ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Votrient 200 mg film-coated tablets
Votrient 400 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Votrient 200 mg film-coated tablets

Each film-coated tablet contains 200 mg pazopanib (as hydrochloride).

Votrient 400 mg film-coated tablets

Each film-coated tablet contains 400 mg pazopanib (as hydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Votrient 200 mg film-coated tablets

Capsule-shaped, pink, film-coated tablet with GS JT debossed on one side.

Votrient 400 mg film-coated tablets

Capsule-shaped, white, film-coated tablet with GS UHL debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Renal cell carcinoma (RCC)

Votrient is indicated in adults for the first line treatment of advanced Renal Cell Carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.

Soft tissue sarcoma (STS)

Votrient is indicated for the treatment of adult patients with selective subtypes of advanced Soft Tissue Sarcoma (STS) who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy.

Efficacy and safety has only been established in certain STS histological tumour subtypes (see section 5.1).

4.2 Posology and method of administration

Votrient treatment should only be initiated by a physician experienced in the administration of anti-cancer agents.

Posology

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

Dose modifications
Dose modification should be in 200 mg 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 on organ growth and maturation (see section 4.4 and 5.3).

The safety and efficacy of pazopanib in children aged 2 to 18 years of age have not yet been established (see section 5.1).

Elderly
There are limited data of the use of pazopanib in patients aged 65 years and older. In the 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 older individuals 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 (see section 5.2). 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 (see section 5.2). All patients should have liver function tests to determine whether they have hepatic impairment before starting and during pazopanib therapy (see section 4.4). 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 as either 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 values) (see section 5.2).

Pazopanib is not recommended in patients with severe hepatic impairment (defined as total bilirubin > 3 X ULN regardless of any level of ALT).

See section 4.4 for liver monitoring and dose modification for patients with drug induced hepatotoxicity.

Method of administration

Pazopanib should be taken without food, at least one hour before or two hours after a meal (see section 5.2). Votrient film-coated tablets should be taken whole with water and not broken or crushed (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 as an 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 values) (see section 4.2 and 5.2). Pazopanib is not recommended in patients with severe hepatic impairment (total bilirubin > 3 x ULN regardless of any level of ALT) (see section 4.2 and 5.2). 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 clinical studies with pazopanib, increase in serum transaminases (ALT, aspartate aminotransferase [AST]) and bilirubin were observed (see section 4.8). 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 (>3xULN) to severe (>8xULN) 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 (see section 5.1).

Serum liver tests should be monitored before initiation of treatment with pazopanib and at weeks 3, 5, 7 and 9. Thereafter, monitored at month 3 and at month 4, and as clinically indicated. Periodic monitoring 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:

Table 1: 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	Interupt pazopanib until transaminases return to Grade 1 or baseline. If the potential benefit for reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce pazopanib at a reduced dose of 400 mg daily and measure 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 (see section 4.5) 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 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 judgment) (see section 4.2 and 4.8). 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 (see section 4.8). Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis and discontinue pazopanib 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 LVEF has not been studied.

In clinical trials with pazopanib, events of cardiac dysfunction such as congestive heart failure and decreased left ventricular ejection fraction (LVEF) have occurred (see section 4.8). In a randomised trial 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 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 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 hypertension (if present, refer to hypertension warning section above) 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 (see section 4.8). 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 those with relevant pre-existing cardiac disease. When using pazopanib, base line 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, ischemic stroke, and transient ischemic attack were observed (see section 4.8). 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 upon 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

Thrombotic microangiopathy (TMA) has been reported in clinical trials of pazopanib as monotherapy, in combination with bevacizumab, and in combination with topotecan (see section 4.8). 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 clinical studies with pazopanib haemorrhagic events have been reported (see section 4.8). Fatal haemorragic events have occurred. Pazopanib has not been studied in patients who had a history of haemoptysis, cerebral, or clinically significant gastrointestinal (GI) haemorrhage in the past 6 months. Pazopanib should be used with caution in patients with significant risk of haemorrhage.

Gastrointestinal perforations and fistula

In clinical studies with pazopanib, events of GI perforation or fistula have occurred (see section 4.8). 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 on 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 clinical studies with pazopanib, events of hypothyroidism have occurred (see section 4.8). 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.

Pneumothorax

In clinical studies with pazopanib in advanced soft tissue sarcoma, events of pneumothorax have occurred (see section 4.8). 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 (see section 5.3), 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

Clinical trials of pazopanib in combination with pemetrexed (non-small cell lung cancer (NSCLC)) and lapatinib (cervical cancer) 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 (see section 5.3). 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 (see section 4.6).

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 (see section 4.5). 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 (see section 4.5).

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 (see section 4.5).

Grapefruit juice should be avoided during treatment with pazopanib (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on pazopanib

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). 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 (see section 4.4). 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 medication 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 alternate concomitant medication with no or minimal enzyme or transporter induction potential is recommended.

Effects of pazopanib on other medicinal products

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. 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/m^2 (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 25 % and 31 % in paclitaxel AUC and C_{max}, respectively.

Based on *in vitro* IC_{50} 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/m^2 and irinotecan 150 mg/m^2 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 with11/41 (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 (see section 4.4). 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.

Medicines that raise gastric pH

Concomitant administration of pazopanib with esomeprazole decreases the bioavailability of pazopanib by approximately 40% (AUC and Cmax), 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 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of pazopanib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Pazopanib should not be used during pregnancy unless the clinical condition of the women 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 the treatment and at least 2 weeks after treatment and 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 drug exposure to pregnant partners and female partners of reproductive potential.

Breast-feeding

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

Fertility

Animal studies indicate that male and female fertility may be affected by treatment with pazopanib (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. 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

Pooled data from the pivotal RCC trial (VEG105192, n=290), extension study (VEG107769, n=71), the supportive Phase II trial (VEG102616, n=225) and the randomised, open-label, parallel group Phase III non-inferiority study (VEG108844, n=557) was evaluated in the overall evaluation of safety and tolerability of pazopanib (total n=1149) in subjects with RCC (see section 5.1).

Pooled data from the pivotal STS trial (VEG110727, n=369) and the supportive Phase II trial (VEG20002, n=142) was evaluated in the overall evaluation of safety and tolerability of pazopanib (total safety population n=382) in subjects with STS (see section 5.1).

The most important serious adverse reactions identified in the RCC or STS trials were transient ischaemic attack, ischaemic stroke, myocardial ischaemia, myocardial and cerebral infarction, cardiac dysfunction, gastrointestinal perforation and fistula, QT prolongation and pulmonary, gastrointestinal and cerebral haemorrhage, all adverse reactions being reported in < 1 % of treated patients. Other important serious adverse reactions identified in STS trials 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 ischemic stroke.

The most common adverse reactions (experienced by at least 10 % of the patients) of any grade in the RCC and STS 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.

