VOTRIENT™
Pazopanib

Qualitative and Quantitative Composition

200 mg Tablet

The 200 mg tablets contain 217 mg of pazopanib hydrochloride, equivalent to 200 mg of pazopanib free base. Modified capsule-shaped, pink; with GS JT debossed on one side.

400 mg Tablet

The 400 mg tablets contain 433 mg of pazopanib hydrochloride, equivalent to 400 mg of pazopanib free base. Modified capsule-shaped, white; with GS UHL debossed on one side.

Pharmaceutical Form

Film-coated tablets

CLINICAL INFORMATION

Indications

Renal cell carcinoma (RCC)
Votrient is indicated for the treatment of patient with advanced Renal Cell Carcinoma (RCC).

Soft tissue sarcoma (STS)
Votrient is indicated for the treatment of patients with Soft Tissue Sarcoma (STS) who have received prior chemotherapy.

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

Dosage and Administration

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

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

Votrient should be taken without food (at least one hour before or 2 hours after meal) (*see Pharmacokinetics*).

Votrient should be taken whole with water and must not be broken or crushed (*see Pharmacokinetics*).

If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.

Dose modifications

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

Renal Impairment

There is no experience of Votrient in patients with severe renal impairment or in patients undergoing peritoneal dialysis or haemodialysis; therefore, use of Votrient is not recommended in these patients. Renal impairment is not expected to have a clinically relevant effect on pazopanib pharmacokinetics given the low renal excretion of pazopanib and metabolites, and dose adjustment is not necessary in patients with creatine clearance ≥ 30 ml/min (*see Elimination*).

Hepatic impairment

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

Administration of pazopanib 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.

The dose of Votrient should be reduced to 200 mg per day in patients with moderate hepatic impairment (*see Pharmacokinetics*). There are insufficient data in patients with severe hepatic impairment (total bilirubin >3 X the upper limit of normal ULN regardless of any level of ALT); therefore, use of Votrient is not recommended in these patients.

Children

The safety and efficacy of Votrient in children have not been established (*see Warnings and Precautions, Pre-clinical Safety Data*).

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.

Contraindications

Votrient is contraindicated in patients with hypersensitivity to any of the excipients and severe hepatic impairment.

Warnings and Precautions

Hepatic Effects

Cases of hepatic failure (including fatalities) have been reported during use of pazopanib. In clinical trials with pazopanib, increase in serum transaminases (ALT, aspartate aminotransferase [AST]) and bilirubin were observed (*see Adverse drug 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 greater risk for ALT >3 X ULN. Patients who carry the *HLA-B**57:01 allele also have an increased risk of pazopanib-associated ALT elevations. Liver function should be monitored in all subjects receiving pazopanib, regardless of genotype or age (*see Clinical Pharmacology)*.

In clinical trials with Votrient, increase in serum transaminases (ALT, aspartate aminotransferase [AST]) and bilirubin were observed (*see Adverse drug 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. 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).

Monitor serum liver tests before initiation of treatment with Votrient and at weeks 3, 5, 7 and 9. Thereafter monitor at Month 3 and at Month 4, and as clinically indicated. Periodic monitoring 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 for reinitiating Votrient treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce Votrient at a reduced dose of 400 mg once daily and measure serum liver tests weekly for 8 weeks *(see Dosage 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) 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 Votrient and simvastatin increases the risk of ALT elevations (*see Interactions*) and should be undertaken with caution and close monitoring.

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 drug reactions*). 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.

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. Permanently discontinue Votrient in patients developing PRES/RPLS.

Interstitial Lung Disease (ILD) / Pneumonitis

ILD, which can be fatal, has been reported in association with Votrient (*see Adverse drug reactions*). Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis and discontinue Votrient in patients developing ILD or pneumonitis.

Cardiac Dysfunction

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 the phase III STS clinical trials. In this trial decreases in LVEF in subjects who had post-baseline measurement were detected in 11 % (16/142) in the arm compared with 5 % (2/40) in the placebo arm. Fourteen of the 16 subjects in the 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 drug reactions*). Votrient should be used with caution in patients with a history of QT interval prolongation, patients taking antiarrythmics or other medications that may potentially prolong QT interval, or those 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.

Venous Thromboembolic Events

In clinical studies with pazopanib, 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

Thrombotic microangiopathy (TMA) has been reported in clinical trials of Votrient as monotherapy, in combination with bevacizumab, and in combination with topotecan (*see Adverse drug reactions*). Permanently discontinue Votrient 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.

