PRODUCT INFORMATION

VOTRIENT® TABLETS

(pazopanib hydrochloride)

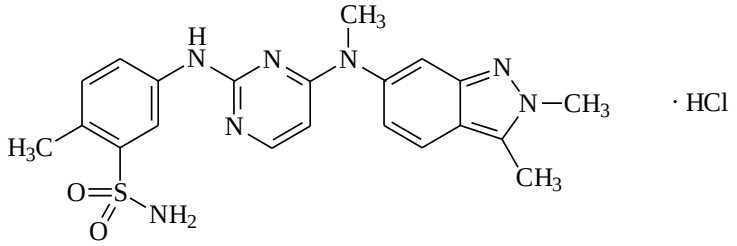
Severe and fatal hepatotoxicity has been observed in clinical studies. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. *[See PRECAUTIONS.]*

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:



Molecular formula: $C_{21}H_{23}N_7O_2S$•HCl

Molecular weight: 473.99 g/mol.

CAS number: 635702-64-6

BCS Classification: Class II (High Permeability, Low Solubility)

DESCRIPTION

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. Two basic ionisation constants (pKa) of pazopanib free base were determined to be 6.4 and 2.1, and one weakly acidic pKa was determined to be 10.2. The partition coefficient of the free base between octanol and water is 4470 (cLogP = 3.65). The pH of a 0.04% w/v solution of pazopanib hydrochloride in water is about 2.2.

VOTRIENT is supplied for oral administration in two strengths: 200 and 400 mg film-coated tablets. Each film-coated tablet contains either 217 mg or 433 mg of pazopanib hydrochloride, equivalent to either 200 mg or 400 mg of pazopanib free base respectively. The tablets also contain

the following inactive ingredients: magnesium stearate, cellulose - microcrystalline, povidone, sodium starch glycolate, hypromellose, macrogol 400, titanium dioxide, polysorbate 80, and iron oxide red CI77491 (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 (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. Pazopanib also inhibited ligand-induced auto-phosphorylation of VEGFR-2, c-Kit and PDGFR-β receptors in cells *in vitro*. *In vivo*, pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in mouse models, and the growth of some human tumour xenografts in mice.

Pharmacogenomics

In a pharmacogenetic meta-analysis of data from 31 clinical studies of pazopanib administered as either monotherapy or in combination with other agents, ALT > 5x 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 PRECAUTIONS). The incidence of pazopanib-related ALT elevation was estimated in a clinical (not pharmacogenetic) meta-analysis (study 200276) for liver safety, using data from pazopanib monotherapy clinical studies, in which ALT > 5x ULN events occurs in 11 % of the patients.

Pharmacokinetics

The pharmacokinetics of pazopanib have been evaluated in 408 patients. The reported pharmacokinetic parameters such as absolute bioavailability and clearance were obtained from only three patients.

Absorption:

Pazopanib is absorbed orally with an absolute oral bioavailability of 13.5 – 38.9 % and 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 µg/ml. After 5 mg IV administration, pazopanib displayed a volume of distribution of 9.2 – 13.1 L (< 40 % of total body water). *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.

Excretion:

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. Pazopanib plasma clearance after a 5 mg IV dose ranged from 0.206 to 0.347 L/h (approximately 0.5 % of liver blood flow and 5 % of glomerular filtration rate).

Special Populations:

Renal Impairment

In a population pharmacokinetic analysis using 408 patients 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 alanine transaminase [ALT] elevations or as an elevation of bilirubin up to 1.5 times the upper limit of normal [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 > 1.5x to 3x 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 patients with moderate hepatic impairment were approximately 45 % and 39 %, respectively, that of the corresponding median values after administration of 800 mg once daily in patients with normal hepatic function (*see* DOSAGE AND ADMINISTRATION).

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

CLINICAL TRIALS

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 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 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 1 Overall Efficacy Results in RCC by Independent Review Committee (IRC) (VEG105192)

Endpoints/ Study population	VOTRIENT	Placebo	HR (95% CI)	P value (one-sided)
PFS	**Median (months)**			
Overall ITT	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.

