib clinical studies).

*Treatment-related adverse reaction reported only during the post-marketing period. Frequency cannot be estimated from the available data.

The following terms have been combined:

a) Abdominal pain, abdominal pain upper and gastrointestinal pain
b) Oedema, oedema peripheral and eyelid oedema
c) The majority of these cases were Palmar-plantar erythrodysaesthesia syndrome
d) Venous thromboembolic events – includes Deep vein thrombosis, Pulmonary embolism and Thrombosis terms
e) The majority of these cases describe mucositis
f) Frequency is based on laboratory value tables from VEG110727 (N=240). These were reported as adverse events less frequently by investigators than as indicated by laboratory value tables.
g) Cardiac dysfunction events – includes Left ventricular dysfunction, Cardiac failure and Restrictive cardiomyopathy
h) Frequency is based on adverse events reported by investigators. Laboratory abnormalities were reported as adverse events less frequently by investigators than as indicated by laboratory value tables.

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

Paediatric population

The safety profile in paediatric patients was similar to that reported with pazopanib in adults in the approved indications based on data from 44 paediatric patients from reported Phase I study ADVL0815 and 57 paediatric patients from the reported Phase II study PZP034X2203.

Reporting of suspected adverse reactions:

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.
By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Pazopanib doses up to 2000 mg have been evaluated in clinical studies. Grade 3 fatigue (dose-limiting toxicity) and Grade 3 hypertension were each observed in 1 of 3 patients dosed at 2000 mg and 1000 mg daily, respectively.

There is no specific antidote for overdose with pazopanib and treatment of overdose should consist of general supportive measures.

5 Pharmacological properties

5.1 Mechanism of Action

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) -α and –β, and stem cell factor receptor (c-KIT), with IC50 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-β 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 tumour xenografts in mice.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, other protein kinase inhibitors, ATC code: L01EX03

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.

Clinical studies

Paediatric population

A Phase I reported study (ADVL0815) of pazopanib was conducted in 44 paediatric patients with various recurrent or refractory solid tumours. The primary objective was to investigate the maximum tolerated dose (MTD), the safety profile and the pharmacokinetic properties of pazopanib in children. The median duration of exposure in this study was 3 months (1-23 months).

A Phase II reported study (PZP034X2203) of pazopanib was conducted in 57 paediatric patients with refractory solid tumours including rhabdomyosarcoma (N=12), non-rhabdomyosarcoma soft tissue sarcoma (N=11), Ewing sarcoma/pPNET (N=10), osteosarcoma (N=10), neuroblastoma (N=8) and hepatoblastoma (N=6). The study was a single-agent, non-controlled, open-label study to determine the therapeutic activity of pazopanib in children and adolescents aged 1 to <18 years of age. Pazopanib was administered daily as a tablet at a dose of 450 mg/m2/dose or as an oral suspension at 225 mg/m2/dose. The maximum daily dose permitted was 800 mg for the tablet and 400 mg for the oral suspension. The median duration of exposure was 1.8 months (1 day-29 months).

Results of this study did not show any meaningful anti-tumour activity in the respective paediatric population. Pazopanib is therefore not recommended for treatment of these tumours in the paediatric population.

The European Medicines Agency has waived the obligation to submit the results of studies with pazopanib in all subsets of the paediatric population in treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney).

5.3 Pharmacokinetic properties

Absorption

Upon oral administration of a single pazopanib 800 mg dose to patients with solid tumours, maximum plasma concentration (C_{max}) of approximately 19 ± 13 µg/ml was obtained after median 3.5 hours (range 1.0-11.9 hours) and an $AUC_{0-\infty}$ of approximately 650 ± 500 µg.h/ml was obtained. Daily dosing results in 1.23- to 4-fold increase in AUC_{0-T}.

There was no consistent increase in AUC or C_{max} at pazopanib doses above 800 mg.

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 two hours after food or at least one hour before food.

Administration of a 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.

Distribution

Binding of pazopanib to human plasma protein in vivo was greater than 99% with no concentration dependence over the range of 10-100 µg/ml. In vitro studies suggest that pazopanib is a substrate for P-gp and BCRP.

Biotransformation

Results from reported in vitro studies demonstrated that metabolism of pazopanib is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. The four principle pazopanib metabolites account for only 6% of the exposure in plasma. One of these metabolites inhibits the proliferation of VEGF-stimulated human umbilical vein endothelial cells with a similar potency to that of pazopanib, the others are 10- to 20-fold less active. Therefore, activity of pazopanib is mainly dependent on parent pazopanib exposure.

