NOVARTIS

VOTRIENT™
Antineoplastic agents – Protein kinase inhibitor

DESCRIPTION AND COMPOSITION

Pharmaceutical forms(s)

Film-coated tablet

200mg Tablet: Modified capsule-shaped, pink; with GS JT debossed on one side.

400mg Tablet: Modified capsule-shaped, white; with GS UHL debossed on one side.

Active substance(s)

Each 200 mg tablet contains 216.7 mg of pazopanib hydrochloride, which is equivalent to 200 mg of pazopanib as free base.

Each 400 mg tablet contains 433.4 mg of pazopanib hydrochloride, which is equivalent to 400 mg of pazopanib as free base.

Excipients

Tablet core

Magnesium stearate; microcrystalline cellulose; povidone (K30); sodium starch glycollate

Tablet coating

200 mg (Opadry Pink): Hypromellose; Iron Oxide Red (E172); Macrogol / PEG 400; Polysorbate 80; Titanium dioxide (E171)

400 mg (Opadry White): Hypromellose; Macrogol / PEG 400; Polysorbate 80; Titanium dioxide (E171)

CLINICAL INFORMATION

Indications

Renal cell carcinoma (RCC)

VOTRIENT is indicated 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 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 Clinical Studies*).

Dosage Regimen and Administration

Dosage Regimen

General target population

The recommended dose of VOTRIENT is 800 mg orally once daily. (see Method of administration)

Dose Modifications

Initial dose reduction should be from 800 mg to 400 mg daily. Subsequent dose modification, either an increase or decrease in dose, should be in 200 mg increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions. The daily dose of VOTRIENT should not exceed 800 mg.

CYP3A4 inhibitor: The concomitant use of strong CYP3A4 inhibitors may increase pazopanib concentrations and should be avoided (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). If co-administration of a strong CYP3A4 inhibitor is warranted a dose reduction to 400 mg of VOTRIENT is recommended based on pharmacokinetic studies. This dose is predicted to adjust the pazopanib AUC to the range observed without inhibitors (*see Interactions*). However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors.

Special populations

- **Pediatric patients (below 18 years)**

Votrient is not recommended for use in children and adolescents under 18 years (*see Warnings and Precautions, Pre-Clinical Safety Data*).

- **Geriatric patients (above 65 years)**

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.

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

- **Renal impairment**

Renal impairment is not expected to have a clinically relevant effect on Votrient pharmacokinetics given the low renal excretion of pazopanib and metabolites (see section CLINICAL PHARMACOLOGY, Pharmacokinetics, Elimination). Renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary in patients with creatine clearance $\geq$ 30 mL/min. There is no experience of VOTRIENT in patients with severe renal impairment or in patients undergoing peritoneal dialysis or hemodialysis; therefore, use of VOTRIENT is not recommended in these patients.

- **Hepatic impairment**

The safety and pharmacokinetics of VOTRIENT in patients with pre-existing hepatic impairment have not been fully established (*see Warnings and Precautions*).

No dose adjustment is required in patients with mild hepatic impairment as defined by alanine

aminotransferase (ALT) and bilirubin (*see Clinical Pharmacology*).

The dose of VOTRIENT should be reduced to 200 mg per day in patients with moderate hepatic impairment. (see section Clinical pharmacology)

Administration of VOTRIENT to patients with mild or moderate hepatic impairment should be undertaken with caution and close monitoring due to potentially increased exposure to the medicinal product. There are insufficient data in patients with severe hepatic impairment (total bilirubin > 3 times the upper limit of normal [X ULN] regardless of the ALT value), therefore, use of VOTRIENT is not recommended in these patients.

Method of administration

Votrient should be taken without food (at least one hour before or two hours after a meal) (see sections Interactions and Clinical Pharmacology). Votrient should be taken whole with water and must not be broken or crushed (see section CLINICAL PHARMACOLOGY, Pharmacokinetics). If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.

Contraindications

VOTRIENT is contraindicated in patients with severe hepatic impairment and hypersensitivity to any of the ingredients.

Warnings and Precautions

Hepatic Effects: Cases of hepatic failure (including fatalities) have been reported during use of VOTRIENT. In clinical trials with VOTRIENT, increase in serum transaminases (ALT, aspartate aminotransferase [AST]) and bilirubin were observed (*see Adverse Reactions*). 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 a greater risk for ALT > 3 X ULN. Patients who carry the HLA-B*57:01 allele also have an increased risk of VOTRIENT-associated ALT elevations. Liver function should be monitored in all subjects receiving VOTRIENT, regardless of genotype or age (see Clinical Pharmacology). The vast majority (over 90 %) of all transaminase elevations of any grade occurred in the first 18 weeks. Grades are based on the National Cancer Institute Common Terminology Criteria for Adverse
Events, Version 3 (NCI CTCAE).