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

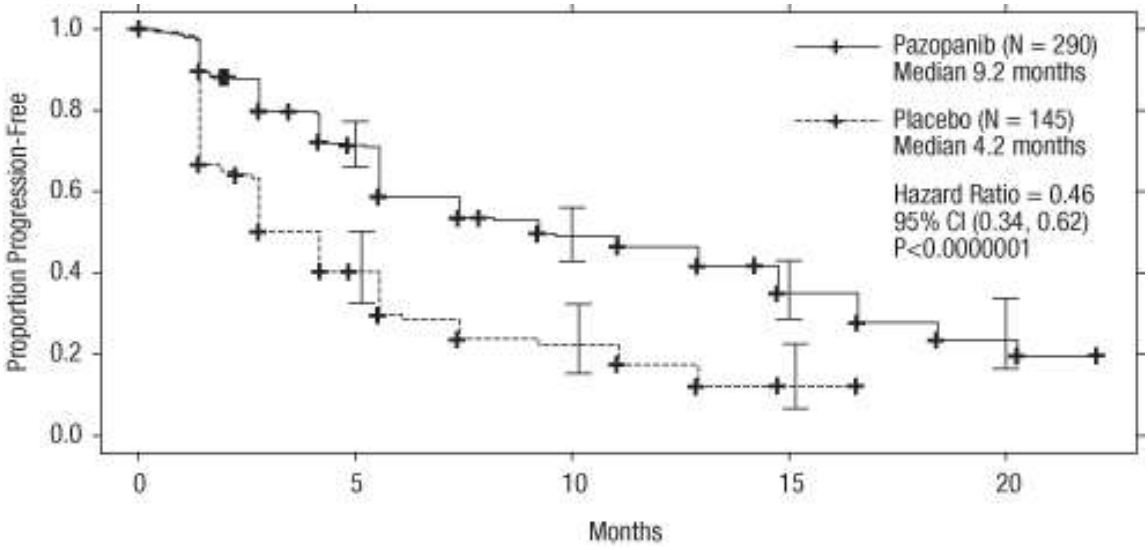


Figure 2 Kaplan-Meier Curve for Progression-Free Survival by Independent Assessment for the Treatment-Naïve Population