Elimination

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

Special populations

Renal impairment

Results indicate that less than 4% of an orally administered pazopanib dose is excreted in the urine as pazopanib and metabolites. Results from population pharmacokinetic modelling (data from subjects with baseline CLCR values ranging from 30.8 ml/min to 150 ml/min) indicated that renal impairment is unlikely to have clinically relevant effect on pazopanib pharmacokinetics. No dose adjustment is required in patients with creatinine clearance above 30 ml/min. Caution is advised in patients with creatinine clearance below 30 ml/min as there is no experience of pazopanib in this patient population.

Hepatic impairment

Mild

The median steady-state pazopanib C_{max} and AUC (0-24) in patients with mild abnormalities in hepatic parameters (defined as either normal bilirubin and any degree of ALT elevation or as an elevation of bilirubin up to 1.5 x ULN regardless of the ALT value) after administration of 800 mg once daily are similar to the median in patients with normal hepatic function. 800 mg pazopanib once daily is the recommended dose in patients with mild abnormalities of serum liver tests.

Moderate

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 C_{max} and AUC(0-24) values after administration of 200 mg pazopanib once daily in patients with moderate hepatic impairment were approximately 44% and 39%, of the corresponding median values after administration of 800 mg once daily in patients with normal hepatic function, respectively.

Based on safety and tolerability data, the dose of pazopanib should be reduced to 200 mg once daily in subjects with moderate hepatic impairment.

Severe

The median steady-state C_{max} and AUC(0-24) values after administration of 200 mg pazopanib once daily in patients with severe hepatic impairment were approximately 18% and 15%, of the corresponding median values after administration of 800 mg once daily in patients with normal hepatic function. Based on the diminished exposure and limited hepatic reserve pazopanib is not recommended in patients with severe hepatic impairment (defined as total bilirubin >3 X ULN regardless of any level of ALT).

Median steady-state pazopanib pharmacokinetics measured in subjects with hepatic impairment.

Group	Investigated dose	C_{max} (µg/ml)	AUC (0-24) (µg x hr/ml)	Recommended dose
Normal hepatic function	800 mg OD	52.0 (17.1-85.7)	888.2 (345.5-1482)	800 mg OD
Mild HI	800 mg OD	33.5	774.2	800 mg OD

		(11.3-104.2)	(214.7-2034.4)	
Moderate HI	200 mg OD	22.2 (4.2-32.9)	256.8 (65.7-487.7)	200 mg OD
Severe HI	200 mg OD	9.4 (2.4-24.3)	130.6 (46.9-473.2)	Not recommended

Paediatric population

Upon administration of pazopanib 225 mg/m2 (as oral suspension) in paediatric patients, the pharmacokinetic parameters (C_{max}, T_{max} and AUC) were similar to those previously reported in adult patients treated with 800 mg pazopanib. Results indicated no marked difference in the clearance of pazopanib, normalised by body surface area, between children and adults.

6. Nonclinical properties

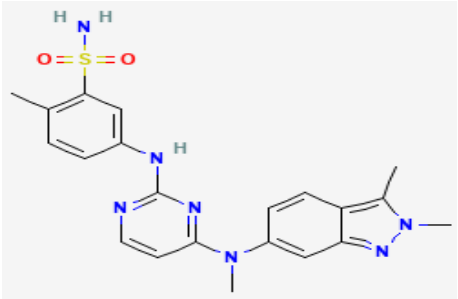
The reported preclinical safety profile of pazopanib was assessed in mice, rats, rabbits and monkeys. In repeat dose studies in rodents, effects in a variety of tissues (bone, teeth, nail beds, reproductive organs, hematological tissues, kidney and pancreas) appear related to the pharmacology of VEGFR inhibition and/or disruption of VEGF signaling pathways, with most effects occurring at plasma exposure levels below those observed in the clinic. Other observed effects include body weight loss, diarrhoea and/or morbidity that were either secondary to local gastrointestinal effects caused by high local mucosal medicinal product exposure (monkeys) or pharmacological effects (rodents). Proliferative hepatic lesions (eosinophilic foci and adenoma) were seen in female mice at exposures 2.5 times human exposure based on AUC.