Treatment related adverse reactions, all grades, which were reported in RCC and STS subjects or during 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
Not known	(cannot be estimated from the available data)

Categories have been assigned based on absolute frequencies in the clinical trial data. Post marketing data on safety and tolerability across all pazopanib clinical trials 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

Table 2: 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	Uncommon	Infections (with or without neutropenia)†	not known	not known	not known
	Uncommon	Gingival infection	1 (< 1 %)	0	0
	Uncommon	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 %)
	Common	Neutropenia	79 (7 %)	20 (2 %)	4 (< 1 %)
	Common	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
Metabolism and nutrition disorders	Very common	Decreased appetite[e]	317 (28 %)	14 (1 %)	0
	Common	Hypophosphataemia	21 (2 %)	7 (< 1 %)	0
	Common	Dehydration	16 (1 %)	5 (< 1 %)	0
	Uncommon	Hypomagnesaemia	10 (< 1 %)	0	0
Psychiatric disorders	Common	Insomnia	30 (3 %)	0	0

Nervous system disorders	Very common	Dysgeusia[c]	254 (22 %)	1 (< 1 %)	0
	Very common	Headache	122 (11 %)	11 (< 1 %)	0
	Common	Dizziness	55 (5 %)	3 (< 1 %)	1 (< 1 %)
	Common	Lethargy	30 (3 %)	3 (< 1 %)	0
	Common	Paraesthesia	20 (2 %)	2 (< 1 %)	0
	Common	Peripheral sensory neuropathy	17 (1 %)	0	0
	Uncommon	Hypoaesthesia	8 (< 1 %)	0	0
	Uncommon	Transient ischaemic attack	7 (< 1 %)	4 (< 1 %)	0
	Uncommon	Somnolence	3 (< 1 %)	1 (< 1 %)	0
	Uncommon	Cerebrovascular accident	2 (< 1 %)	1 (< 1 %)	1 (< 1 %)
	Uncommon	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
	Uncommon	Retinal tear†	1 (<1%)	1 (<1%)	0
	Uncommon	Eyelash discolouration	4 (< 1 %)	0	0
Cardiac disorders	Uncommon	Bradycardia	6 (< 1 %)	0	0
	Uncommon	Myocardial infarction	5 (< 1 %)	1 (< 1 %)	4 (< 1 %)
	Uncommon	Cardiac dysfunction[f]	4 (< 1 %)	1 (< 1 %)	0
	Uncommon	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
	Common	Venous thromboembolic event[g]	13 (1 %)	6 (< 1 %)	7 (< 1 %)
	Common	Flushing	12 (1 %)	0	0
	Uncommon	Hypertensive crisis	6 (< 1 %)	0	2 (< 1 %)
	Uncommon	Haemorrhage	1 (< 1 %)	0	0
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis	50 (4 %)	1 (< 1 %)	0
	Common	Dysphonia	48 (4 %)	0	0
	Common	Dyspnoea	42 (4 %)	8 (< 1 %)	1 (< 1 %)
	Common	Haemoptysis	15 (1 %)	1 (< 1 %)	0
	Uncommon	Rhinorrhoea	8 (< 1 %)	0	0
	Uncommon	Pulmonary haemorrhage	2 (< 1 %)	0	0
	Uncommon	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 %)
	Very common	Nausea	386 (34 %)	14 (1%)	0
	Very common	Vomiting	225 (20 %)	18 (2 %)	1 (< 1 %)
	Very common	Abdominal pain[a]	139 (12 %)	15 (1 %)	0
	Common	Stomatitis	96 (8 %)	4 (< 1 %)	0
	Common	Dyspepsia	83 (7 %)	2 (< 1 %)	0
	Common	Flatulence	43 (4 %)	0	0
	Common	Abdominal distension	36 (3 %)	2 (< 1 %)	0
	Common	Mouth ulceration	28 (2 %)	3 (< 1 %)	0
	Common	Dry mouth	27 (2 %)	0	0
	Uncommon	Pancreatitis	8 (< 1 %)	4 (< 1 %)	0
	Uncommon	Rectal haemorrhage	8 (< 1 %)	2 (< 1 %)	0
	Uncommon	Haematochezia	6 (< 1 %)	0	0
	Uncommon	Gastrointestinal haemorrhage	4 (< 1 %)	2 (< 1 %)	0
	Uncommon	Melaena	4 (< 1 %)	1(< 1 %)	0
	Uncommon	Frequent bowel movements	3 (< 1 %)	0	0
	Uncommon	Anal haemorrhage	2 (< 1 %)	0	0
	Uncommon	Large intestine perforation	2 (< 1 %)	1 (< 1 %)	0
	Uncommon	Mouth haemorrhage	2 (< 1 %)	0	0
	Uncommon	Upper gastrointestinal haemorrhage	2 (< 1 %)	1 (< 1 %)	0
	Uncommon	Enterocutaneous fistula	1 (< 1 %)	0	0
	Uncommon	Haematemesis	1 (< 1 %)	0	0
	Uncommon	Haemorrhoidal haemorrhage	1 (< 1 %)	0	0
	Uncommon	Ileal perforation	1 (< 1 %)	0	1 (< 1 %)
	Uncommon	Oesophageal haemorrhage	1 (< 1 %)	0	0
	Uncommon	Retroperitoneal haemorrhage	1 (< 1 %)	0	0
Hepatobiliary disorders	Common	Hyperbilirubinaemia	38 (3 %)	2 (< 1 %)	1 (< 1 %)
	Common	Hepatic function abnormal	29 (3 %)	13 (1 %)	2 (< 1 %)
	Common	Hepatotoxicity	18 (2 %)	11(< 1 %)	2 (< 1 %)
	Uncommon	Jaundice	3 (< 1 %)	1 (< 1 %)	0
	Uncommon	Drug induced liver injury	2 (< 1 %)	2 (< 1 %)	0
	Uncommon	Hepatic failure	1 (< 1 %)	0	1 (< 1 %)

Skin and subcutaneous disorders	Very common	Hair colour change	404 (35 %)	1 (< 1 %)	0
	Very common	Palmar-plantar erythrodysaesthesia syndrome	206 (18 %)	39 (3 %)	0
	Very common	Alopecia	130 (11 %)	0	0
	Very common	Rash	129 (11 %)	7 (< 1 %)	0
	Common	Skin hypopigmentation	52 (5 %)	0	0
	Common	Dry skin	50 (4 %)	0	0
	Common	Pruritus	29 (3 %)	0	0
	Common	Erythema	25 (2 %)	0	0
	Common	Skin depigmentation	20 (2 %)	0	0
	Common	Hyperhidrosis	17 (1 %)	0	0
	Uncommon	Nail disorders	11 (< 1 %)	0	0
	Uncommon	Skin exfoliation	10 (< 1 %)	0	0
	Uncommon	Photosensitivity reaction	7 (< 1 %)	0	0
	Uncommon	Rash erythematous	6 (< 1 %)	0	0
	Uncommon	Skin disorder	5 (< 1 %)	0	0
	Uncommon	Rash macular	4 (< 1 %)	0	0
	Uncommon	Rash pruritic	3 (< 1 %)	0	0
	Uncommon	Rash vesicular	3 (< 1 %)	0	0
	Uncommon	Pruritus generalised	2 (< 1 %)	1 (< 1 %)	0
	Uncommon	Rash generalised	2 (< 1 %)	0	0
	Uncommon	Rash papular	2 (< 1 %)	0	0
	Uncommon	Plantar erythema	1 (< 1 %)	0	0
Musculoskeletal and connective tissue disorders	Common	Arthralgia	48 (4 %)	8 (< 1 %)	0
	Common	Myalgia	35 (3 %)	2 (< 1 %)	0
	Common	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
	Uncommon	Vaginal haemorrhage	3 (< 1 %)	0	0
	Uncommon	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
	Common	Asthenia	82 (7 %)	20 (2 %)	1 (< 1 %)
	Common	Oedema[b]	72 (6 %)	1 (< 1 %)	0
	Common	Chest pain	18 (2 %)	2 (< 1 %)	0
	Uncommon	Chills	4 (< 1 %)	0	0
	Uncommon	Mucous membrane disorder	1 (< 1 %)	0	0

