

DATA SHEET

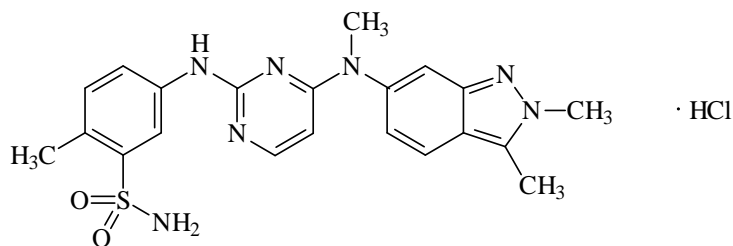
VOTRIENT[®] TABLETS

NAME OF THE MEDICINE

VOTRIENT[®] (Pazopanib hydrochloride)

Pazopanib is a member of the tyrosine kinase inhibitor family. It is supplied as the hydrochloride salt, with chemical name 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride.

The structural formula is:



Pazopanib hydrochloride is a white to slightly yellow solid. It is very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media.

Molecular formula: C₂₁H₂₃N₇O₂S•HCl

Molecular weight: 473.99 g/mol.

CAS number: 635702-64-6

DESCRIPTION

Each film-coated tablet contains pazopanib hydrochloride equivalent to either 200 mg or 400 mg of pazopanib free base.

Each film-coated tablet also contains magnesium stearate, cellulose - microcrystalline, povidone, sodium starch glycolate, hypromellose, macrogol 400, titanium dioxide, polysorbate 80, and iron oxide red C177491 (200 mg tablet only).

PHARMACOLOGY

Mechanism of Action

Pazopanib is an orally administered, potent multi-target tyrosine kinase inhibitor (TKI) of Vascular Endothelial Growth Factor Receptors (VEGFR)-1, -2, and -3, platelet-derived growth factor receptor (PDGFR)- α 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 VEGF-2, c-Kit and PDGF- 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 C_{max} when the pazopanib dose increased above 800 mg.

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

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

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 \geq 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 μ g/ml, range 12.5-47.3 and 841.8 μ g.hr/ml, range 600.4-1078) are similar to the median in patients with no hepatic impairment (49.4 μ g/ml, range 17.1-85.7 and 888.2 μ g.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 μ g/ml, range 6.4-32.9) and $AUC_{(0-24)}$ (350.0 μ g.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.

CLINICAL TRIALS

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 monotherapy 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 α -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 1. Overall Efficacy Results by Independent Review Committee (IRC)

Endpoints/ Study population	VOTRIENT	Placebo	HR (95% CI)	P value (one-sided)
PFS	Median (months)			
Overall ITT	N=290 9.2	N=145 4.2	0.46 (0.34, 0.62)	<0.0000001
Treatment-naïve	N=155 11.1	N=78 2.8		
Cytokine pre-treated	N=135 7.4	N=67 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.

Figure 1 Kaplan-Meier Curve for Progression-Free Survival by Independent Assessment for the Overall Population (Treatment-Naïve and Cytokine Pre-Treated Populations)

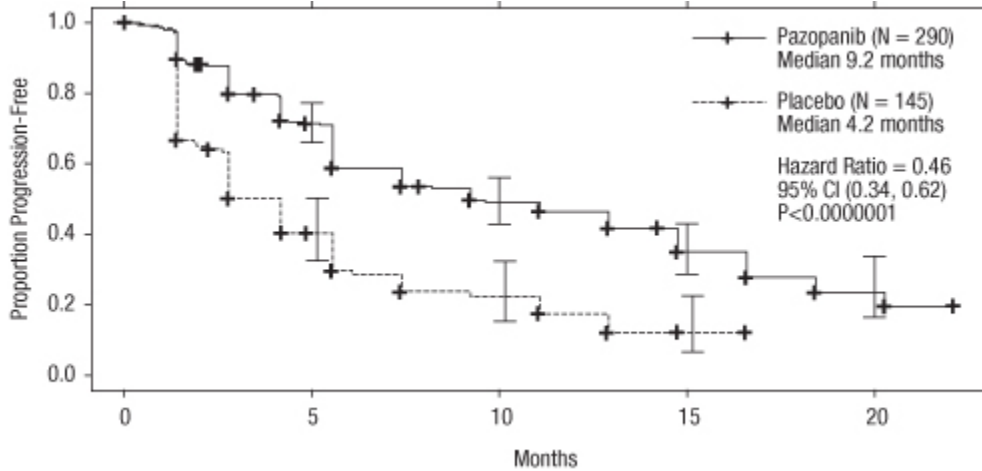


Figure 2 Kaplan-Meier Curve for Progression-Free Survival by Independent Assessment for the Treatment-Naïve Population