In reported juvenile toxicity studies, when pre-weaning rats were dosed from day 9 post-partum through today 14 post-partum, pazopanib caused mortalities and abnormal organ growth/maturation in kidney, lung, liver and heart, at a dose approximately 0.1 times the clinical exposure based on AUC in adult humans. When post-weaning rats were dosed from day 21 post-partum to day 62 post-partum, toxicological findings were similar to adult rats at comparable exposures. Human paediatric patients are at increased risk for bone and teeth effects as compared to adults, as these changes, including inhibition of growth (shortened limbs), fragile bones and remodelling of teeth, were present in juvenile rats at ≥10 mg/kg/day (equal to approximately 0.1-0.2 times the clinical exposure based on AUC in adult humans).

.7 Description

Pazopanib

Pazopanib is 5-[[4-[(2,3-dimethylindazol-6-yl)-methylamino]pyrimidin-2-yl]amino]-2-methylbenzenesulfonamide. The empirical formula of pazopanib is $C_{21}H_{23}N_7O_2S$ and its molecular weight is 437.5. Its structural formula is



PAZOBRITE 200

Pazopanib Tablets are pink coloured, capsule shaped, biconvex, film coated tablets plain on both sides. The excipients used are Mannitol, Pregelatinized Starch, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Talc, Hydroxyl Propyl Cellulose, Sepitrap 80, Magnesium Stearate, Croscarmellose Sodium, Opadry Pink 15B24005.

PAZOBRITE 400

Pazopanib Tablets are pink coloured, oval shaped, biconvex, film coated tablets plain on both sides. The excipients used are Mannitol, Pregelatinized Starch, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Talc, Hydroxyl Propyl Cellulose, Sepitrap 80, Magnesium Stearate, Croscarmellose Sodium, Opadry Pink 15B24005.

8 Pharmaceutical particulars

8.1 Incompatibilities

Not Applicable

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

PAZOBRITE is available in bottle pack of 30 tablets

8.4 Storage and handing instructions

Store at a temperature below 30°C,

Keep out of reach of children.

Keep container tightly closed

Dispense in original container

Do not use if seal over bottle opening is broken or missing.

9 Patient Counselling Information

Package leaflet: Information for the user

PAZOBRITE
Pazopanib

- Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

What is in this leaflet

9.3 How to take PAZOBRITE
9.4. Possible side effects
9.5. How to store PAZOBRITE Tablets
9.6. Contents of the pack and other information

9.1 What is Pazobrite and what it is used for

Pazobrite is a type of medicine called a protein kinase inhibitor. It works by preventing the activity of proteins that are involved in the growth and spread of cancer cells.

Pazobrite is used to treat patients with advanced renal cell carcinoma and for the treatment of patients with advanced Soft Tissue Sarcoma (STS) who have received prior chemotherapy.

9.2 What you need to know before you take Pazobrite

Do not take Pazobrite

- If you are allergic to pazopanib or any of the other ingredients of this medicine.
- Check with your doctor if you think this applies to you.

Warnings and precautions

- Talk to your doctor before taking Pazobrite
- If you have heart disease.
- If you have liver disease.
- If you have had heart failure or a heart attack.
- If you have had prior collapse of a lung.
- If you have had problems with bleeding, blood clots or narrowing of the arteries
- If you have had stomach or bowel problems such as perforation (hole) or fistula (abnormal passages forming between parts of the intestine).
- If you have thyroid problems.
- If you have problems with your kidney function.
- If you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.

Tell your doctor if any of these apply to you. Your doctor will decide whether pazobrite is suitable for you. You may need extra tests to check that your kidneys, heart and liver are working properly.

High blood pressure and Pazobrite

Pazobrite can raise your blood pressure. Your blood pressure will be checked before you take pazobrite and while you are taking it. If you have high blood pressure you will be treated with medicines to reduce it.

Tell your doctor if you have high blood pressure.

If you are going to have an operation

Your doctor will stop Pazobrite at least 7 days before your operation as it may affect wound healing. Your treatment will be restarted when the wound has adequately healed.

Conditions you need to look out for

Pazobrite can make some conditions worse or cause serious side effects. You must look out for certain symptoms while you are taking Pazobrite to reduce the risk of any problems.

Children and adolescents

Pazobrite is not recommended for people aged under 18. It is not yet known how well it works in this age group. Moreover it should not be used in children younger than 2 years of age because of safety concerns.

Other medicines and Pazobrite

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Some medicines may affect how Pazobrite works or make it more likely that you'll have side effects. Pazobrite can also affect how some other medicines work. These include:

- clarithromycin, ketoconazole, itraconazole, rifamicin, telithromycin, voriconazzole (used to treat infection).