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

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

- Patients with isolated ALT elevations between 3 X ULN and 8 X ULN may be continued on VOTRIENT with weekly monitoring of liver function until ALT return to Grade 1 (NCI CTCAE) or baseline.

- Patients with ALT of > 8 X ULN should have VOTRIENT interrupted until they return to Grade 1 (NCI CTCAE) or baseline. If the potential benefit of reinitiating VOTRIENT treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce VOTRIENT at a reduced dose of 400 mg once daily and perform serum liver tests weekly for 8 weeks (*see Dosage*

Regimen and Administration). Following reintroduction of VOTRIENT, if ALT elevations > 3 X ULN recur, then VOTRIENT should be permanently discontinued.

- If ALT elevations > 3 X ULN occur concurrently with bilirubin elevations > 2 X ULN, VOTRIENT should be permanently discontinued. Patients should be monitored until return to Grade 1 (NCI CTCAE) or baseline. VOTRIENT is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinemia, known or suspected Gilbert's syndrome, and elevation in ALT > 3 X ULN should be managed as per the recommendations outlined for isolated ALT elevations.

Concomitant use of VOTRIENT and simvastatin increases the risk of ALT elevations (*see Interactions*) and should be undertaken with caution and close monitoring.

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

Hypertension: In clinical studies with VOTRIENT, events of hypertension including hypertensive crisis have occurred. Blood pressure should be well controlled prior to initiating VOTRIENT. Patients should be monitored for hypertension early after starting treatment (no longer than one week after starting VOTRIENT) and frequently thereafter to ensure blood pressure control, and treated promptly with a combination of standard anti-hypertensive therapy and VOTRIENT dose reduction or interruption as clinically warranted (*see Dosage and Administration, Adverse Reactions)*. VOTRIENT treatment may be resumed once hypertension is appropriately controlled. Hypertension (systolic blood pressure ≥ 150 or diastolic blood pressure ≥ 100 mm Hg) occurs early in the course of VOTRIENT treatment (approximately 40 % of cases occurred by Day 9 and approximately 90 % of cases occurred in the first 18 weeks). VOTRIENT should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persists despite anti-hypertensive therapy and VOTRIENT dose reduction. Serious cases of artery dissection have been reported in patients using VEGFR TKIs, including VOTRIENT, with or without hypertension.

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

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

Cardiac dysfunction: The risks and benefits of Votrient should be considered before beginning therapy in patients who have pre-existing cardiac dysfunction. The safety and pharmacokinetics of Votrient in patients with moderate to severe heart failure or those with a below normal LVEF has not been studied. In clinical trials with VOTRIENT, events of cardiac dysfunction such as congestive heart failure and decreased left ventricular ejection fraction (LVEF) have occurred. In a randomised RCC trial of VOTRIENT compared with sunitinib, in subjects who had baseline and follow-up LVEF measurements, myocardial dysfunction was observed in 13% (47/362) of subjects in the VOTRIENT arm compared to 11% (42/369) of subjects in the sunitinib arm. Congestive heart

failure was observed in 0.5% of subjects in each treatment arm. In the Phase III STS clinical trial, congestive heart failure was reported in 3 out of 240 subjects (1%). In this trial decreases in LVEF in subjects who had post-baseline measurement were detected in
11% (16/140) in the VOTRIENT arm compared with 5% (2/40) in the placebo arm. Fourteen of the 16 subjects in the VOTRIENT arm had concurrent hypertension which may have exacerbated cardiac dysfunction in patients at risk (e.g., those with prior anthracycline therapy) by increasing cardiac after-load.

Blood pressure should be monitored and managed promptly using a combination of anti-hypertensive therapy and dose modification of VOTRIENT (interruption and re-initiation at a reduced dose based on clinical judgment). Patients should be carefully monitored for clinical signs or symptoms of congestive heart failure. Baseline and periodic evaluation
of LVEF is recommended in patients at risk of cardiac dysfunction.

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

Arterial thrombotic events: In clinical studies with VOTRIENT, myocardial infarctions, angina, ischaemic stroke and transient ischaemic attack were observed (*see Adverse Reactions*). Fatal events have been observed. VOTRIENT should be used with caution in patients who are at increased risk of thrombotic events or who have had a history of these events. VOTRIENT has not been studied in patients who have had an event within the previous 6 months and should not be used in those patients. A treatment decision should be made based upon the assessment of individual patient's benefit/risk.

Venous thromboembolic events: In clinical studies with VOTRIENT, venous thromboembolic events including venous thrombosis and fatal pulmonary embolus have occurred. The incidence was higher in the STS population (5%) than in the RCC population (2%).

Thrombotic microangiopathy (TMA): Thrombotic microangiopathy (TMA) has been reported in clinical trials of VOTRIENT as monotherapy, in combination with bevacizumab, and in combination with topotecan (*see Adverse Reactions*). VOTRIENT should be permanently discontinued in patients developing TMA. Reversal of effects of TMA has been observed after treatment was discontinued. VOTRIENT is not indicated for use in combination with other agents.