Investigations	Very common	Alanine aminotransferase increased	246 (21 %)	84 (7 %)	14 (1 %)
	Very common	Aspartate aminotransferase increased	211 (18 %)	51 (4 %)	10 (< 1 %)
	Common	Weight decreased	96 (8 %)	7 (< 1 %)	0
	Common	Blood bilirubin increased	61 (5 %)	6 (< 1 %)	1 (< 1 %)
	Common	Blood creatinine increased	55 (5 %)	3 (< 1 %)	0
	Common	Lipase increased	51 (4 %)	21 (2 %)	7 (< 1 %)
	Common	White blood cell count decreased[d]	51 (4 %)	3 (< 1 %)	0
	Common	Blood thyroid stimulating hormone increased	36 (3 %)	0	0
	Common	Amylase increased	35 (3 %)	7 (< 1 %)	0
	Common	Gamma-glutamyltransferase increased	31 (3 %)	9 (< 1 %)	4 (< 1 %)
	Common	Blood pressure increased	15 (1 %)	2 (< 1 %)	0
	Common	Blood urea increased	12 (1 %)	1 (< 1 %)	0
	Common	Liver function test abnormal	12 (1 %)	6 (< 1 %)	1 (< 1 %)
	Uncommon	Hepatic enzyme increased	11 (< 1 %)	4 (< 1 %)	3 (< 1 %)
	Uncommon	Blood glucose decreased	7 (< 1 %)	0	1 (< 1 %)
	Uncommon	Electrocardiogram QT prolonged	7 (< 1 %)	2 (< 1 %)	0
	Uncommon	Transaminase increased	7 (< 1 %)	1 (< 1 %)	0
	Uncommon	Thyroid function test abnormal	3 (< 1 %)	0	0
	Uncommon	Blood pressure diastolic increased	2 (< 1 %)	0	0
	Uncommon	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 trials).
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.

Table 3: Treatment-related adverse reactions reported in STS trials (n=382)

System Organ Class	Frequency (all grades)	Adverse Reactions	All Grades n (%)	Grade 3 n (%)	Grade 4 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
	Very common	Thrombocytopenia	86 (36 %	7 (3 %)	2 (< 1 %)
	Very common	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
	Very common	Hypoalbuminemia[f]	81 (34 %)	2 (< 1 %)	0
	Common	Dehydration	4 (1 %)	2 (1 %)	0
	Uncommon	Hypomagnesaemia	1 (< 1 %)	0	0
Psychiatric disorders	Common	Insomnia	5 (1 %)	1 (< 1 %)	0
Nervous system disorders	Very common	Dysgeusia[c]	79 (21 %)	0	0
	Very common	Headache	54 (14 %)	2 (< 1 %)	0
	Common	Peripheral sensory neuropathy	30 (8 %)	1 (< 1 %)	0
	Common	Dizziness	15 (4 %)	0	0
	Uncommon	Somnolence	3 (< 1 %)	0	0
	Uncommon	Paresthesia	1 (< 1 %)	0	0
	Uncommon	Cerebral infarction	1 (< 1 %)	0	1 (< 1 %)
Eye disorders	Common	Vision blurred	15 (4 %)	0	0
Cardiac disorders	Common	Cardiac dysfunction[g]	21 (5 %)	3 (< 1 %)	1 (< 1 %)
	Common	Left ventricular dysfunction	13 (3 %)	3 (< 1 %)	0
	Common	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 %)
	Common	Hot flush	12 (3 %)	0	0
	Common	Flushing	4 (1 %)	0	0
	Uncommon	Haemorrhage	2 (< 1 %)	1 (< 1 %)	0
Respiratory, thoracic and mediastinal disorders	Common	Epistaxis	22 (6 %)	0	0
	Common	Dysphonia	20 (5 %)	0	0
	Common	Dyspnoea	14 (4 %)	3 (< 1 %)	0
	Common	Cough	12 (3 %)	0	0
	Common	Pneumothorax	7 (2 %)	2 (< 1 %)	1 (< 1 %)
	Common	Hiccups	4 (1 %)	0	0
	Common	Pulmonary haemorrhage	4 (1 %)	1 (< 1 %)	0
	Uncommon	Oropharyngeal pain	3 (< 1 %)	0	0
	Uncommon	Bronchial haemorrhage	2 (< 1 %)	0	0
	Uncommon	Rhinorrhoea	1 (< 1 %)	0	0
	Uncommon	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
	Very common	Nausea	167 (44 %)	8 (2 %)	0
	Very common	Vomiting	96 (25 %)	7 (2 %)	0
	Very common	Abdominal pain[a]	55 (14 %)	4 (1 %)	0
	Very common	Stomatitis	41 (11 %)	1 (< 1 %)	0
	Common	Abdominal distension	16 (4 %)	2 (1 %)	0
	Common	Dry mouth	14 (4 %)	0	0
	Common	Dyspepsia	12 (3 %)	0	0
	Common	Mouth haemorrhage	5 (1 %)	0	0
	Common	Flatulence	5 (1 %)	0	0
	Common	Anal haemorrhage	4 (1 %)	0	0
	Uncommon	Gastrointestinal haemorrhage	2 (< 1 %)	0	0
	Uncommon	Rectal haemorrhage	2 (< 1 %)	0	0
	Uncommon	Enterocutaneous fistula	1 (< 1 %)	1 (< 1 %)	0
	Uncommon	Gastric haemorrhage	1 (< 1 %)	0	0
	Uncommon	Melaena	2 (< 1 %)	0	0
	Uncommon	Oesophageal haemorrhage	1 (< 1 %)	0	1 (< 1 %)
	Uncommon	Peritonitis	1 (< 1 %)	0	0
	Uncommon	Retroperitoneal haemorrhage	1 (< 1 %)	0	0
	Uncommon	Upper gastrointestinal haemorrhage	1 (< 1 %)	1 (< 1 %)	0
	Uncommon	Ileal perforation	1 (< 1 %)	0	1 (< 1 %)