- atazanavir, indinavir, nelfinavir, ritonavir, saquinavir (used to treat HIV).

- nefazodone (used to treat depression).

- simvastatin and possibly other statins (used to treat high cholesterol levels).

- medicines that reduce stomach acid. The type of medicine that you are taking to reduce your stomach acid (e.g. proton pump inhibitor, H2 antagonists or antacids) may affect how Pazobrite is taken. Please consult your doctor or nurse for advice.

Tell your doctor or pharmacist if you take any of these.

Pazobrite with food and drink

Don't take Pazobrite with food, as it affects the way the medicine is absorbed. Take it at least two hours after a meal or one hour before a meal.

Do not drink grapefruit juice while you are being treated with Pazobrite as this may increase the chance of side effects.

Pregnancy, breast-feeding and fertility

Pregnancy

Pazobrite is not recommended if you are pregnant. The effect of Pazobrite during pregnancy is not known.

- Tell your doctor if you are pregnant or planning to get pregnant.

- Use a reliable method of contraception while you're taking Pazobrite, and at least for 2 weeks after, to prevent pregnancy.

- If you do become pregnant during treatment with Pazobrite, tell your doctor.

Breast-feeding

It is not known whether the ingredients in Pazobrite pass into breast milk. Talk to your doctor about this.

Male patients (including those who have had vasectomies) who have partners who are either pregnant or who could become pregnant (including those who use other methods of contraception) should use condoms during sexual intercourse while taking Pazobrite and for at least 2 weeks after the last dose.

Fertility

This may be affected by treatment with Pazobrite. Talk to your doctor about this.

Driving and using machines

Pazobrite can have side effects that may affect your ability to drive or use machines.

Avoid driving or using machines if you feel dizzy, tired or weak, or if your energy levels are low.

9.3 How to take Pazobrite

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take

The usual dose is two Pazobrite 400 mg tablets (800 mg pazopanib) taken once a day. This is the maximum dose per day. Your doctor may need to reduce your dose if you get side effects.

When to take

Don't take Pazobrite with food. Take it at least two hours after a meal, or one hour before a meal.

For example, you could take it two hours after breakfast or one hour before lunch. Take Pazobrite at about the same time each day.

Swallow the tablets whole with water, one after the other. Do not break or crush the tablets as this affects the way the medicine is absorbed and may increase the chance of side effects.

If you take more Pazobrite than you should:

If you take too many tablets, **contact a doctor or pharmacist** for advice. If possible show them the pack, or this leaflet.

If you forget to take Pazobrite

Do not take a double dose to make up for a forgotten dose. Just take your next dose at the usual time.

If you stop taking Pazobrite

Take Pazobrite for as long as your doctor recommends. Don't stop unless your doctor advises you to.

9.4 Possible side effects

Swelling of the brain (reversible posterior leukoencephalopathy syndrome).

Pazobrite can, on rare occasions, cause swelling of the brain, which may be life threatening. Symptoms include:

- loss of speech
- change of vision
- seizure (fits)
- confusion
- high blood pressure

Stop taking Pazobrite and seek medical help immediately if you get any of these symptoms, or if you get headache accompanied with any of these symptoms.

Hypertensive crisis (sudden and severe rise in blood pressure)

Pazobrite can on occasion cause a sudden and severe rise in blood pressure. This is known as a hypertensive crisis. Your doctor will monitor your blood pressure while you are taking Pazobrite. Signs and symptoms of a hypertensive crisis may include:

- severe chest pain

- severe headache
- blurred vision
- confusion
- nausea
- vomiting
- severe anxiety
- shortness of breath
- seizures (fits)
- fainting

Stop taking Pazobrite and seek medical help immediately if you develop hypertensive crisis**.**

Heart conditions

The risks of these problems may be higher for people with an existing heart problem, or who are taking other medicines. You will be checked for any heart problems while you are taking Pazobrite

Cardiac dysfunction/heart failure, heart attack

Pazobrite can affect how well your heart pumps or can increase the likelihood of having a heart attack.

Signs and symptoms include:

- irregular or fast heartbeat
- rapid fluttering of your heart
- fainting
- chest pain or pressure
- pain in your arms, back, neck or jaw
- shortness of breath
- leg swelling

Seek medical help immediately if you get any of these symptoms.

Changes in heart rhythm (QT prolongation)

Pazobrite can affect heart rhythm which in some people can develop into a potentially serious heart condition known as torsade de pointes. This can result in a very fast heartbeat causing a sudden loss of consciousness.