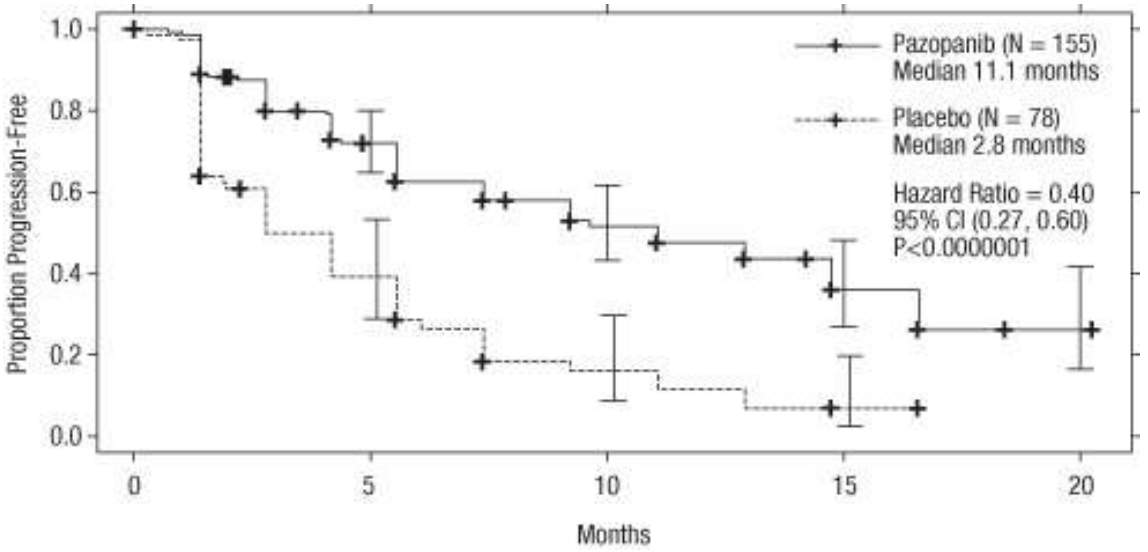
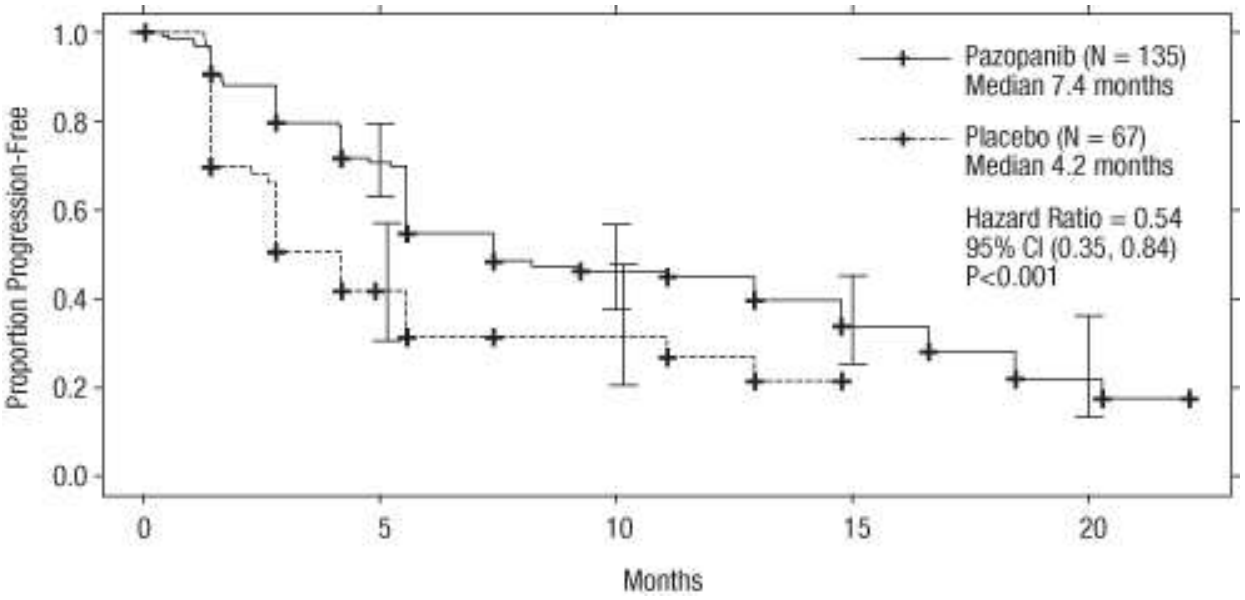


Figure 3 Kaplan-Meier Curve for Progression-Free Survival by Independent Assessment for the Cytokine Pre-Treated Population



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.

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 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.

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.

The safety, efficacy and quality of life of VOTRIENT versus sunitinib have been evaluated in a randomised, open-label, parallel group Phase III non-inferiority study in patients with metastatic or locally advanced renal cell carcinoma (VEG108844& VEG113078).

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 ongoing treatment, 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. The majority of patients had stage IV disease at screening.

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 2.

Table 2 Overall efficacy results (VEG108844)

Endpoint	VOTRIENT N=557	Sunitinib N=553	Adjusted HR[a] (95 % CI)
PFS Overall Median (months) (95 % CI)	 8.4 (8.3, 10.9)	 9.5 (8.3, 11.1)	
			1.047 (0.898,1.220)
Overall Survival Median (months) (95 % CI)	 28.4 (26.2, 35.6)	 29.3 (25.3, 32.5)	
			0.908[b] (0.762, 1.082)

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

[a] Hazard Ratio (HR) is adjusted for Karnofsky Performance Scale (70 or 80, 90 or 100), prior nephrectomy (Yes, No), and baseline levels of lactate dehydrogenase (≤1.5xULN, >1.5xULN).