Hemorrhagic events: In clinical studies with VOTRIENT hemorrhagic events have been reported (*see Adverse Reactions*). Fatal hemorrhagic events have occurred. VOTRIENT has not been studied in patients who had a history of hemoptysis, cerebral hemorrhage, or clinically significant gastrointestinal hemorrhage in the past 6 months and should not be used in those patients. VOTRIENT should be used with caution in patients with significant risk of hemorrhage.

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

Gastrointestinal perforations and fistula: In clinical studies with VOTRIENT, events
of gastrointestinal (GI) perforation or fistula have occurred (*see Adverse Reactions*). Fatal

perforation events have occurred. VOTRIENT should be used with caution in patients at risk for GI perforation or fistula.

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

Hypothyroidism: In clinical studies with VOTRIENT, events of hypothyroidism have occurred (*see Adverse Reactions*). Proactive monitoring of thyroid function tests is recommended.

Proteinuria: In clinical studies with VOTRIENT, proteinuria has been reported (*see Adverse Reactions*). Baseline and periodic urinalyses during treatment are recommended and patients should be monitored for worsening proteinuria. VOTRIENT should be discontinued if the patient develops nephrotic syndrome.

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

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

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

Juvenile animal toxicity: Because the mechanism of action of VOTRIENT can severely affect organ growth and maturation during early post-natal development (*see Pre-clinical Safety Data*), VOTRIENT should not be given to human pediatric patients.

Pregnancy: Pre-clinical studies in animals have shown reproductive toxicity (*see Pregnancy*).

Based on animal reproduction studies and its mechanism of action, VOTRIENT can cause fetal harm when administered to a pregnant woman. . Pregnant women should be advised of the potential risk to a fetus. Females of reproductive potential should be advised to avoid becoming pregnant while receiving treatment with VOTRIENT (*see Pregnancy and Females and Males of Reproductive Potential*).

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 VOTRIENT (*see Interactions*). Selection of alternative concomitant medicinal products with no or minimal potential to inhibit CYP3A4 or P-gp or BCRP should be considered.

Concomitant treatment with inducers of CYP3A4 should be avoided due to risk of decreased exposure to VOTRIENT (*see Interactions*).

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

Grapefruit juice should be avoided during treatment with VOTRIENT (*see Interactions*).

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

Interactions

Drugs that inhibit or induce cytochrome P450 3A4 enzymes
In vitro studies suggested that the oxidative metabolism of VOTRIENT 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 VOTRIENT

CYP3A4, P-gp, BCRP Inhibitors:

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

Concurrent administration of VOTRIENT (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 VOTRIENT alone (400 mg once daily for 7 days). Pazopanib C_{max} and AUC increase in a less than dose proportional fashion with increasing dose over the range of 50 mg to 2000 mg. Therefore, a dose reduction to 400 mg VOTRIENT once daily in the presence of strong CYP3A4 inhibitors will, in the majority of patients, result in systemic exposure similar to that observed after administration of 800 mg VOTRIENT once daily alone. Some patients however may have systemic pazopanib exposure greater than what has been observed after administration of 800 mg VOTRIENT alone.

Co-administration of VOTRIENT with strong inhibitors of the CYP3A4 family (e.g. ketoconazole, 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.

Concomitant use of VOTRIENT with a strong CYP3A4 inhibitor should be avoided. Ifno medically acceptable alternative to a strong CYP3A4 inhibitor is available, the dose of VOTRIENT should be reduced to 400 mg daily during concomitant administration (*see Warnings and Precautions*). Further dose reduction may be considered if possible drug- related adverse events are observed.

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 system (CNS).

Combination with strong CYP3A4, P-gp or BCRP inhibitors should therefore be avoided, or selection of an alternate concomitant medication with no or minimal potential toinhibit CYP3A4, P-gp or BCRP is recommended.

CYP3A4, P-gp, BCRP Inducers:

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

Effects of Votrient on other medicinal products

In vitro studies with human liver microsomes showed that Votrient 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 Votrient 800 mg once daily, have demonstrated that Votrient 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. Votrient resulted in an increase of approximately 30% in the mean AUC and C_{max} of midazolam (CYP3A4 probe substrate) and increases of 33% to 64% in the ratio of dextromethorphan to dextrophan concentrations in the urine after oral administration of dextromethorphan (CYP2D6 probe substrate). Co-administration of Votrient 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* C_{max} values, Votrient metabolites GSK1268992 and GSK1268997 may contribute to the net inhibitory effect of Votrient towards BCRP. Furthermore, inhibition of BCRP and P-gp by Votrient in the gastrointestinal tract cannot be excluded. Care should be taken when Votrient is co-administered with other oral BCRP and P-gp substrates.