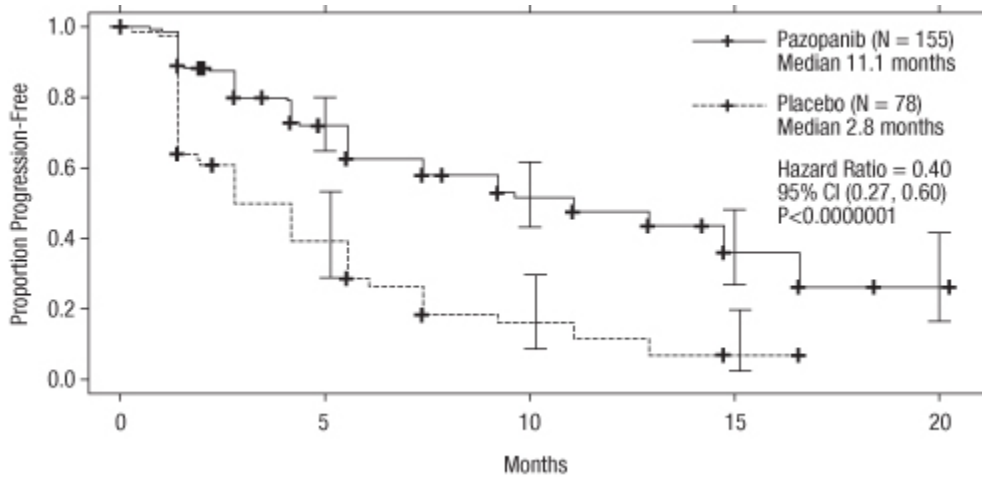
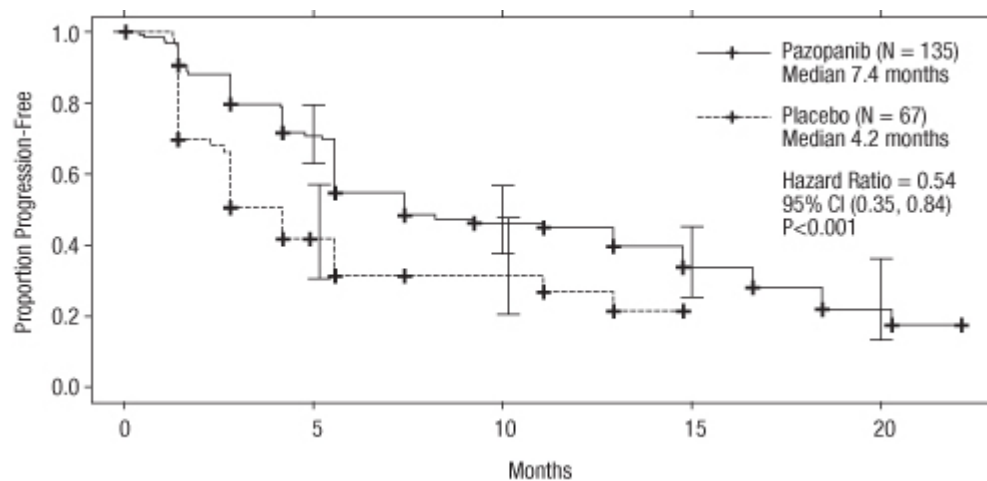


Figure 3 Kaplan-Meier Curve for Progression-Free Survival by Independent Assessment for the Cytokine Pre-Treated Population



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

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. Median PFS was 11.9 months.

INDICATIONS

VOTRIENT is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (RCC).

CONTRAINDICATIONS

VOTRIENT is contraindicated in patients with hypersensitivity to the active substance pazopanib hydrochloride or to any of the excipients (*see Description*).