Tell your doctor if you notice any unusual changes in your heart beat, such as beating too fast or too slow.

Stroke

Pazobrite can increase your likelihood of having a stroke. Signs and symptoms of stroke may include:

- numbness or weakness on one side of your body
- difficulty talking
- headache
- dizziness

Bleeding

Pazobrite can cause severe bleeding in the digestive system (such as stomach, oesophagus, rectum or intestine), or the lungs, kidneys, mouth, vagina and brain, although this is uncommon. Symptoms include:

- passing blood in the stools or passing black stools

- passing blood in the urine
- Stomach pain
- coughing or vomiting up blood

Perforation and fistula

Pazobrite can cause a tear (perforation) in your stomach or intestinal wall or the development of an abnormal connection between two parts of your digestive tract (a fistula). Signs and symptoms may include:

- Severe stomach pain
- Nausea and/or vomiting
- Fever
- Development of a hole (perforation) in the stomach, intestine or bowel from which bloody or foul smelling pus is released

Liver problems

Pazobrite can cause problems with your liver which may develop into serious conditions such as liver dysfunction and liver failure, which may be fatal. Your doctor will be checking your liver enzymes while you are taking Pazobrite Signs that your liver may not be working properly may include:

- yellowing of your skin or the whites of your eyes (jaundice)
- dark urine
- tiredness
- nausea
- vomiting
- loss of appetite
- pain on the right side of your stomach area (abdomen)
- bruising easily

Blood clots

Deep vein thrombosis (DVT) and pulmonary embolism

Pazobrite may cause blood clots in your veins, especially in your legs (deep vein thrombosis or DVT), which may also travel to your lungs (pulmonary embolism). Signs and symptoms may include:

- sharp chest pain
- shortness of breath
- rapid breathing
- leg pain
- swelling of your arms and hands or legs and feet

Thrombotic microangiopathy (TMA)

Pazobrite may cause blood clots in the small blood vessels in the kidneys and brain accompanied by a decrease in red blood cells and cells involved in clotting (thrombotic microangiopathy, TMA). Signs and symptoms may include:

- bruising easily
- high blood pressure
- fever
- confusion
- drowsiness

- seizures (fits)
- decrease in urine output

Tumour lysis syndrome

Pazobrite can cause a fast breakdown of cancer cells resulting in tumour lysis syndrome, which in some people may be fatal. Symptoms may include irregular heartbeat, seizures (fits), confusion, muscle cramps or spasms, or decrease in urine output. Seek medical help immediately if you get any of these symptoms.

Infections

Infections occurring while you take Pazobrite may possibly become serious. Symptoms of infections may include:

- fever
- flu-like symptoms such as cough, tiredness and body aches that do not go away
- shortness of breath and/or wheezing
- pain while urinating
- cuts, scrapes or wounds that are red, warm, swollen or painful

Seek medical help immediately if you get any of these symptoms.

Lung inflammation

Pazobrite can, on rare occasions, cause lung inflammation (interstitial lung disease, pneumonitis), which in some people can be fatal. Symptoms include shortness of breath or cough that will not go away. You will be checked for any lung problems while you are taking Pazobrite

Seek medical help immediately if you get any of these symptoms.

Thyroid problems

Pazobrite can lower the amount of thyroid hormone produced in your body. This can result in weight increase and tiredness. You will be checked for thyroid hormone levels while you are taking Pazobrite.

Tell your doctor if you notice significant weight gain or tiredness.

Blurry or impaired vision

Pazobrite can cause separation or tear of the lining of the back part of the eye (retinal detachment or tear). This can result in blurry or impaired vision.

Tell your doctor if you notice any change in your vision.

Possible side effects (including possible serious side effects under the relevant frequency category).

Very common side effects (may affect more than 1 in 10 people):

- High blood pressure

- Diarrhoea

- Feeling or being sick (nausea or vomiting)

- Stomach pain

- Loss of appetite

- Weight loss

- Taste disturbance or loss of taste

- Sore mouth
- Headache
- Tumour pain
- Lack of energy, feeling weak or tired
- Changes in hair colour
- Unusual hair loss or thinning
- Loss of skin pigment
- Skin rash, possibly involving peeling of the skin
- Redness and swelling of the palms of the hands or soles of the feet

Tell your doctor or pharmacist if any of these side effects becomes troublesome.