Hepatobiliary disorders	Uncommon	Hepatic function abnormal	2 (< 1 %)	0	1 (< 1 %)
Skin and subcutaneous disorders	Very common	Hair colour change	93 (24 %)	0	0
	Very common	Skin hypopigmentation	80 (21 %)	0	0
	Very common	Exfoliative rash	52 (14 %)	2 (< 1 %)	0
	Common	Alopecia	30 (8 %)	0	0
	Common	Skin disorder[c]	26 (7 %)	4 (1 %)	0
	Common	Dry skin	21 (5 %)	0	0
	Common	Hyperhydrosis	18 (5 %)	0	0
	Common	Nail disorder	13 (3 %)	0	0
	Common	Pruritus	11 (3 %)	0	0
	Common	Erythema	4 (1 %)	0	0
	Uncommon	Skin ulcer	3 (< 1 %)	1 (< 1 %)	0
	Uncommon	Rash	1 (< 1 %)	0	0
	Uncommon	Rash papular	1 (< 1 %)	0	0
	Uncommon	Photosensitivity reaction	1 (< 1 %)	0	0
	Uncommon	Palmar-plantar erythrodysaesthesia syndrome	2 (<1 %)	0	0
Musculoskeletal and connective tissue disorders	Common	Musculoskeletal pain	35 (9 %)	2 (< 1 %)	0
	Common	Myalgia	28 (7 %)	2 (< 1 %)	0
	Common	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
	Uncommon	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
	Common	Chest pain	12 (3 %)	4 (1 %)	0
	Common	Chills	10 (3 %)	0	0
	Uncommon	Mucosal inflammation[e]	1 (<1 %)	0	0
	Uncommon	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
	Common	Alanine aminotransferase increased	8 (2 %)	4 (1 %)	2 (< 1 %)
	Common	Blood cholesterol abnormal	6 (2 %)	0	0
	Common	Aspartate aminotransferase increased	5 (1 %)	2 (< 1 %)	2 (< 1 %)
	Common	Gamma glutamyltransferase increased	4 (1 %)	0	3 (< 1 %)
	Uncommon	Blood bilirubin increased	2 (<1 %)	0	0
	Uncommon	Aspartate aminotransferase	2 (< 1 %)	0	2 (< 1 %)
	Uncommon	Alanine aminotransferase	1 (< 1 %)	0	1 (< 1 %)
	Uncommon	Platelet count decreased	1 (< 1 %)	0	1 (< 1 %)
	Uncommon	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 trials).
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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, protein- kinase inhibitors, ATC code: L01XE11

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 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-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.

Pharmacogenomics

In a pharmacogenetic meta-analysis of data from 31 clinical studies of pazopanib administered as either 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 (see section 4.4).

Clinical studies

Renal Cell Carcinoma (RCC)
The safety and efficacy of pazopanib in RCC were evaluated in a randomised, double-blind, placebo-controlled multi-centre study. Patients (N = 435) with locally advanced and/or metastatic RCC were randomised to receive pazopanib 800 mg once daily or placebo. The primary objective of the study was to evaluate and compare the two treatment arms for progression-free survival (PFS) and the principle secondary endpoint is overall survival (OS). The other objectives were to evaluate the overall response rate and duration of response.

From the total of 435 patients in this study, 233 patients were treatment naïve and 202 were second line patients who received one prior IL-2 or INFα-based therapy. The performance status (ECOG) was similar between the pazopanib and placebo groups (ECOG 0: 42 % vs. 41 %, ECOG 1: 58 % vs. 59 %). The majority of patients had either favourable (39 %) or intermediate (54 %), MSKCC (Memorial Sloan Kettering Cancer Centre) / Motzer prognostic factors. All patients had clear cell histology or predominantly clear cell histology. Approximately half of all patients had 3 or more organs involved in their disease and most patients had the lung (74 %), and/or lymph nodes (54 %) as a metastatic location for disease at baseline.

A similar proportion of patients in each arm were treatment-naïve and cytokine-pre-treated (53 % and 47 % in pazopanib arm, 54 % and 46 % in placebo arm). In the cytokine-pre-treated subgroup, the majority (75 %) had received interferon based treatment.

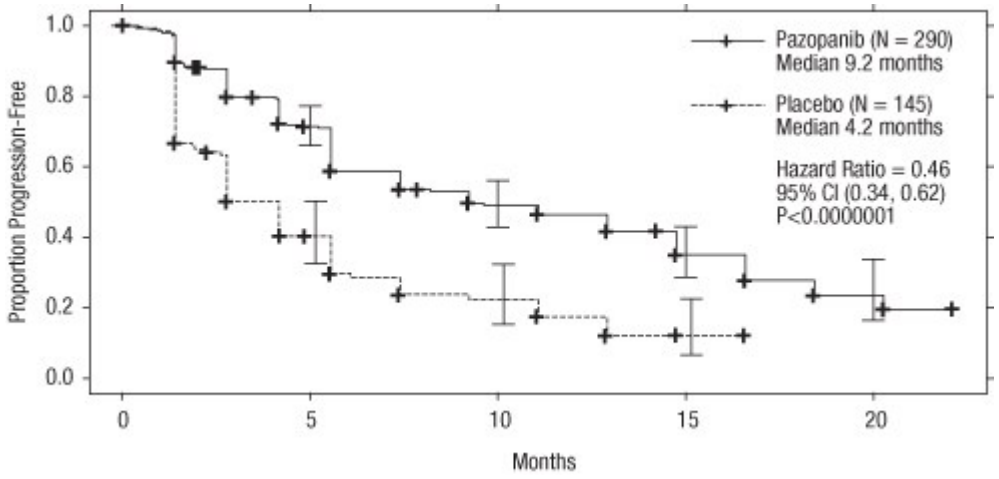
Similar proportions of patients in each arm had prior nephrectomy (89 % and 88 % in the pazopanib and placebo arms, respectively) and/or prior radiotherapy (22 % and 15 % in the pazopanib and placebo arms, respectively.

The primary analysis of the primary endpoint PFS is based on disease assessment by independent radiological review in the entire study population (treatment naïve and cytokine pre-treated).