[b] P value = 0.275 (2-sided)

In VEG108844, health-related QoL was assessed using the following patient-reported questionnaires: Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F), 19-item Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI-19), Cancer Therapy Satisfaction Questionnaire (CTSQ), and Supplementary Quality of Life Questionnaire (SQLQ). Overall compliance with SQLQ was 86%. Statistically significant differences in 11 of the 14 total domains favoured Votrient over sunitinib ($p<0.05$) reflecting the adverse effects profile. The differences in fatigue, mouth/throat and hand/foot soreness and their limitations, feelings about sides effects and satisfaction with therapy were considered likely to be important (effect size >0.20).

Soft Tissue Sarcoma (STS)

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

More common tumour types studied were leiomyosarcoma (excluding skin) and synovial sarcoma. Patients with various rare STS types were analysed collectively in an "Other STS" subgroup. STS types *ineligible* for study included: adipocytic STS; gastrointestinal stromal tumour; rhabdomyosarcoma other than alveolar or pleomorphic; chondrosarcoma; osteosarcoma; Ewings tumour/primitive neuroectodermal tumour; dermofibromatosis sarcoma protuberans; inflammatory myofibroblastic sarcoma; malignant mesothelioma; and mixed mesodermal tumour of the uterus.

Patients with WHO performance status >1 (i.e. unable to carry out light work) were excluded from enrolment. Patients with inadequate bone marrow, renal or liver function were excluded. Patients with abnormal cardiac function (LV ejection fraction below institutional lower limit of normal; QTc prolongation >480 msecs; presence within the last 6 months of cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery bypass graft surgery, symptomatic peripheral vascular disease, or NYHA Class III-IV congestive heart failure) and patients with poorly controlled hypertension were excluded. Patients with any history of a cerebrovascular accident, or with a transient ischaemic attack within the last 6 months, or with a pulmonary embolus within the last 6 months, were excluded. Patients with a history of clinically significant gastrointestinal disorders were excluded. Patients with a bleeding diathesis, active bleeding or haemoptysis within the last 6 weeks were also excluded.

Prior to randomization, eligible 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 patients 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). There were slightly more patients with a WHO PS of 1 at baseline. The median duration of follow-up of patients (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 to evaluate and compare the two treatment arms for progression-free survival (PFS); the secondary endpoints included overall survival (OS), overall response rate and duration of response.

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

Table 3 Overall efficacy results in STS by independent assessment (VEG110727)

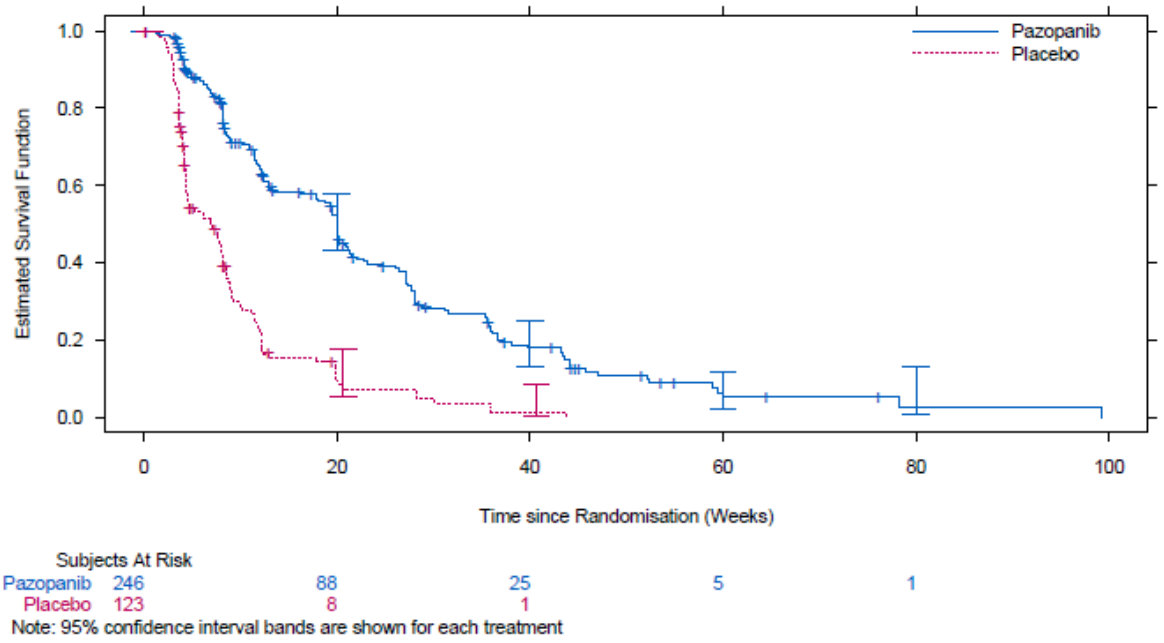
Endpoints / study population	VOTRIENT	Placebo	HR (95% CI)	P value (one-sided)
PFS				
Overall ITT	N = 246	N = 123	0.35 (0.26, 0.48)	< 0.001
Median (weeks)	20.0	7.0		
Leiomyosarcoma	N = 109	N = 49	0.37 (0.23, 0.60)	< 0.001
Median (weeks)	20.1	8.1		