Arterial Thrombotic Events

In clinical studies with Votrient, myocardial infarctions, angina, ischemic stroke and transient ischemic attack were observed (*see Adverse drug reactions*). Fatal events have been observed. Votrient should be used with caution in patients who are at increased risk for these events of thrombotic events or 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.

Haemorrhagic Events

In clinical studies with Votrient haemorrhagic events have been reported (*see Adverse drug reactions*). Votrient is not recommended in patients who had a history of haemoptysis, cerebral, or clinically significant gastrointestinal haemorrhage in the past 6 months. Votrient should be used with caution in patients with significant risk of haemorrhage.

Aneurysms and artery dissections

Artery dissections and aneurysms have been reported in association with VEGF pathway inhibitors, including Votrient (see section 7 Adverse drug 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 drug reactions*). Votrient should be used with caution in patients at risk for GI perforation or fistula.

Wound Healing

No formal studies on 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 pazopanib, events of hypothyroidism have occurred (*see Adverse drug reactions*). Proactive monitoring of thyroid function tests is recommended.

Proteinuria

In clinical studies with pazopanib, proteinuria has been reported (*see Adverse drug reactions*). Baseline and periodic urine analysis during treatment is recommended and patients should be monitored for worsening proteinuria. Pazopanib should be discontinued if the patient develops nephrotic syndrome.

Tumor lysis syndrome (TLS)

Cases of TLS, including fatal cases, have been reported in patients treated with Votrient (*see Adverse drug 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 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 regimens. Pazopanib is not indicated for use in combination with other agents.

Juvenile animal toxicity

Because the mechanism of action of pazopanib can severely affect organ growth and maturation during early post-natal development (*see Non-clinical Information*), pazopanib should not be given to human paediatric patients younger than 2 years of age.

Pregnancy

Pre-clinical studies in animals have shown reproductive toxicity (*see Non-clinical Information*).

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 avoid becoming pregnant while receiving treatment with pazopanib (*see Pregnancy and Lactation*).

Interactions

Concomitant treatment with strong inhibitors of CYP3A4, P-glycoprotein (P-gp) or breast cancer resistance protein (BRCP) should be avoided due to risk of increased exposure to pazopanib (*see Interactions*). Selection of alternative concomitant medicinal products with no or minimal potential to inhibit CYP3A4, P-gp or BRCP should be considered.

Interactions

Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes

In vitro studies suggested that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib.

CYP3A4, 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 Cmax, respectively, relative to administration of pazopanib alone (400 mg once daily for 7 days).Pazopanib Cmax and AUC increase in a less than dose proportional fashion with increasing dose over the range of 50 mg to 2000 mg. Therefore, a dose reduction to 400 mg pazopanib once daily in the presence of strong CYP3A4 inhibitors will, in the majority of patients, result in systemic exposure similar to that observed

after administration of 800 mg pazopanib once daily alone. Some patients however may have systemic pazopanib exposure greater than what has been observed after administration of 800 mg pazopanib alone.

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

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

Concomitant use of pazopanib with a strong CYP3A4 inhibitors should be avoided.

If no medically acceptable alternative to a strong CYP34A inhibitor is available, the dose of pazopanib should be reduced to 400 mg daily during concomitant administration (*see Warnings and Precautions)*. Further dose reduction may be considered if possible drug-related adverse events are observed.

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

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

Effects of Votrient *on CYP Substrates*

In vitro studies with human liver microsomes showed that pazopanib inhibited CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, and 2E1. Potential induction of human CYP3A4 was demonstrated in an *in vitro* human PXR assay. 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 dextrometrophan to dextrorphan 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 26 % and 31 % in paclitaxel AUC and C_{max}, respectively.

Effects of Votrient on Other Enzymes and Transporters

In vitro studies also showed that Votrient is a potent inhibitor of UGT1A1 and OATP1B1 with IC50 of 1.2 and 0.79 μM, 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 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 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.

Effect of Food on Votrient

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 and Administration).*

Medicines that raise gastric pH

Concomitant administration of Votrient with esomeprazole decreases the bioavailability of pazopanib by approximately 40% (AUC and Cmax), and co-administration of Votrient with medicines that increase gastric pH should be avoided.

Pregnancy and Lactation

Fertility

Votrient may impair fertility in human males and females. In female reproductive toxicity studies in rats, reduced female fertility has been observed *(see Pre-clinical Safety Data).*

Pregnancy

There are no adequate data from the use of Votrient in pregnant women. Studies in animals have shown reproductive toxicity *(see Pre-clinical Safety Data)*. The potential risk for humans is unknown. Votrient should be not be used during pregnancy unless the clinical condition of the woman requires treatment with Votrient. If Votrient is used during pregnancy, or if the patient becomes pregnant while receiving Votrient, the potential hazard to the foetus should be explained to the patient.