Table 4: Overall efficacy results in RCC by independent assessment (VEG105192)

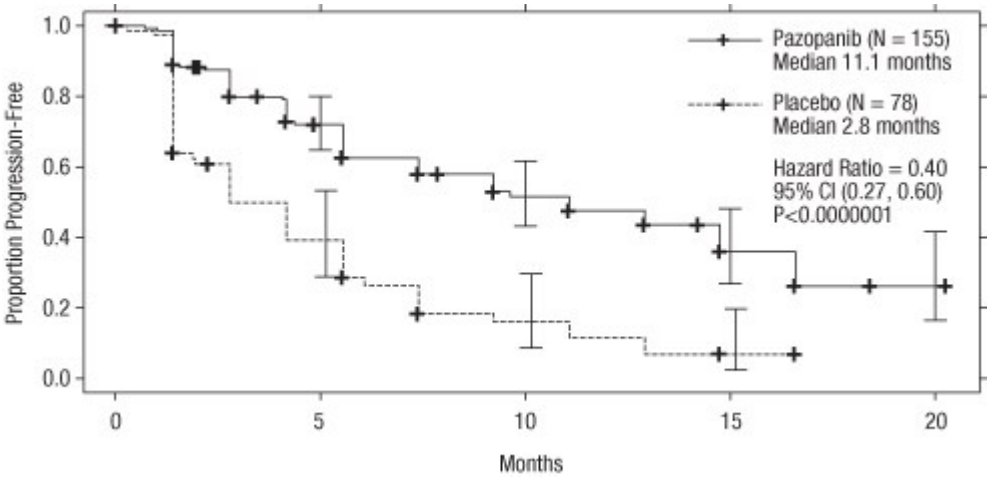
Endpoints/Study Population	Pazopanib	Placebo	HR (95% CI)	P value (one-sided)
PFS Overall* ITT Median (months)	 N = 290 9.2	 N = 145 4.2	 0.46 (0.34, 0.62)	 < 0.0000001
Response rate % (95% CI)	N = 290 30 (25.1,35.6)	N = 145 3 (0.5, 6.4)	 –	 < 0.001
HR = Hazard ratio; ITT = Intent to treat; PFS = Progression-free survival. * - Treatment-Naïve and Cytokine Pre-treated Populations.				

Figure 1: Kaplan-Meier curve for progression-free survival by independent assessment for the overall population (treatment-naïve and cytokine pre-treated populations) (VEG105192)



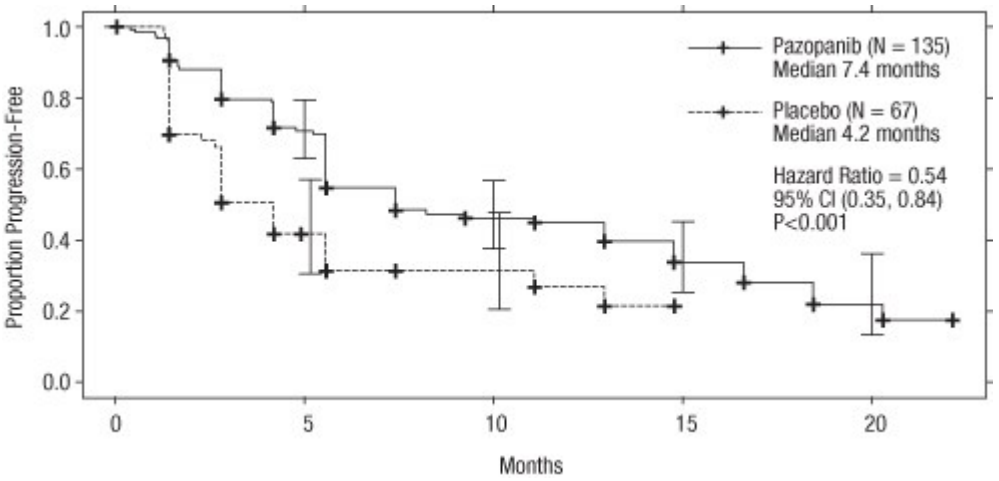
x axis; Months, y axis; Proportion Progression Free, Pazopanib ——— (N = 290) Median 9.2 months; Placebo -------- (N = 145) Median 4.2 months; Hazard Ratio = 0.46, 95 % CI (0.34, 0.62), P < 0.0000001

Figure 2: Kaplan-Meier curve for progression-free survival by independent assessment for the treatment-naïve population (VEG105192)



x axis; Months, y axis; Proportion Progression Free, Pazopanib ——— (N = 155) Median 11.1 months; Placebo -------- (N = 78) Median 2.8 months; Hazard Ratio = 0.40, 95 % CI (0.27, 0.60), P < 0.0000001

Figure 3: Kaplan-Meier Curve for progression-free survival by independent assessment for the cytokine pre-treated population (VEG105192)



x axis; Months, y axis; Proportion Progression Free, Pazopanib ——— (N = 135) Median 7.4 months; Placebo -------- (N = 67) Median 4.2 months; Hazard Ratio = 0.54, 95 % CI (0.35, 0.84), P < 0.001

For patients who responded to treatment, the median time to response was 11.9 weeks and the median duration of response was 58.7 weeks as per independent review (VEG105192).

The median overall survival (OS) data at the protocol specified final survival analysis were 22.9 months and 20.5 months [HR = 0.91 (95 % CI: 0.71, 1.16; p = 0.224)] for patients randomised to the pazopanib and placebo arms, respectively. The OS results are subject to potential bias as 54 % of patients in the placebo arm also received pazopanib in the extension part of this study following disease progression. Sixty-six percent of placebo patients received post-study therapy compared to 30 % of pazopanib patients.

No statistical differences were observed between treatment groups for Global Quality of Life using EORTC QLQ-C30 and EuroQoL EQ-5D.

In a Phase 2 study of 225 patients with locally recurrent or metastatic clear cell renal cell carcinoma, objective response rate was 35 % and median duration of response was 68 weeks, as per independent review. Median PFS was 11.9 months.

The safety, efficacy and quality of life of pazopanib versus sunitinib has been evaluated in a randomised, open-label, parallel group Phase III non-inferiority study (VEG108844).

In VEG108844, patients (N = 1110) with locally advanced and/or metastatic RCC who had not received prior systemic therapy, were randomised to receive either pazopanib 800 mg once daily continuously or sunitinib 50 mg once daily in 6-week cycles of dosing with 4 weeks on treatment followed by 2 weeks without treatment.

The primary objective of this study was to evaluate and compare PFS in patients treated with pazopanib to those treated with sunitinib. Demographic characteristics were similar between the treatment arms. Disease characteristics at initial diagnosis and at screening were balanced between the treatment arms with the majority of patients having clear cell histology and Stage IV disease.