In vitro, Votrient inhibited human organic anion transporting polypeptide (OATP1B1). It cannot be excluded that Votrient will affect the pharmacokinetics of substrates of OATP1B1 (e.g. rosuvastatin).

Effects of VOTRIENT on other enzymes and transporters

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

Effect of concomitant use of VOTRIENT and simvastatin

Concomitant use of VOTRIENT and simvastatin increases the incidence of ALT elevations. Across monotherapy studies with VOTRIENT, ALT > 3xULN was reported in 126 / 895 (14 %) of patients who did not use statins, compared with 11/41 (27 %) of patients who had concomitant use of simvastatin ($p = 0.038$). If a patient receiving concomitant simvastatin develops ALT elevations, follow guidelines for VOTRIENT posology and discontinue simvastatin (*see Warnings and Precautions*). Insufficient data are available to assess the risk of concomitant administration of alternative statins and VOTRIENT.

Drug-food/drink interactions

Administration of VOTRIENT with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C_{max}. Therefore, VOTRIENT should be administered at least 1 hour before or 2 hours after a meal (*see Dosage Regimen and Administration and Clinical Pharmacology).*

Medicines that raise gastric pH

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

Pregnancy, Lactation, Females and Males of Reproductive Potential

Pregnancy
Risk Summary

Based on animal reproduction studies and its mechanism of action, VOTRIENT can cause fetal harm when administered to a pregnant women (see section 11 Clinical pharmacology). There are no adequate data from the use of VOTRIENT in pregnant women.. In animal development toxicity studies, oral administration of pazopanib to pregnant rats and rabbit throughout organogenesis resulted in teratogenicity and abortion at systemic exposures lower than that observed at the maximum recommended human dose of 800mg/day (based on AUC). VOTRIENT should not be used during pregnancy unless the clinical condition of the woman requires treatment with VOTRIENT. Pregnant women or females of reproductive potential should be advised of the potential risk to the foetus.

Animal data

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

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

Lactation

Risk Summary

There is no information regarding the presence of pazopanib or its metabolites in human milk, or their effects on the breastfed infant, or on milk production. Because of the potential for serious adverse reactions in breastfed infants from VOTRIENT, a lactating woman should be advised not to breastfeed during treatment with VOTRIENT.

Females and Males of Reproductive Potential

Contraception

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

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

Infertility

Based on findings from animal studies, VOTRIENT may impair fertility in males and females of reproductive potential while receiving treatment. (see Non-clinical Safety Data).

Adverse Reactions

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Potentially serious adverse reactions with VOTRIENT included hepatotoxicity, QT prolongation and torsade de pointes, cardiac dysfunction, haemorrhagic events, arterial thrombotic events, gastrointestinal perforation and fistula, Reversible Posterior Leukoencephalopathy Syndrome (RPLS), hypertension, infection, increased toxicity with other cancer therapies *(see Warnings and Precautions).*

Renal Cell Carcinoma: The safety of VOTRIENT has been evaluated in 977 patients in the monotherapy studies which included 586 patients with RCC. With a median duration of treatment of 7.4 months (range 0.1 to 27.6), the most commonly observed adverse reactions (≥ 20 %) in the 586 patients were diarrhoea, hypertension, hair colour change, nausea, fatigue, anorexia and vomiting.

The data described below reflect the safety profile of VOTRIENT in 290 RCC patients who participated in a randomised, double-blind, placebo-controlled study *(see Clinical Studies)*. The median duration of treatment was 7.4 months (range 0 to 23) for patients who received VOTRIENT and 3.8 months (range 0 to 22) for the placebo arm. Forty-two percent (42 %) of patients on VOTRIENT required a dose interruption. Thirty-six percent (36 %) of patients on

VOTRIENT were dose reduced. Table 1 presents the most common adverse reactions occurring in ≥ 10 % of patients who received VOTRIENT.

Table 1. Adverse Reactions Occurring in ≥ 10 % of Patients with RCC who Received VOTRIENT

	VOTRIENT (N = 290)			Placebo (N = 145)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Adverse Reactions	**%**	**%**	**%**	**%**	**%**	**%**
Diarrhoea	52	3	<1	9	<1	0
Hypertension	40	4	0	10	<1	0
Hair colour changes	38	<1	0	3	0	0
Nausea	26	<1	0	9	0	0
Decreased appetite	22	2	0	10	<1	0
Vomiting	21	2	<1	8	2	0
Fatigue	19	2	0	8	1	1
Asthenia	14	3	0	8	0	0
Abdominal pain	11	2	0	1	0	0
Headache	10	0	0	5	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Asymptomatic bradycardia was seen more frequently in pazopanib than in placebo based on calculation of heart rates.