Women of childbearing potential should be advised to use adequate contraception during treatment and for 2 weeks after discontinuing treatment with pazopanib and to avoid becoming pregnant while receiving treatment with pazopanib *(see Warnings and Precautions)*.

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

Lactation

The safe use of Votrient during lactation has not been established. It is not known whether pazopanib is excreted in human milk. Breast feeding should be discontinued during treatment with Votrient.

Ability to perform tasks that require judgment, motor or cognitive skills

There have been no studies to investigate the effect of Votrient on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology of pazopanib. The clinical status of the patient and the adverse event profile of Votrient should be borne in mind when considering the patient's ability to perform task that require judgment, motor and cognitive skills.

Adverse drug reactions

Summary of the safety profile

The safety and efficacy of Votrient in renal cell carcinoma (RCC) were evaluated in a randomized, double-blind, placebo-controlled multi-centre study. Patients with locally advanced and/or metastatic RCC were randomized to receive Votrient 800 mg once daily (N=290) or placebo (N=145). The median duration of treatment was 7.4 months for the Votrient arm and 3.8 months for the placebo arm.

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

Tabulated summary of adverse drug reactions from clinical trials

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

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

Adverse drug reactions	Frequency classification	
	RCC VEG105192 n=290	STS VEG110727 n=240
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		
Tumour pain	♦	Very common
Blood and lymphatic system disorders		
Neutropenia	Common	♦
Thrombocytopenia	Common	♦
Endocrine disorders		
Hypothyroidism*	Common	Common
Metabolism and nutrition disorders		
Anorexia	Very common	Very common
Weight decreased	Common	Very common
Nervous system disorders		
Dizziness	♦	Very common
Dysgeusia	Common	Very common
Headache	Very common	Very common
Insomnia	♦	Common
Ischaemic stroke*	Uncommon	Uncommon
Transient ischaemic attack*	Common	♦
Cardiac disorders		
Cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure)*	Uncommon	Common
Bradycardia (asymptomatic)	Very common†	Very common†
Myocardial infarction*	Uncommon	Common
Myocardial ischaemia*	Common	♦
QT prolongation*	Common	Common
Torsade de Pointes*	Uncommon	♦
Vascular disorders		
Cerebral haemorrhage*	Uncommon	Uncommon
Epistaxis	Common	Common

Adverse drug reactions	Frequency classification	
	RCC VEG105192 n=290	STS VEG110727 n=240
Gastrointestinal haemorrhage*	Common	Common
Haematuria	Common	Uncommon
Hypertension*	Very common	Very common
Pulmonary haemorrhage*	Uncommon	Common
Venous thromboembolic events*	Common	Common
Respiratory, thoracic and mediastinal disorders		
Cough	♦	Very common
Dysphonia	Common	Common
Dyspnoea	♦	Very common
Pneumothorax	♦	Common
Gastrointestinal disorders		
Abdominal pain	Very common	Very common
Diarrhoea	Very common	Very common
Dyspepsia	Common	Common
Gastrointestinal perforation*	Uncommon	♦
Gastrointestinal fistula*	Uncommon	Uncommon
Lipase elevations	Common	♦
Nausea	Very common	Very common
Stomatitis	♦	Very common
Vomiting	Very common	Very common
Hepatobiliary disorders		
Alanine aminotransferase increased*	Very common	Common
Aspartate aminotransferase increased*	Very common	Common
Hepatic function abnormal*	Common	♦
Hyperbilirubinaemia*	Common	Uncommon
Skin and subcutaneous tissue disorders		
Alopecia	Common	Very common
Dry skin	♦	Common
Exfoliative rash	♦	Very common
Hair depigmentation	Very common	Very common
Nail disorder	♦	Common
Palmar-plantar erythrodysaesthesia syndrome	Common	Very common
Rash	Common	Uncommon
Skin depigmentation	Common	Very common
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	♦	Very common
Myalgia	♦	Very common
Renal and urinary disorders		
Proteinuria*	Common	Uncommon
General disorders and administration site disorders		
Asthenia	Very common	Uncommon
Chest pain*	Common	Very common
Chills	♦	Common
Fatigue	Very common	Very common
Oedema peripheral	♦	Very common
Vision blurred	♦	Common

** See Warnings and Precautions for additional information.*

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

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

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

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

Table-2 presents laboratory abnormalities occurring in ≥ 15 % of patients who received Votrient in the pivotal RCC studies. Grades are base on the NCI CTCAE.