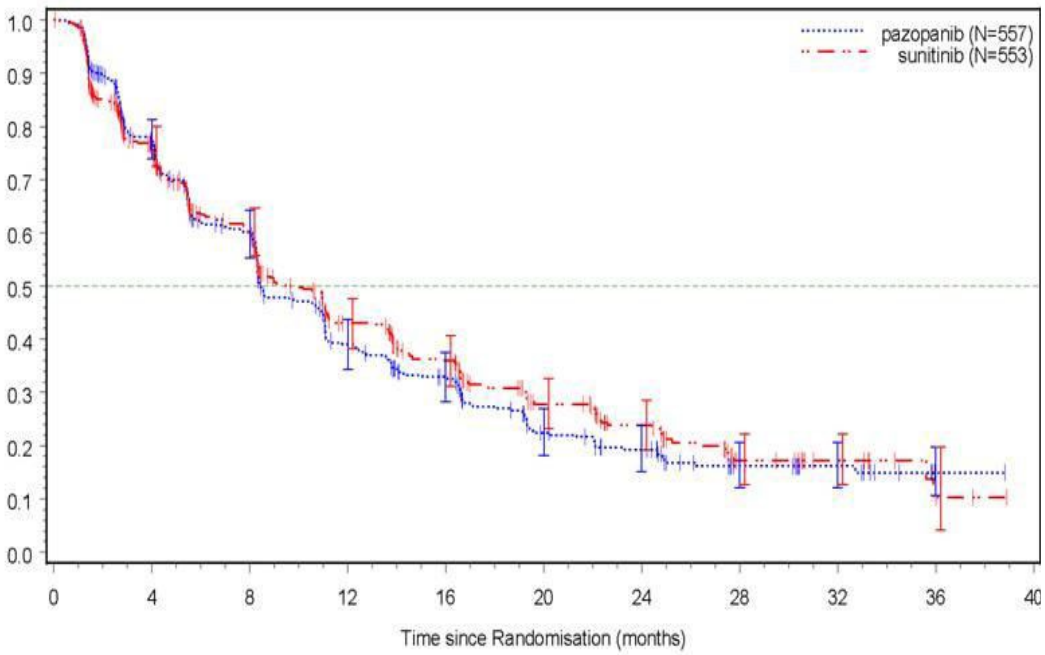
VEG108844 achieved its primary endpoint of PFS and demonstrated that pazopanib was non-inferior to sunitinib, as the upper bound of the 95 % CI for the hazard ratio was less than the protocol-specified non-inferiority margin of 1.25. Overall efficacy results are summarised in Table 5.

Table 5: Overall efficacy results (VEG108844)

Endpoint	Pazopanib N = 557	Sunitinib N = 553	HR (95% CI)
PFS			
Overall			
Median (months)	8.4	9.5	1.047
(95 % CI)	(8.3, 10.9)	(8.3, 11.0)	(0.898, 1.220)
Overall Survival			
Median (months)	28.3	29.1	0.915[a]
(95 % CI)	(26.0, 35.5)	(25.4, 33.1)	(0.786, 1.065)

HR = Hazard Ratio; PFS = Progression-free Survival; [a] *P* value = 0.245 (2-sided)

Figure 4: Kaplan-Meier Curve for progression-free survival by independent assessment for the overall population (VEG108844)



Subgroup analyses of PFS were performed for 20 demographic and prognostic factors. The 95 % confidence intervals for all subgroups include a hazard ratio of 1. In the three smallest of these 20 subgroups, the point estimate of the hazard ratio exceeded 1.25; i.e., in subjects with no prior nephrectomy (n=186, HR=1.403, 95 % CI (0.955, 2.061)), baseline LDH > 1.5 x ULN (n=68, HR=1.72, 95 % CI (0.943, 3.139)), and MSKCC: poor risk (n=119, HR=1.472, 95 % CI (0.937, 2.313)).

Soft Tissue Sarcoma (STS)
The efficacy and safety of pazopanib in STS were evaluated in a pivotal phase III randomised, double-blind, placebo-controlled multi-centre trial (VEG110727). A total of 369 patients with advanced STS were randomised to receive pazopanib 800 mg once daily or placebo. Importantly, only patients with selective histological subtypes of STS were allowed to participate to the study, therefore efficacy and safety of pazopanib can only be considered established for those subgroups of STS and treatment with pazopanib should be restricted to such STS subtypes.

The following tumour types were eligible:
Fibroblastic (adult fibrosarcoma, myxofibrosarcoma, sclerosing epithelioid fibrosarcoma, malignant solitary fibrous tumours), so-called fibrohistiocytic (pleomorphic malignant fibrous histiocytoma [MFH], giant cell MFH, inflammatory MFH), leiomyosarcoma, malignant glomus tumours, skeletal muscles (pleomorphic and alveolar rhabdomyosarcoma), vascular (epithelioid hemangioendothelioma, angiosarcoma), uncertain differentiation (synovial, epithelioid, alveolar soft part, clear cell, desmoplastic small round cell, extra-renal rhabdoid, malignant mesenchymoma, PEComa, intimal sarcoma), malignant peripheral nerve sheath tumours, undifferentiated soft tissue sarcomas not otherwise specified (NOS) and other types of sarcoma (not listed as ineligible).

The following tumour types were not eligible:
Adipocytic sarcoma (all subtypes), all rhabdomyosarcoma that were not alveolar or pleomorphic, chondrosarcoma, osteosarcoma, Ewing tumours/Primitive neuroectodermal tumours (PNET), GIST, dermofibromatosis sarcoma protuberans, inflammatory myofibroblastic sarcoma, malignant mesothelioma and mixed mesodermal tumours of the uterus.
Of note, patients with adipocytic sarcoma were excluded from the pivotal phase III study as in a preliminary phase II study (VEG20002), activity (PFS at week12) observed with pazopanib in adipocytic did not meet the prerequisite rate to allow further clinical testing.

Other key eligibility criteria of the VEG110727 study were: histological evidence of high or intermediate grade malignant STS and disease progression within 6 months of therapy for metastatic disease, or recurrence within 12 months of (neo)-/adjuvant therapy.

Ninety-eight percent (98 %) of subjects received prior doxorubicin, 70 % prior ifosfamide, and 65 % of subjects had received at least three or more chemotherapeutic agents prior to study enrolment.

Patients were stratified by the factors of WHO performance status (WHO PS) (0 or 1) at baseline and the number of lines of prior systemic therapy for advanced disease (0 or 1 vs. 2+). In each treatment group, there was a slightly greater percentage of subjects in the 2+ lines of prior systemic therapy for advanced disease (58 % and 55 % respectively for placebo and pazopanib treatment arms) compared with 0 or 1 lines of prior systemic therapy (42 % and 45 % respectively for placebo and pazopanib treatment arms). The median duration of follow-up of subjects (defined as date of randomization to date of last contact or death) was similar for both treatment arms (9.36 months for placebo [range 0.69 to 23.0 months] and 10.04 months for pazopanib [range 0.2 to 24.3 months].

The primary objective of the trial was progression-free survival (PFS assessed by independent radiological review); the secondary endpoints included overall survival (OS), overall response rate and duration of response.