Endpoints / study population	VOTRIENT	Placebo	HR (95% CI)	P value (one-sided)
'Other STS' subgroups Median (weeks)	N = 112 20.1	N = 61 4.3	0.39 (0.25, 0.60)	< 0.001
Response Rate (CR+PR) % (95 % CI) Duration of response Median (weeks) (95 % CI)	 4 (2.3, 7.9) 38.9 (16.7, 40.0)	 0 (0.0, 3.0) -	 - -	 - -

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 pazopanib arm compared with the placebo arm (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)



The hazard ratio at the pre-specified interim analysis for overall survival in favour of pazopanib 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 pazopanib arm; HR = 0.82 (97.87 % CI: 0.59 to 1.14, p = 0.156). The overall survival in this study is potentially confounded due an imbalance of active treatments after disease progression, with more patients in the placebo arm receiving active therapy.

Changes in quality of life were assessed for up to 12 weeks on treatment. Scores for the individual domains of fatigue, diarrhoea, loss of appetite, nausea and vomiting were worse for pazopanib, reflecting the adverse effects profile. However, this was not reflected in global quality of life

assessment. Comparison was hindered by the small number of assessments, dropout of subjects due to disease progression (particularly in the placebo arm), and the absence of health outcome assessments after disease progression.

In a smaller, uncontrolled Phase 2 study of pazopanib in STS (VEG20002), median progression-free survival was 11.1 weeks in adipocytic STS and 14.0-23.4 weeks in other STS groups, although fewer adipocytic STS subjects were studied (n=19 vs n=37-41 in other groups).

INDICATIONS

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

VOTRIENT is indicated for the treatment of advanced (unresectable and/or metastatic) soft tissue sarcoma (STS) in patients who, unless otherwise contraindicated, have received prior chemotherapy including an anthracycline treatment.

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

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, aspartate aminotransferase [AST]) and bilirubin were observed (see ADVERSE EFFECTS). 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 >3x 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 PHARMACOLOGY). 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 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 ≤ 1.5x ULN and AST and ALT ≤ 2x ULN.

- Patients with isolated ALT elevations between 3x ULN and 8x 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 > 8x 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 transaminase elevations > 3x ULN recur, then VOTRIENT should be permanently discontinued.

- If ALT elevations > 3x ULN occur concurrently with bilirubin elevations > 2x 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 pazopanib and simvastatin increases the risk of ALT elevations (see INTERACTIONS WITH OTHER MEDICINES) 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 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 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 a 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 Effects*). Hypertension (systolic blood pressure ≥ 150 or diastolic blood pressure ≥ 100 mm Hg) occurs early in the course of VOTRIENT treatment (39 % of cases occurred by Day 9 and 88 % 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 leuko encephalopathy syndrome (RPLS):