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

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

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

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

Parameters	VOTRIENT (N = 240)			Placebo (N = 123)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Haematological						
Leukopenia	44	1	0	15	0	0
Neutropenia	33	4	0	7	0	0
Thrombocytopenia	36	3	<1	6	0	0
Lymphocytopenia	43	10	0	36	9	2
Anaemia	27	5	2	23	<1	<1
Chemistry						
ALKP increased	32	3	0	23	<1	0
ALT increased	46	8	2	18	2	<1
AST increased	51	5	3	22	2	0
Albumin decreased	34	<1	0	21	0	0
Glucose increased	45	<1	0	35	2	0
Total Bilirubin increased	29	1	0	7	2	0
Sodium decreased	31	4	0	20	3	0
Potassium increased	16	1	0	11	0	0

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

Table 14 Adverse drug reactions identified during post-approval use

Infections and infestations	
Common	Infections (with or without neutropenia); see Warnings and precautions
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	
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)
Eye disorders	
Uncommon	Retinal detachment/tear
Respiratory, thoracic and mediastinal disorders	
Rare	Interstitial lung disease (ILD)/pneumonitis (see Warnings and precautions)
Gastrointestinal disorders	
Common	Flatulence
Uncommon	Pancreatitis

Hepatobiliary disorders	
Common	Gamma-glutamyl transpeptidase increased
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia
Common	Muscle spasms
Vascular disorders	
Rare	Aneurysms and artery dissections
Skin and subcutaneous tissue disorders	
Uncommon	Skin ulcer

Overdosage

Votrient doses up to 2,000 mg 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 centre, where available. Haemodialysis 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

Pharmacodynamics

ATC Code

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

Mechanism of Action

Votrient 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.

Pharmacokinetics

Absorption

Pazopanib is absorbed orally with median time to achieve peak concentrations of 2.0 to 4.0 hours after the dose. Daily dosing results in 1.23- to 4-fold increase in AUC. There was no consistent increase in AUC and Cmax when the Votrient dose increased above 800 mg.

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

Administration of a single Votrient 400 mg crushed tablet increased AUC (0-72) by 46% and Cmax by approximately 2 fold and decreased tmax 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 increase after administration of the crushed tablet relative to administration of the whole tablet Therefore, due to this potential for increased exposure, tablets should not be crushed (*see Dosage and Administration*).

Distribution

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

Metabolism

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

Elimination

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

Special population

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

Hepatic impairment:
The median steady-state pazopanib C_{max} and $AUC_{(0-24)}$ in patients with mild hepatic impairment (defined as either normal bilirubin and any degree of ALT elevations or as an elevation of bilirubin up to 1.5 x ULN regardless of the ALT value) after a once daily dose of 800 mg/day (30.9 µg/ml, range 12.5-47.3 and 841.8 µg.hr/ml, range 600.4-1078) are similar to the median in patients with no hepatic impairment (49.4 µg/ml, range 17.1-85.7 and 888.2 µg.hr/ml, range 345.5-1482) (*see Dosage and Administration*).

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

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

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).*

Clinical Studies

Renal Cell Carcinoma (RCC)

The safety and efficacy of Votrient in renal cell carcinoma (RCC) were evaluated in a randomized, double-blind, placebo-controlled multi-centre study. Patients (N= 435) with locally advanced and/or metastatic RCC were randomized 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 INFα-based therapy. The performance status (ECOG) was similar between the Votrient and placebo groups (ECOG 0: 42 % vs. 41 %, ECOG 1: 58 % vs. 59 %). 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-5 Overall Efficacy Results by Independent Review Committee (IRC)(VEG105192)

Endpoints/ Study population	**VOTRIENT**	**Placebo**	**HR (95 % CI)**	**P value (one-sided)**
PFS	**Median (months)**			
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 30 (25.1 ,35.6)	N=145 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 randomized 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.

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 impact of Votrient on global quality of life. 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.

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 randomized 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 6.

Table 6: Overall efficacy results (VEG108844)

Endpoint	**Pazopanib** 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, 1.065)

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 safety and efficacy of Votrient in STS were evaluated in a randomized, double-blind, placebo-controlled multi-centre study. Patients (N=369) with advanced STS who had received prior chemotherapy, including anthracycline treatment, or were unsuited for such therapy, were randomized to receive Votrient 800 mg once daily or placebo.

Prior to randomization, eligible subjects 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 were a slightly greater percentage of subjects in the 2+ lines of prior systemic therapy for advanced disease (58 % and 55 % respectively for placebo and Votrient treatment arms) compared with 0 or 1 lines of prior systemic therapy (42 % and 45 % respectively for placebo and Votrient treatment arms). There were slightly more subjects with a WHO PS of 1 at baseline. 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 Votrient [range 0.2 to 24.3 months].