Other adverse reactions observed more commonly in patients treated with VOTRIENT than placebo and that occurred in < 10 % (any grade) were alopecia (8 % versus < 1 %), chest pain (5 % versus 1 %), dysgeusia (altered taste) (8 % versus < 1 %), dyspepsia (5 % versus < 1 %), facial oedema (1 % versus 0 %), dysphonia (4 % versus < 1 %), palmar- plantar erythrodysaesthesia (hand-foot syndrome) (6 % versus < 1 %), proteinuria (9 % versus 0 %), rash (8 % versus 3 %), skin depigmentation (3 % versus 0 %) and weight decreased (9 % versus 3 %).

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

Table 2 presents the most common laboratory abnormalities occurring >10% of patients who received VOTRIENT and more commonly (≥5%) in patients who received VOTRIENT versus placebo.

Table 2. Selected Laboratory Abnormalities Occurring in >10% of Patients with RCC who Received VOTRIENT and More Commonly (≥5%) in Patients who Received VOTRIENT Versus Placebo

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

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Soft Tissue Sarcoma: The safety of VOTRIENT has been evaluated in 382 patients with advanced soft tissue sarcoma, with a median duration of treatment of 3.6 months (range 0 to 53). The most commonly observed adverse reactions (≥20%) in the 382 patients were fatigue, diarrhea, nausea, decreased weight, hypertension, decreased appetite, vomiting, tumor pain, hair color changes, musculoskeletal pain, headache, dysgeusia, dyspnea, and skin hypopigmentation.

The data described below reflect the safety profile of VOTRIENT in 240 patients who participated in a randomized, double-blind, placebo-controlled trial *[see Clinical Studies (14.2)]*. The median duration of treatment was 4.5 months (range 0 to 24) for patients who received VOTRIENT and 1.9 months (range 0 to 24) for the placebo arm. Fifty-eight percent of patients on VOTRIENT required a dose interruption. Thirty-eight percent of patients on VOTRIENT had their dose reduced. Fourteen percent of patients who received VOTRIENT discontinued therapy due to adverse reactions. Table 3 presents the most common adverse reactions occurring in ≥10% of patients who received VOTRIENT.

Table 3. Adverse Reactions Occurring in ≥10% of Patients with STS who Received VOTRIENT

	VOTRIENT			Placebo		
	(N = 240)			(N = 123)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Adverse Reactions	%	%	%	%	%	%
Fatigue	65	13	1	48	4	1
Diarrhea	59	5	0	15	1	0
Nausea	56	3	0	22	2	0
Weight decreased	48	4	0	15	0	0
Hypertension	42	7	0	6	0	0
Appetite decreased	40	6	0	19	0	0
Hair color changes	39	0	0	2	0	0
Vomiting	33	3	0	11	1	0
Tumor pain	29	8	0	21	7	2
Dysgeusia	28	0	0	3	0	0
Headache	23	1	0	8	0	0
Musculoskeletal pain	23	2	0	20	2	0
Myalgia	23	2	0	9	0	0
Gastrointestinal pain	23	3	0	9	4	0
Dyspnea	20	5	<1	17	5	1
Exfoliative rash	18	<1	0	9	0	0
Cough	17	<1	0	12	<1	0
Peripheral edema	14	2	0	9	2	0
Mucositis	12	2	0	2	0	0
Alopecia	12	0	0	1	0	0
Dizziness	11	1	0	4	0	0
Skin disorder[b]	11	2	0	1	0	0
Skin hypopigmentation	11	0	0	0	0	0
Stomatitis	11	<1	0	3	0	0
Chest pain	10	2	0	6	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

[b] 27 of the 28 cases of skin disorder were palmar-plantar erythrodysesthesia.

Other adverse reactions observed more commonly in patients treated with VOTRIENT that occurred in ≥5% of patients and at an incidence of more than 2% difference from placebo included insomnia (9% versus 6%), hypothyroidism (8% versus 0), dysphonia (8% versus 2%), epistaxis (8% versus 2%), left ventricular dysfunction (8% versus 4%), dyspepsia (7% versus 2%), dry skin (6% versus <1%), chills (5% versus 1%), vision blurred (5% versus 2%), and nail disorder (5% versus 0%).

Table 4 presents the most common laboratory abnormalities occurring in >10% of patients who received VOTRIENT and more commonly (≥5%) in patients who received VOTRIENT versus placebo.

Table 4. Selected Laboratory Abnormalities Occurring in >10% of Patients with STS who Received VOTRIENT and More Commonly (≥5%) in Patients who Received VOTRIENT Versus Placebo

	VOTRIENT (N = 240)			**Placebo (N = 123)**		
	All Grades[a]	**Grade 3**	**Grade 4**	**All Grades[a]**	**Grade 3**	**Grade 4**
Parameters	**%**	**%**	**%**	**%**	**%**	**%**
Hematologic						
Leukopenia	44	1	0	15	0	0
Lymphocytopenia	43	10	0	36	9	2
Thrombocytopenia	36	3	1	6	0	0
Neutropenia	33	4	0	7	0	0
Chemistry						
AST increased	51	5	3	22	2	0
ALT increased	46	8	2	18	2	1
Glucose increased	45	<1	0	35	2	0
Albumin decreased	34	1	0	21	0	0
Alkaline phosphatase increased	32	3	0	23	1	0
Sodium decreased	31	4	0	20	3	0
Total bilirubin increased	29	1	0	7	2	0
Potassium increased	16	1	0	11	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Diarrhoea: Diarrhoea occurred frequently and was predominantly mild to moderate in severity in both the RCC and STS clinical trials. Patients should be advised how to manage mild diarrhoea and to notify their healthcare provider if moderate to severe diarrhoea occurs so appropriate management can be implemented to minimise its impact.