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, AST) and bilirubin were observed (see *Adverse Events*). In the majority of the cases, isolated increases in ALT and AST have been reported, without concomitant elevations of alkaline phosphatase or bilirubin. The vast majority (92.5%) 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 least once every 4 weeks for at least the first 4 months of treatment, and as clinically indicated. Periodic monitoring should then continue after this time period.

The following guidelines are provided for patients with baseline values of total bilirubin $\leq 1.5 \times$ ULN and AST and ALT $\leq 2 \times$ ULN.

- Patients with isolated ALT elevations between $3 \times$ ULN and $8 \times$ ULN may be continued on VOTRIENT with weekly monitoring of liver function until ALT returns to Grade 1 (NCI CTCAE) or baseline.
- Patients with ALT of $> 8 \times$ 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 (400 mg daily) and measure serum liver tests weekly for 8 weeks (see *Dosage and Administration*). Following reintroduction of VOTRIENT, if ALT elevations $> 3 \times$ ULN recur, then VOTRIENT should be permanently discontinued.
- If ALT elevations $> 3 \times$ ULN occur concurrently with bilirubin elevations $> 2 \times$ 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 $> 3 \times$ 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 pazopanib once daily and reducing the initial starting dose to 200mg 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 pazopanib, 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 Events*). 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.

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.

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 judgement). 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 Events*). VOTRIENT should be used with caution in patients with a history of QT interval prolongation, patients taking antiarrhythmics 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.

Arterial Thrombotic Events: In clinical studies with VOTRIENT, myocardial infarctions, angina, ischemic stroke and transient ischemic attack were observed (*see Adverse Events*). 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 thrombotic events. VOTRIENT has not been studied in patients who have had an event within the previous 6 months. A treatment decision should be made based upon the assessment of individual patient's benefit/risk.

Venous Thromboembolic Events: In clinical studies with VOTRIENT, venous thromboembolic events including venous thrombosis and fatal pulmonary embolus have occurred.

Haemorrhagic Events: In clinical studies with VOTRIENT haemorrhagic events have been reported (*see Adverse Events*). Fatal haemorrhagic events have occurred. VOTRIENT has not

been studied 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.

Gastrointestinal Perforations and Fistula: In clinical studies with VOTRIENT, events of gastrointestinal (GI) perforation or fistula have occurred (*see Adverse Events*). 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 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 VOTRIENT, events of hypothyroidism have occurred (*see Adverse Events*). Proactive monitoring of thyroid function tests is recommended.

Proteinuria: In clinical studies with VOTRIENT, proteinuria has been reported (*see Adverse Events*). 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.

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

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

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

In juvenile toxicity studies, when rats were dosed from day 9 post partum through day 21 postpartum (equating to human age range of less than 2 years), 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 rats were dosed from day 21 post partum to day 62 post partum (equating to human age range of greater than 2 years), 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. 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 times the clinical exposure based on AUC in adults).

Effects on fertility

VOTRIENT may impair fertility in human males and females. In female reproductive toxicity studies in rats, reduced female fertility has been observed. Decreased corpora lutea, increased cysts and ovarian atrophy have also been noted in rodents.

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).

Use in Pregnancy (Category D)

There are no adequate data from the use of pazopanib in pregnant women.

Pazopanib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits at exposures below clinical exposure. Effects included cardiovascular malformations, delayed ossification, reduced female fertility, increased pre- and post-implantation loss, early resorptions, embryo lethality, and decreased foetal body weight. The potential risk for humans is unknown.

VOTRIENT should not be used during pregnancy unless, in the opinion of the physician, the potential benefits of treatment to the mother outweigh any possible risks to the developing foetus.

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 avoid becoming pregnant while receiving treatment with VOTRIENT.

Use in 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 judgement, 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 cannot be predicted from the pharmacology of VOTRIENT. 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.