Table 6: Overall efficacy results in STS by independent assessment (VEG110727)

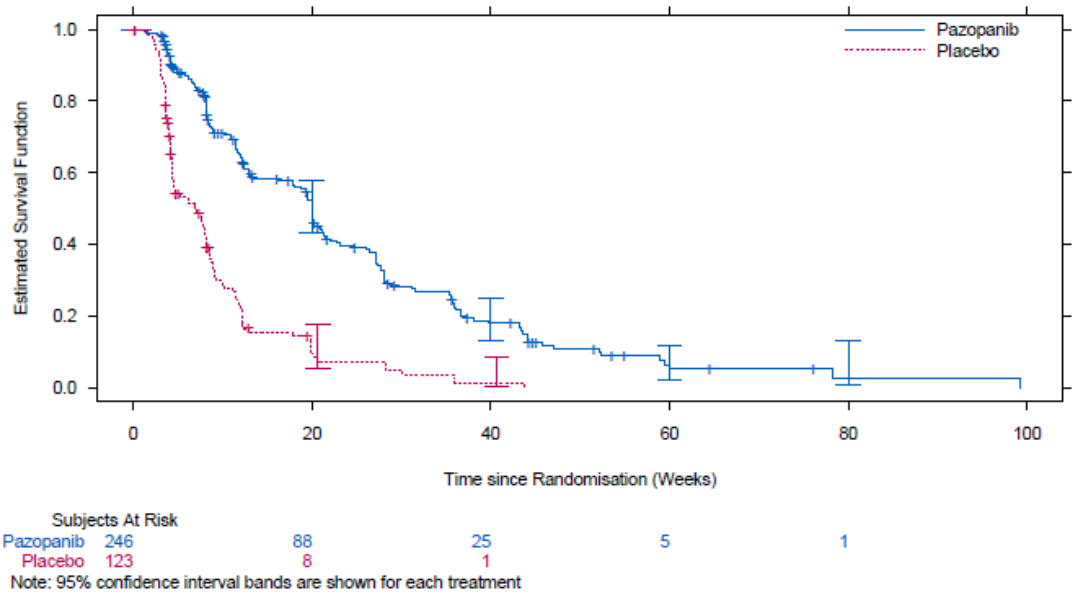
Endpoints / study population	Pazopanib	Placebo	HR (95 % CI)	P value (two-sided)
PFS				
Overall ITT	N = 246	N = 123		
Median (weeks)	20.0	7.0	0.35 (0.26, 0.48)	< 0.001
Leiomyosarcoma	N = 109	N = 49		
Median (weeks)	20.1	8.1	0.37 (0.23, 0.60)	< 0.001
Synovial sarcoma subgroups	N = 25	N = 13		
Median (weeks)	17.9	4.1	0.43 (0.19, 0.98)	0.005
'Other STS' subgroups	N = 112	N = 61		
Median (weeks)	20.1	4.3	0.39 (0.25, 0.60)	< 0.001
OS				
Overall ITT	N = 246	N = 123		
Median (months)	12.6	10.7	0.87 (0.67,1.12)	0.256
Leiomyosarcoma*	N = 109	N = 49		
Median (months)	16.7	14.1	0.84 (0.56, 1.26	0.363
Synovial sarcoma subgroups*	N = 25	N = 13		
Median (months)	8.7	21.6	1.62 (0.79, 3.33)	0.115
'Other STS' subgroups*	N = 112	N = 61		
Median (months)	10.3	9.5	0.84 (0.59, 1.21)	0.325
Response Rate (CR+PR)				
% (95 % CI)	4 (2.3, 7.9)	0 (0.0, 3.0)		
Duration of response				
Median (weeks) (95 % CI)	38.9 (16.7, 40.0)			

HR = Hazard ratio; ITT = Intent to treat; PFS = Progression-free survival; CR = Complete Response; PR = Partial Response. OS = Overall survival

***** Overall survival for the respective STS histological subgroups (leiomyosarcoma, synovial sarcoma and "Other" STS) should be interpreted with caution due to the small number of subjects and wide confidence intervals

A similar improvement in PFS based on investigator assessments was observed in the pazopanib arm compared with the placebo arm (in the overall ITT population HR: 0.39; 95 % CI, 0.30 to 0.52, p < 0.001).

Figure 5: Kaplan-Meier Curve for Progression-Free Survival in STS by Independent Assessment for the Overall Population (VEG110727)



No significant difference in OS was observed between the two treatment arms at the final OS analysis performed after 76% (280/369) of the events had occurred (HR 0.87, 95% CI 0.67, 1.12 p=0.256).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Votrient 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) (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Votrient in one or more subsets of the paediatric population in the treatment of rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma and Ewing sarcoma family of tumours (see section 4.2 for information on paediatric use).

5.2 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 were 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 (see section 4.2).

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 (see section 4.2).

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 *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 (see section 4.2).

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 (see Table 7). 800 mg pazopanib once daily is the recommended dose in patients with mild abnormalities of serum liver tests (see section 4.2).

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 (see Table 7).

Based on safety and tolerability data, the dosage of pazopanib should be reduced to 200 mg once daily in subjects with moderate hepatic impairment (see section 4.2).

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) (see section 4.2).

Table 7: 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 (11.3-104.2)	774.2 (214.7-2034.4)	800 mg OD
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
OD – Once daily				

5.3 Preclinical safety data

The 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, haematological tissues, kidney and pancreas) appear related to the pharmacology of VEGFR inhibition and/or disruption of VEGF signalling 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 pharmacologic 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 juvenile toxicity studies, when pre-weaning rats were dosed from day 9 post partum through day 14 postpartum, 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, toxicologic 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) (see section 4.4).

Reproductive, fertility and teratogenic effects

Pazopanib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits at exposures more than 300-fold lower than the human exposure (based on AUC). Effects included reduced female fertility, increased pre- and post-implantation loss, early resorptions, embryo lethality, decreased foetal body weight and cardiovascular malformation. Decreased corpora lutea, increased cysts and ovarian atrophy have also been noted in rodents. In a rat male fertility study, there was no effect on mating or fertility, but decreased testicular and epididymal weights were noted with reductions in sperm production rates, sperm motility, and epididymal and testicular sperm concentrations observed at exposures 0.3 times human exposure based on AUC.

Genotoxicity

Pazopanib did not cause genetic damage when tested in genotoxicity assays (Ames assay, human peripheral lymphocyte chromosome aberration assay and rat in vivo micronucleus). A synthetic intermediate in manufacture of pazopanib, which is also present in the final drug substance in low amounts, was not mutagenic in the Ames assay but genotoxic in the mouse lymphoma assay and in vivo mouse micronucleus assay.

Carcinogenicity

In two-year carcinogenicity studies with pazopanib, there were increased numbers of liver adenomas noted in mice and duodenal adenocarcinomas noted in rats. Based on the rodent-specific pathogenesis and mechanism for these findings, they are not considered to represent an increased carcinogenic risk for patients taking pazopanib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Votrient 200 mg film-coated tablets

Tablet core
Magnesium stearate
Microcrystalline cellulose
Povidone (K30)
Sodium starch glycolate (type A)

Tablet coating
Hypromellose
Iron oxide red (E172)
Macrogol 400
Polysorbate 80
Titanium dioxide (E171)

Votrient 400 mg film-coated tablets

Tablet core
Magnesium stearate
Microcrystalline cellulose
Povidone (K30)
Sodium starch glycolate (type A)

Tablet coating
Hypromellose
Macrogol 400
Polysorbate 80
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Votrient 200 mg film-coated tablets

HDPE bottles with polypropylene child resistant closures containing either 30 or 90 tablets.