PRES/RPLS has been reported in association with VOTRIENT. PRES/RPLS is a neurological disorder which can present with headache, hypertension (mild to severe), seizure, lethargy, confusion, blindness and other visual and neurological disturbances, and can be fatal. The diagnosis of RPLS is optimally confirmed by magnetic resonance imaging. 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 Effects). 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. Serious treatment-related left ventricular dysfunction was reported in 4 out of 240 patients (1.7%) in the placebo-controlled study VEG110727. In this trial decreases in LVEF in patients who had post-baseline measurement were detected in 11% (16/142) in the VOTRIENT arm compared with 5% (2/40) in the placebo arm. Fourteen of the 16 patients 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 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 Effects*). 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.

Arterial Thrombotic Events:

In clinical studies with VOTRIENT, myocardial infarctions, angina, ischemic stroke and transient ischemic attack were observed (*see Adverse Effects*). 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. 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 Effects*). 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.

Haemorrhagic Events:

In clinical studies with VOTRIENT haemorrhagic events have been reported (*see Adverse Effects*). 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 Effects*). 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 Effects*). Proactive monitoring of thyroid function tests is recommended.

Proteinuria:

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

VOTRIENT is not recommended for use in children and adolescents below 18 years of age due to insufficient data on safety and efficacy. Because the mechanism of action of VOTRIENT can severely affect organ growth and maturation during early post natal development, VOTRIENT is predicted to cause severe or life-threatening toxicity in patients younger than 2 years of age and should not be given.

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. In rats, weaning occurs at day 21 postpartum which approximately equates to a human paediatric age of 2 years.

Interactions with CYP3A4 Inhibitors:

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

Effects on fertility

Pazopanib may impair fertility in human males and females. In a female reproductive toxicity study in rats, reduced fertility has been observed. Decreased corpora lutea and increased incidence of ovarian cysts and atrophy have also been noted in rodents. Decreased corpora lutea was also noted in cynomolgus monkeys given 500 mg/kg/day pazopanib (equivalent to the human clinical exposure based on AUC) for up to 34 weeks.

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 at doses ≥ 100 mg/kg/day (approximately 0.3 times the human clinical exposure based on AUC) following 15 weeks of dosing. Following 15 and 26 weeks of dosing, there were decreased testicular and epididymal weights at ≥ 30 mg/kg/day (approximately 0.4 times the human clinical exposure based on AUC). Atrophy and degeneration of the testes with aspermia, hypospermia and cribriform change in the epididymis was also observed in male rats given ≥ 30 mg/kg/day in the 26-week toxicity study.

Use in Pregnancy (Category D)

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

VOTRIENT can cause fetal harm when administered to a pregnant woman. Pazopanib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits at exposures below clinical exposure. Effects included cardiovascular malformations, incomplete or absent ossification, increased pre- and post-implantation loss, early resorptions, embryo lethality, and decreased foetal body weight.

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 use adequate contraception during treatment and for 2 weeks after discontinuing treatment with pazopanib and to avoid becoming pregnant while receiving treatment with VOTRIENT (see PRECAUTION).

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.

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. Many drugs are excreted into human milk. VOTRIENT should not be used by breastfeeding women.

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.

Genotoxicity

Pazopanib was negative for genotoxicity in genotoxicity assays (Ames assay, human peripheral lymphocyte chromosome aberration assay and rat micronucleus assay). A synthetic intermediate in the manufacture of pazopanib, which is also present in the final drug substance, was not mutagenic in the Ames assay but was genotoxic in the mouse lymphoma L5178Y TK +/- and micronucleus assays and is controlled to below a daily intake of 0.1 mg.

Carcinogenicity

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

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

Concurrent administration of pazopanib (400 mg once daily) with the strong CYP3A4 and P-gp inhibitor, ketoconazole (400 mg once daily) for 5 consecutive days, resulted in a 66 % and 45 % increase in mean pazopanib $AUC_{(0-24)}$ and C_{max}, respectively, relative to administration of pazopanib alone (400 mg once daily for 7 days). There was also a greater degree of inter-subject variability in pazopanib pharmacokinetic parameters when pazopanib was administered with ketoconazole compared to when pazopanib was administered alone. 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.