Pre-clinical Safety Data

The preclinical safety profile of pazopanib was assessed in mice, rats, rabbits and monkeys. In repeat dose studies in rodents, effects in a variety of tissues (bone, teeth, nail beds, reproductive organs, haematological tissues, kidney and pancreas) appear related to the pharmacology of VEGFR inhibition and/or disruption of VEGF signalling pathways with most effects occurring at plasma exposure levels below those observed in the clinic. Higher exposures were not tolerated by rats in studies over 13 weeks duration, with body weight loss and morbidity secondary to pharmacologic effects. In the monkey, exposures equivalent to human exposure based on AUC resulted in diarrhoea, severe weight loss and morbidity associated with gastrointestinal effects secondary to high local mucosal drug exposure. Hepatic effects in animals have included mild elevations of liver enzymes or bilirubin without associated pathology. These enzyme changes were noted as early as 4 days, but were non-progressive in studies of 6 to 12 months duration. Female mice had proliferative hepatic lesions (eosinophilic foci and adenoma) following 13 weeks at exposures 2.5 times human exposure based on AUC.

Genotoxicity

Pazopanib did not cause genetic damage when tested in genotoxicity assays (Ames assay, human peripheral lymphocyte chromosome aberration assay and rat in vivo micronucleus). A synthetic intermediate in manufacture of pazopanib, which is also present in the final drug substance, was not mutagenic but genotoxic in the mouse lymphoma assay and in vivo mouse micronucleus assay and is controlled below a daily intake of 0.1 mg.

Carcinogenicity

Carcinogenicity studies with pazopanib have not been performed.

Interactions with other medicines

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 VOTRIENT.

CYP3A4 Inhibitors: Concurrent administration of a single dose VOTRIENT eye drops with the strong CYP3A4 inhibitor, ketoconazole, in healthy volunteers resulted in 220 % and 150 % increases in mean $AUC_{(0-t)}$ and C_{max} values, respectively.

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 may also increase plasma concentrations of VOTRIENT.

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.

Combination with strong CYP3A4 inhibitors should therefore be avoided, or selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended. A dose reduction of VOTRIENT should be considered when it must be co-administered with strong CYP3A4 inhibitors (see *Dosage and Administration*).

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 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 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/m² (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 26 % and 31 % in paclitaxel AUC and C_{max} , respectively.

Effect of concomitant use of Pazopanib and Simvastatin

Concomitant use of pazopanib and simvastatin increases the incidence of ALT elevations. Across monotherapy studies with pazopanib, 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 pazopanib posology and discontinue simvastatin (see *Precautions*). Insufficient data are available to assess the risk of concomitant administration of alternative statins and pazopanib.

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*).

ADVERSE EVENTS

Clinical Trial Data

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.

Adverse reactions are listed below by MedDRA body system organ class.

The following convention has been utilised for the classification of frequency:

Very common	≥ 1 in 10
Common	≥ 1 in 100 and < 1 in 10
Uncommon	≥ 1 in 1,000 and < 1 in 100

Categories have been assigned based on absolute frequencies in the clinical trial data.

Blood and lymphatic system disorders

<i>Common</i>	Thrombocytopenia Neutropenia
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Endocrine disorders

<i>Common</i>	Hypothyroidism
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Metabolism and nutrition disorders

<i>Very common</i>	Anorexia
<i>Common</i>	Weight decreased

Nervous system disorders

<i>Very common</i>	Headache
<i>Common</i>	Transient ischaemic attack* Dysgeusia
<i>Uncommon</i>	Ischaemic stroke*

Cardiac disorders

<i>Common</i>	Myocardial ischaemia* QT prolongation*
<i>Uncommon</i>	Torsade de Pointes* Cardiac Dysfunction (such as a decrease in ejection fraction and congestive heart failure) Myocardial infarction*

Vascular disorders

<i>Very common</i>	Hypertension*
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Haemorrhages*

<i>Common</i>	Epistaxis Haematuria
<i>Uncommon</i>	Pulmonary haemorrhage Gastrointestinal haemorrhage Cerebral haemorrhage

Respiratory, thoracic and mediastinal disorders

<i>Common</i>	Dysphonia
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Gastrointestinal disorders

<i>Very common</i>	Diarrhoea Nausea Vomiting Abdominal pain
<i>Common</i>	Dyspepsia

	Lipase elevations
<i>Uncommon</i>	Gastrointestinal perforation* Gastrointestinal fistula*