Votrient 400 mg film-coated tablets

HDPE bottles with polypropylene child resistant closures containing either 30 or 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

Votrient 200 mg film-coated tablets

EU/1/10/628/001
EU/1/10/628/002

Votrient 400 mg film-coated tablets

EU/1/10/628/003
EU/1/10/628/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 June 2010
Date of latest renewal: 18 June 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Glaxo Operations UK Ltd (trading as Glaxo Wellcome Operations)
Priory Street
Ware
Hertfordshire
SG12 0DJ
United Kingdom

Glaxo Wellcome, S.A.
Avda. Extremadura, 3
09400 Aranda De Duero, Burgos
Spain

Novartis Pharmaceuticals UK Limited
Frimley Business Park
Frimley
Camberley, Surrey GU16 7SR
United Kingdom

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 200 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Votrient 200 mg film-coated tablets
pazopanib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 mg pazopanib (as hydrochloride)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/628/001
EU/1/10/628/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

votrient 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL – 200 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Votrient 200 mg film-coated tablets
Pazopanib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 mg pazopanib (as hydrochloride)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/628/001
EU/1/10/628/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – 400 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Votrient 400 mg film-coated tablets
Pazopanib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 400 mg pazopanib (as hydrochloride)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/628/003
EU/1/10/628/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

votrient 400 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL – 400 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Votrient 400 mg film-coated tablets
pazopanib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 400 mg pazopanib (as hydrochloride)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/628/003
EU/1/10/628/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Votrient 200 mg film-coated tablets
Votrient 400 mg film-coated tablets

Pazopanib

Read all of this leaflet carefully before you start taking 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. See section 4.

What is in this leaflet

1. What Votrient is and what it is used for

Votrient 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.

Votrient is used in adults to treat:
- kidney cancer that is advanced or has spread to other organs.
- certain forms of soft tissue sarcoma a type of cancer that affects the supportive tissues of the body. It can occur in muscles, blood vessels, fat tissue or in other tissues that support, surround and protect the organs.

2. What you need to know before you take Votrient

Do not take Votrient
- **if you are allergic** to pazopanib or any of the other ingredients of this medicine (listed in section 6).

Check with your doctor if you think this applies to you. Don't take Votrient.

Warnings and precautions
Talk to your doctor before taking Votrient:
- 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).

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

High blood pressure and Votrient
Votrient can raise your blood pressure. Your blood pressure will be checked before you take Votrient 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 Votrient 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 may need to look out for
Votrient can make some conditions worse or cause serious side effects, such as heart conditions, bleeding and thyroid probems. You must look out for certain symptoms while you are taking Votrient to reduce the risk of any problems. See '*Conditions you need to look out for'* **in Section 4.**

Children and adolescents
Votrient 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 Votrient
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. This includes herbal medicines and other medicines you've bought without a prescription.

Some medicines may affect how Votrient works or make it more likely that you'll have side effects. Votrient 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, H_2 antagonists or antacids) may affect how Votrient is taken. Please consult your doctor or nurse for advice.

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

Votrient with food and drink
Don't take Votrient 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 Votrient as this may increase the chance of side effects.

Pregnancy, breast-feeding and fertility
Votrient is not recommended if you are pregnant. The effect of Votrient 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 Votrient, and at least for 2 weeks after, to prevent pregnancy.
- **If you do become pregnant during treatment** with Votrient, tell your doctor.

Don't breast-feed while taking Votrient. It is not known whether the ingredients in Votrient 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 Votrient and for at least 2 weeks after the last dose.

Fertility may be affected by treatment with Votrient. Talk to your doctor about this.

Driving and using machines
Votrient 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.

3. How to take Votrient

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 Votrient 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 Votrient 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 Votrient 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 it affects the way the medicine is absorbed and may increase the chance of side effects.

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

Don't stop Votrient without advice
Take Votrient for as long as your doctor recommends. Don't stop unless your doctor advises you to.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Conditions you need to look out for

Swelling of the brain (*reversible posterior leukoencephalopathy syndrome* which is a disorder of the brain)
Votrient can in rare occasions cause swelling of the brain, which may be life threatening. Symptoms include:
- loss of speech
- change of vision
- seizure (fits)
- confusion

Stop taking Votrient and **seek medical advice immediately** if you get any of these symptoms, or if you get headache accompanied with any of these symptoms.

Heart conditions
Votrient can affect heart rhythm (*QT prolongation*) 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. 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 Votrient.

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

Lung Inflammation
Votrient can in rare occasions cause lung inflammation (pneumonitis), which in some people can be fatal. Symptoms include shortness of breath or cough. You will be checked for any lung problems while you are taking Votrient.

- **Tell your doctor** as soon as possible if you get any of these symptoms.

Bleeding
Votrient can cause severe bleeding in the digestive system (such as stomach, gullet, 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 / vomiting up blood

Tell your doctor as soon as possible if you get any of these symptoms.

Thyroid problems
Votrient can lower the amount of thyroid hormone produced in your body. You will be checked for this while you are taking Votrient.

Blurry or impaired vision
Votrient 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.

Very common side effects
These 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 painlack of energy, feeling weak or tired
- changes in hair colour
- unusual hair loss or thinning
- loss of skin pigment
- skin rash where the skin may peel
- 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 effect 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
These may affect **up to 1 in 10** people:
- indigestion, bloating, flatulence
- nose bleed
- dry mouth or mouth ulcers
- infections
- abnormal drowsiness
- difficulty in 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
- lung collapses and air gets 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:
- under-active thyroid gland
- abnormal liver function
- increase in *bilirubin* (a substan*ce produce*d 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
These may affect **up to 1 in 100** people:
- stroke
- temporary fall in blood supply to the brain (mini-stroke)
- interruption of blood supply to part of the heart or heart attack (*myocardial infarction*)
- blood clots accompanied by a decrease in red blood cells and cells involved in clotting. 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, gullet 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
- 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
These may affect **up to 1 in 1,000** people:
- inflammation of the lung *(pneumonitis)*

Reporting of side effects
If you get any side effects, **talk to your doctor or pharmacist**. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Votrient

Keep this medicine out of the sight and reach of children.

Do not use Votrient after the expiry date (EXP) which is stated on the bottle and the carton. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Votrient contains
The active substance in Votrient is pazopanib (as hydrochloride). Votrient tablets come in different strengths.
Votrient 200 mg: each tablet contains 200 mg pazopanib.
Votrient 400 mg: each tablet contains 400 mg pazopanib.

The other ingredients in the 200 mg and 400 mg tablets are: hypromellose, macrogol 400, magnesium stearate, microcrystalline cellulose, polysorbate 80, povidone (K30), sodium starch glycolate (type A), titanium dioxide (E171). The 200 mg tablets also contain iron oxide red (E172).

What Votrient looks like and contents of the pack
Votrient 200 mg film-coated tablets are capsule-shaped, pink with GS JT marked on one side. They are supplied in bottles of 30 or 90 tablets.

Votrient 400 mg film-coated tablets are capsule-shaped, white with GS UHL marked on one side. They are supplied in bottles of 30 or 60 tablets.

Not all pack sizes or tablet strengths may be available in your country.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.