Very common side effects that may show up in your blood or urine tests:

- Increase in liver enzymes
- Decrease in albumin in the blood
- Protein in the urine
- Decrease in the number of blood platelets (cells that help blood to clot)
- Decrease in the number of white blood cells

Common side effects (may affect up to 1 in 10 people):

- Indigestion, bloating, flatulence
- Nose bleed
- Dry mouth or mouth ulcers
- Infections
- Abnormal drowsiness
- Difficulty sleeping
- Chest pain, shortness of breath, leg pain, and swelling of the legs/feet. These could be signs of a blood clot in your body (thromboembolism). If the clot breaks off, it may travel to your lungs and this may be life threatening or even fatal.
- Heart becomes less effective at pumping blood around the body (cardiac dysfunction)
- Slow heart beat
- bleeding in the mouth, rectum or lung
- Dizziness
- blurred vision
- Hot flushes
- Swelling caused by fluid of face, hands, ankles, feet or eyelids
- Tingling, weakness or numbness of the hands, arms, legs or feet
- Skin disorders, redness, itching, dry skin
- nail disorders

- Burning, prickling, itching or tingling skin sensation

- Sensation of coldness, with shivering

- Excessive sweating

- Dehydration

- Muscle, joint, tendon or chest pain, muscle spasms

- Hoarseness

- Shortness of breath

- cough

- coughing up blood

- hiccups

- collapsed lung with air trapped in the space between the lung and chest, often causing shortness of breath (pneumothorax)

Tell your doctor or pharmacist if any of these effects become troublesome**.**

Common side effects that may show up in your blood or urine tests:

- underactive thyroid gland

- abnormal liver function

- increase in bilirubin (a substance produced by the liver)

- increase in lipase (an enzyme involved in digestion

- increase in creatinine (a substance produced in muscles)

- changes in the levels of other different chemicals / enzymes in the blood. Your doctor will inform you of the results of the blood tests

Uncommon side effects (may affect up to 1 in 100 people):

- stroke

- temporary fall in blood supply to the brain (transient ischaemic attack)

- interruption of blood supply to part of the heart or heart attack (myocardial infarction)

- partial interruption of blood supply to part of the heart (myocardial ischaemia)

- blood clots accompanied by a decrease in red blood cells and cells involved in clotting (thrombotic microangiopathy, TMA). These may harm organs such as the brain and kidneys.

- increase in the number of red blood cells

- sudden shortness of breath, especially when accompanied with sharp pain in the chest and /or rapid breathing (pulmonary embolism)

- severe bleeding in the digestive system (such as stomach, oesophagus or intestine), or the kidneys, vagina and brain

- heart rhythm disturbance (QT prolongation)

- hole (perforation) in stomach or intestine

- abnormal passages forming between parts of the intestine (fistula)

- heavy or irregular menstrual periods

- sudden sharp increase in blood pressure (hypertensive crisis)
- inflammation of the pancreas (pancreatitis)
- liver inflamed, not working well or damaged
- yellowing of the skin or whites of the eyes (jaundice)
- inflammation of the lining of the abdominal cavity (peritonitis)
- runny nose
- rashes which may be itchy or inflamed (flat or raised spots or blisters)
- frequent bowel movements
- increased sensitivity of the skin to sunlight
- decreased feeling or sensitivity, especially in the skin

Rare side effects (may affect up to 1 in 1,000 people):

- Inflammation of the lung (pneumonitis)

Not known (frequency cannot be estimated from the available data):

- An enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections)
- Tumour lysis syndrome resulting from a fast breakdown of cancer cells
- Liver failure

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
https://torrentpharma.com/index.php/site/info/adverse_event_reporting
By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store PAZOBRITE

Store at a temperature below 30°C.

Keep out of reach of children

Keep container tightly closed

Dispense in original container

Do not use if seal over bottle opening is broken or missing.

9.6 Contents of the pack and other information

The active substance is Pazopanib.

The other excipients used are Mannitol, Pregelatinized Starch, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Talc, Hydroxyl Propyl Cellulose, Sepitrap 80, Magnesium Stearate, Croscarmellose Sodium, Opadry Pink 15B24005.

PAZOBRITE is available in bottle pack of 30 tablets**.**

10 Details of manufacturer

Manufactured by:

Hetero Labs Limited (Unit-I)

Village: Kalyanpur, Chakkan Road, Tehsil: Baddi,

Distt.: Solan, Himachal Pradesh - 173205.

11 Details of permission or licence number with date

Mfg. Lic. No.: MNB/06/328 issued on 21.01.2021

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ PAZOBRITE /DEC-21/01/PI