Lipase Elevations: In a single-arm RCC trial, increases in lipase values were observed for 27 % (48/181) patients. Elevations in lipase as an adverse reaction were reported for 4 % (10/225) of patients and were Grade 3 for 6 patients and Grade 4 for 1 patient. In clinical RCC studies of VOTRIENT, clinical pancreatitis was observed in <1% (4/586) patients.

Pneumothorax: Two of 290 patients treated with VOTRIENT and no patient on the placebo arm in the randomized RCC trial developed a pneumothorax. In the randomized trial of VOTRIENT for the treatment of STS, pneumothorax occurred in 3% (8/240) of patients treated with VOTRIENT and in no patients on the placebo arm.

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

Table 5: Adverse drug reactions identified during post-approval use

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

Rare	Artery dissection and artery aneurysm (including rupture) have been reported in association with VEGFR TKIs, including VOTRIENT
Skin and subcutaneous tissue disorders	
Uncommon	Skin ulcer

Overdosage

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

Symptoms and Signs

There is currently limited experience with overdosage in VOTRIENT.

Treatment

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

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group, ATC

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

Mechanism of Action (MOA)

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

Pharmacogenomics

In a pharmacogenetic meta-analysis of data from 31 clinical studies of VOTRIENT 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 Warnings and Precautions).

Absorption

Pazopanib is absorbed orally. 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_{∞} of approximately 650 ± 500 µg.h/mL was obtained. Daily dosing results in 1.23- to 4-fold increase in AUC. There was no consistent increase in AUC and C_{max} when the VOTRIENT dose increased above 800 mg once daily.

Systemic exposure to pazopanib is increased when administered with food. Administration of VOTRIENT with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C_{max}. Therefore, VOTRIENT should be administered at least 1 hour before or 2 hours after a meal (*see Dosage Regimen and Administration and Interactions*).

Administration of a single VOTRIENT 400 mg crushed tablet increased $AUC_{(0-72)}$ by 46% and C_{max} by approximately 2-fold and decreased t_{max} by approximately 1.5 hours compared to administration of the whole tablet. These results indicate that the bioavailability and the rate of pazopanib oral absorption are increased after administration of the crushed tablet relative to administration of the whole tablet. Therefore, due to this potential for increased exposure, VOTRIENT tablets should not be crushed (*see Dosage Regimen and Administration*).

Distribution

Binding of pazopanib to human plasma protein *in vivo* was greater than 99 % with no concentration dependence over the range of 10 to100 microgram/mL. *In vitro* studies suggest that pazopanib is a substrate for P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP).

Biotransformation/metabolism

Results from *in vitro* studies demonstrated that the metabolism of VOTRIENT is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8.

Elimination

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

Special Populations

Renal impairment

In a population pharmacokinetic analysis using 408 subjects with various cancers, creatinine clearance (30 to150 mL/min) did not influence clearance of pazopanib. Renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary in patients with creatine clearance ≥ 30 mL/min. (see section Dosage Regimen and Administration)

Hepatic impairment

The median steady-state pazopanib C_{max} and $AUC_{(0-24)}$ in patients with mild hepatic impairment (defined as either normal bilirubin and any degree of ALT elevations or as an elevation of bilirubin up to 1.5 X ULN regardless of the ALT value) after a once daily dose of 800 mg/day (30.9 microgram/mL, range 12.5 to47.3 and 841.8 microgram.hr/mL, range 600.4 to 1,078) are similar to the median in patients with no hepatic impairment (49.4 microgram/mL, range 17.1 to 85.7 and 888.2 microgram.hr/mL, range 345.5 to1,482) (*see Dosage Regimen and Administration*).

The maximally tolerated VOTRIENT dose (MTD) in patients with moderate hepatic impairment (defined as an elevation of bilirubin > 1.5 X to 3 X ULN regardless of the ALT values) was 200 mg once daily. The median steady-state values of Cmax (22.4 microgram/mL, range 6.4 to32.9) and AUC(0-24) (350.0 microgram.hr/mL, range 131.8 to 487.7) after administration of 200 mg VOTRIENT once daily in subjects with moderate hepatic impairment were approximately 45 % and 39 %, respectively, that of the corresponding median values after administration of 800 mg once daily in subjects with normal hepatic function (see Dosage Regimen and Administration).