The primary objective of the study was to evaluate and compare the two treatment arms for progression-free survival (PFS), based on the ITT population, and the principle secondary endpoint is overall survival (OS).

The initial analysis of the primary endpoint PFS was based on disease assessment by independent radiological review in the entire ITT study population.

Table-7: Overall efficacy results in STS by independent assessment (VEG110727)

Endpoints/Study Population	VOTRIENT	Placebo	HR (95% CI)	P value (one-sided)
PFS				
Overall* ITT	N = 246	N = 123		
Median (weeks)	20.0	7.0	0.35 (0.26, 0.48)	< 0.001
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)	-	-	-
PFS				
Leiomyosarcoma	N = 109	N = 49		
Median (weeks)	20.1	8.1	0.37 (0.23, 0.60)	< 0.001
Synovial sarcoma	N = 25	N = 13		
Median (weeks)	17.9	4.1	0.43 (0.19, 0.98)	0.005
'Other' STS	N = 112	N = 61		
Median (weeks)	20.1	4.3	0.39 (0.25, 0.60)	< 0.001

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

Similar to the assessments by independent radiology review, a clinically meaningful and statistically significant improvement in PFS based on investigator assessments was observed in the Votrient arm compared with the placebo arm (HR: 0.39; 95 % CI, 0.30 to 0.52, p <0.001).

The hazard ratio at the pre-specified interim analysis for overall survival in favour of Votrient was not statistically significant; the median overall survival in the placebo arm was 10.4 months (95 % CI 8.7 to 12.7) and was 11.9 months (95 % CI 10.7 to 15.1) in the Votrient arm; HR = 0.82 (97.87 % CI: 0.59 to 1.14, p = 0.156).

Non-Clinical Safety Data

Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

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).

In female rats, reduced fertility including increased pre- and post-implantation loss, early resorptions, were noted at dosages ≥ 10 mg/kg/day (approximately 0.3 times the human clinical exposure based on AUC). 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, 2.2 and 1.4 times the human clinical exposure based on AUC, 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 0.8 times the human clinical exposure based on AUC) 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 0.6 times the human clinical exposure based on AUC).

Pazopanib produced foetal teratogenic effects (including cardiovascular malformations and delayed ossification), reduced foetal body weight, and embryo lethality in rats at a dose level of ≥ 3 mg/kg/day (approximately 0.1 times the human clinical exposure based on AUC). In rabbits, maternal toxicity (body weight loss, reduced food consumption, and abortion) were observed at doses ≥ 30 mg/kg/day (approximately 0.6 times the human clinical exposure based on AUC), while foetal weight was reduced at doses ≥ 3 mg/kg/day. (*see Pregnancy and Lactation, Warnings and Precautions*).

Animal Toxicology and/or Pharmacology

In toxicology studies in rats, there were effects in a variety of tissues (bone, teeth, bone marrow, nail beds, reproductive organs, haematological 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 times the human clinical exposure based on AUC).

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.

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 adults. 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 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 postpartum which approximately equates to a human paediatric age of 2 years. Human pediatric 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 times the clinical exposure based on AUC in adults) (*see Warnings and Precautions*).

Pharmaceutical Particulars

List of Excipients

Tablet Core – 200 mg and 400 mg
Magnesium stearate, Microcrystalline cellulose, Povidone (K30), Sodium starch glycollate.

Tablet film-coat - 200 mg (Opadry Pink)
Hypromellose, Iron Oxide Red (E172), Macrogol / PEG 400, Polysorbate 80, Titanium dioxide (E171).

Tablet film-coat 400 mg (Opadry White)
Hypromellose, Macrogol / PEG 400, Polysorbate 80, Titanium dioxide (E171).

Incompatibilities

No known incompatibilities.

Shelf-Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Do not store above 30°C.

Nature and Contents of Container

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

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

Instructions for Use/Handling

No relevant information

Not all presentations are available in every country.

Votrient Tablet 200 mg, Box, Bottle @ 30 tablet Reg. No. DKI1691601117A1
Votrient Tablet 400 mg, Box, Bottle @ 60 tablet Reg. No. DKI1691601117B1

HARUS DENGAN RESEP DOKTER

Manufactured by

Glaxo Operation UK Limited (trading as Glaxo Wellcome Operation)* Ware, UK, for Novartis Pharma AG, Basel, Switzerland

Packed and Released by

Glaxo Wellcome S.A*, Aranda, Spain for Novartis Pharma AG, Basel, Switzerland

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Imported by

PT Novartis Indonesia
Jakarta, Indonesia

Leaflet based on CDS ~~25-Nov-2019~~03 June 2021