Hepatobiliary disorders*

<i>Very common</i>	Alanine aminotransferase increased Aspartate aminotransferase increased
<i>Common</i>	Hepatic function abnormal Hyperbilirubinaemia

Skin and subcutaneous tissue disorders

<i>Very common</i>	Hair depigmentation
<i>Common</i>	Rash Alopecia Skin depigmentation Palmar-plantar erythrodysesthesia syndrome

Renal and urinary disorders

<i>Common</i>	Proteinuria*
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General disorders and administration site conditions

<i>Very common</i>	Fatigue Asthenia
<i>Common:</i>	Chest pain*

**See Precautions for additional information*

Table 2 presents the incidence of very common (>10%) treatment-related adverse events for patients receiving VOTRIENT versus those on placebo.

Table 2. Treatment-related Adverse Events Reported for at least 10% of subjects who received VOTRIENT or Placebo

Adverse Event, n (%)	Number (% of subjects)					
	VOTRIENT (n = 290)			Placebo (n = 145)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any	257 (89)	74 (26)	11 (4)	56 (39)	5 (3)	1(1)
Diarrhoea	128 (44)	9 (3)	2 (<1)	9 (6)	1 (1)	0
Hair colour changes	107 (37)	1 (<1)	0	5 (3)	0	0
Hypertension	106 (37)	12 (4)	0	13 (9)	1 (1)	0
Nausea	63 (22)	2 (<1)	0	8 (6)	0	0
Anorexia	49 (17)	4 (1)	0	6 (4)	0	0
Vomiting	48 (17)	6 (2)	1 (<1)	5 (3)	1 (1)	0
Fatigue	46 (16)	5 (2)	0	2 (1)	0	0
ALT increased	43 (15)	15 (5)	2 (<1)	3 (2)	0	0
AST increase	38 (13)	9 (3)	1 (<1)	4 (3)	0	0

Table 3 presents laboratory abnormalities occurring in $\geq 15\%$ of patients who received VOTRIENT. Grades are based on the NCI CTCAE.

Table 3. Selected Laboratory Abnormalities in $\geq 15\%$ of Patients who Received VOTRIENT and More Commonly than Placebo Arm

Parameters	VOTRIENT (N = 290)			Placebo (N = 145)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Haematologic						
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

Post marketing data

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.

Infections and infestations

Uncommon Infections (with or without neutropenia)

DOSAGE AND ADMINISTRATION

The recommended dose of VOTRIENT is 800 mg orally once daily.

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

VOTRIENT should be taken whole with water and must not be broken or crushed.

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

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 dose of VOTRIENT should not exceed 800 mg.

CYP3A4 inhibitor. The concomitant use of strong CYP3A4 inhibitors may increase VOTRIENT 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 with other Medicines*). However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors.

Populations

Children

The safety and efficacy of VOTRIENT in children have not been established.

Elderly

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 Elimination*). Renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary in patients with creatine clearance ≥ 30 ml/min. There is no experience of pazopanib in patients with severe renal impairment or in patients undergoing peritoneal dialysis or haemodialysis; therefore, use of pazopanib 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 Precautions*). No dose adjustment is required in patients with mild hepatic impairment as defined by alanine aminotransferase (ALT) and bilirubin (*see Precautions*). The dose of VOTRIENT should be reduced to 200 mg per day in patients with moderate hepatic impairment).

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

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 VOTRIENT because pazopanib is not significantly renally excreted and is highly bound to plasma proteins.

PRESENTATION AND STORAGE CONDITIONS

The 200 mg tablets are modified capsule-shaped, pink, film-coated with 'GS JT' debossed on one side.

The 400 mg tablets are modified capsule-shaped, white, film-coated with 'GS UHL' debossed on one side.

Shelf-Life

24 months.

Storage

Store below 30°C.

Nature and Contents of Container

VOTRIENT 200 mg film-coated tablets are supplied in high-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 30 or 90 tablets*.

VOTRIENT 400 mg film-coated tablets are supplied in high-density polyethylene (HDPE) bottles with child resistant polypropylene closures containing 30 or 60 tablets*.

* not all pack sizes may be marketed

NAME AND ADDRESS OF THE SPONSOR:

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MEDICINE CLASSIFICATION

Prescription Medicine

DATE OF PREPARATION

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