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

Clinical Studies

Renal Cell Carcinoma (RCC)

The safety and efficacy of VOTRIENT in renal cell carcinoma (RCC) were evaluated in a randomised, double-blind, placebo-controlled multi-center study. Patients (N=435) with locally advanced and/or metastatic RCC were randomised to receive VOTRIENT 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 INF alpha-based therapy. The performance status (ECOG) was similar between the VOTRIENT 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 VOTRIENT 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 VOTRIENT and placebo arms, respectively) and/or prior radiotherapy (22% and 15% in the VOTRIENT 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 (first line and second line).

Table 6. Overall Efficacy Results by Independent Review Committee (IRC)

Endpoints/ Study population	VOTRIENT	Placebo	HR (95 % CI)	P value
PFS	**Median (months)**			**(one-sided)**
Overall	N=290	N=145		
	9.2	4.2	0.46 (0.34, 0.62)	<0.0000001
Treatment-naïve	N=155	N=78		
	11.1	2.8	0.40 (0.27, 0.60)	<0.0000001
Cytokine pre-treated	N=135	N=67		
	7.4	4.2	0.54 (0.35, 0.84)	<0.001
Response rate	**% (95 % CI)**			
Overall	N=290	N=145		
	30 (25.1 ,35.6)	3 (0.5, 6.4)	-	<0.001

CI: confidence interval; HR: hazard ratio; ITT: Intent-to-treat; PFS: progression free survival.

For patients who responded to treatment, the median duration of response was 58.7 weeks as per independent review. 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 VOTRIENT and placebo arms, respectively. The OS results are subject to potential bias as 54 % of patients in the placebo arm also received VOTRIENT in the extension part of this study following disease progression. Sixty-six percent of placebo patients received post-study therapy compared to 30 % of VOTRIENT patients.

No significant treatment-related difference in overall survival was noted.

In the pivotal study, the QoL assessments were based on blinded self-reported global scores from two protocol-specified questionnaires, EORTC QLQ-C30 and EuroQoL EQ-5D. Analysis was based on patients who continued on therapy in both arms, prior to progression. The assessments showed no difference between treatment with VOTRIENT or placebo ($p > 0.05$), indicating no negative effect of VOTRIENT on global quality of life

In a Phase II 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.

The safety, efficacy and quality of life of VOTRIENT 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 randomized to receive either VOTRIENT 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 VOTRIENT 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 VOTRIENT 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 7.

Table 7: Overall efficacy results (VEG108844)

Endpoint	**VOTRIENT N=557**	**Sunitinib N=553**	**HR (95 % CI)**
PFS Overall			
Median (months) (95 % CI)	8.4 (8.3, 10.9)	9.5 (8.3, 11.0)	
			1.047 (0.898,1.220)
Overall Survival Median (months) (95 % CI)	28.3 (26.0, 35.5)	29.1 (25.4, 33.1)	
			0.915[a] (0.786, 10.65)

HR = Hazard Ratio; ITT = Intent to Treat; PFS = Progression-free Survival based on independent review committee (IRC) assessment

[a] P value = 0.245 (2-sided)

Soft Tissue Sarcoma (STS)

The efficacy and safety of VOTRIENT in STS were evaluated in a pivotal phase III randomized, double-blind, placebo-controlled multi-centre trial (VEG110727). A total of 369 patients with advanced STS were randomized 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) excluding chondrosarcoma, Ewing tumours / Primitive neuroectodermal tumours (PNET), 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/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 8: 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

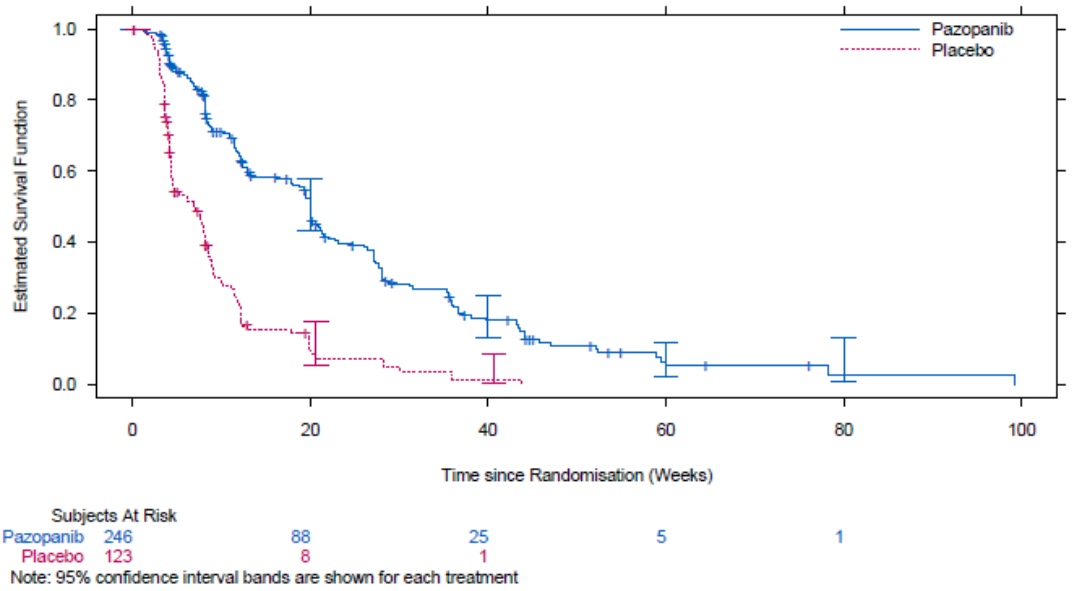
Response Rate (CR+PR)				
% (95 % CI)	4 (2.3, 7.9)	0 (0.0, 3.0)		
Duration of response				
Median (weeks) (95 % CI)	38.9 (16.7, 40.0)			

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 4: 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).

NON-CLINICAL SAFETY DATA

Carcinogenesis and Mutagenicity

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 VOTRIENT.

Pazopanib did not cause genetic damage when tested in genotoxicity assays (Ames assay, human peripheral lymphocyte chromosome aberration assay, and rat *in vivo* micronucleus assay).

Fertility

In female rats, reduced fertility (including increased pre- and post-implantation loss and early resorptions), was noted at dosages ≥ 10 mg/kg/day (approximately 0.2-fold times the human clinical exposure based on AUC at the MRHD of 800mg/day). Decreased corpora lutea were noted in monkeys given 500 mg/kg/day for up to 34 weeks, in mice given ≥ 100 mg/kg/day for 13 weeks and ovarian atrophy was noted in rats given 300 mg/kg/day for 26 weeks (approximately equal to 0.6, 1.4 and 0.9 fold the AUC at the MRHD of 800mg/day, respectively).

Pazopanib did not affect mating or fertility in male rats. However, there were reductions in sperm production rates, sperm motility and epididymal and testicular sperm concentrations observed at ≥ 100 mg/kg/day (approximately 0.5 fold the AUC at the MRHD of 800mg/day) following 15 weeks of dosing. Following 26 weeks of dosing, there were decreased testicular and epididymal weights, atrophy and degeneration of the testes with aspermia, hypospermia and cribiform change in the epididymis of male rats given doses ≥ 30 mg/kg/day (approximately 0.4 fold the AUC at the MRHD of 800mg/day).

Safety pharmacology and repeat dose toxicity

In toxicology studies in rats, there were effects in a variety of tissues (bone, teeth, bone marrow, nail beds, reproductive organs, hematological tissues, kidney, adrenal glands, lymph node, pituitary and pancreas) consistent with VEGFR inhibition and/or disruption of VEGF signalling pathways with some effects occurring at doses of 3 mg/kg/day (approximately 0.1 fold the AUC at the MRHD of 800mg/day).

Hepatic effects included mild elevations of liver transaminases in rodents and bilirubin elevations in monkeys without associated histopathology at doses that produced systemic exposures approximately 0.1 and 0.6 times the human clinical exposure, respectively.

Reproductive toxicity

For information on reproductive toxicity, see section Pregnancy, Lactation, Females and males of reproductive potential

Juvenile animal studies

In juvenile toxicity studies, when pre-weaning rats were dosed from day 9 postpartum through day 14 postpartum, pazopanib caused mortalities and abnormal organ growth/maturation in kidney, lung liver and heart, at a dose approximately 0.1 fold the AUC at the MRHD of 800mg/day. When post weaning rats were dosed from day 21 postpartum to day 62 post-partum, toxicological findings were similar to adult rats at comparable exposures with changes in bone, trachea, teeth, adrenal, pancreas, stomach, duodenum, lymph node, male mammary gland and reproductive organs. In rats, weaning occurs at day 21 post partum which approximately equates to a human paediatric age of 2 years. Human paediatric patients are at increased risk for bone and teeth effects as compared to adults, as these changes, including shortened limbs, were present in juvenile

rats at ≥ 10 mg/kg/day (equal to approximately 0.1-0.2 fold the AUC at the MRHD of 800 mg/day) (*see Warnings and Precautions*).

PHARMACEUTICAL PARTICULARS

Special Precautions for Storage

See folding box

Votrient should not be used after the date marked "EXP" on the pack.

Votrient must be kept out of the sight and reach of children both before and after use.

Nature and Contents of Container

200 mg tablet - High-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 30 or 90 tablets.

400 mg tablet - High-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 30 or 60 tablets.

Instructions for Use/Handling

There are no special requirements for use or handling of this product.

Not all presentations are available in every country.

Novartis Pharma AG, Basel, Switzerland