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

Administration of 1500 mg lapatinib, a substrate and weak inhibitor of CYP3A4, P-gp and 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. Co-administration of pazopanib 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 inhibitor should be avoided (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). If no medically acceptable alternative to a strong CYP3A4 inhibitor is available, the dose of pazopanib should be reduced to 400 mg daily during concomitant administration (*see* PRECAUTIONS). Despite this dose reduction, some patients may still have systematic pazopanib exposure greater that what has been observed after administration of 800mg pazopanib alone. 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 Pazopanib 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 pazopanib 800 mg once daily, have demonstrated that pazopanib does not have a clinically relevant effect on the pharmacokinetics of caffeine (CYP1A2 probe substrate), warfarin (CYP2C9 probe substrate), or omeprazole (CYP2C19 probe substrate) in cancer patients. 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 pazopanib 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. Concomitant use of pazopanib with agents with narrow therapeutic windows that are metabolised by CYP3A4, CYP2D6, or CYP2C8 is not recommended. Coadministration may result in inhibition of the metabolism of these products and create the potential for serious adverse events.

Effects of Pazopanib on Other Enzymes and Transporters

In vitro studies also showed that pazopanib is a potent inhibitor of UGT1A1 and OATP1B1 with IC_{50} of 1.2 and 0.79 μM, respectively. Pazopanib may increase concentrations of drugs primarily eliminated through UGT1A1 (e.g. irinotecan) and OATP1B1 (e.g. rosuvastatin).

Effect of concomitant use of Pazopanib and Simvastatin

Concomitant use of pazopanib and simvastatin increases the incidence of ALT elevations. 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 Pazopanib

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

Medicines that raise gastric pH

Concomitant administration of VOTRIENT with esomeprazole decreases the bioavailability of

VOTRIENT (AUC and C_{max}), and co-administration of VOTRIENT with medicines that increase gastric pH should be avoided.

ADVERSE EFFECTS

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.

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 pazopanib arm and 1.9 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
Rare	≥ 1 in 10,000 and < 1 in 1,000

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

Table 4: Adverse reactions, by organ class and frequency, reported in RCC (VEG105192, VEG108844. VEG113078) and STS (VEG110727) studies

	Frequency Classification	
	RCC VEG105192 , VEG108844, VEG113078 n=844	**STS VEG110727 n=240**
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Tumour pain	♦	Very common
Blood and lymphatic system disorders		
Neutropenia	Common	♦
Thrombocytopenia	Common	♦
Endocrine disorders		
Hypothyroidism*	Very common	Common
Metabolic disorders		
Anorexia	Very common	Very common
Weight decreased	Very common	Very common

	Frequency Classification	
	RCC VEG105192 , VEG108844, VEG113078 n=844	**STS VEG110727 n=240**
Nervous System disorders		
Dizziness	Common	Very common
Dysgeusia	Very common	Very common
Headache	Very common	Very common
Insomnia	♦	Common
Ischaemic stroke*	Uncommon	Uncommon
Transient ischaemic stroke*	Uncommon	♦
Cardiac Disorders		
Cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure)*	Common	Common
Bradycardia	Common†	Common†
Myocardial infarction*	Uncommon	Common
Myocardial ischaemia*	Uncommon	♦
QT prolongation*	Common	Common
Torsade de pointes*	Uncommon	♦
Vascular disorders		
Cerebral haemorrhage*	Uncommon	Uncommon
Epistaxis	Common	Common
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	Very common
Dysphonia	Common	Common
Dyspnoea	Very common	Very common
Pneumothorax	Uncommon	Common
Gastrointestinal disorders		
Abdominal pain	Very common	Very common
Diarrhoea	Very common	Very common
Dyspepsia	Very common	Common
Gastrointestinal perforation*	Uncommon	♦
Gastrointestinal fistula*	Uncommon	Uncommon
Lipase elevations‡	Common	♦
Nausea	Very common	Very common
Stomatitis	Very common	Very common
Vomiting	Very common	Very common

	Frequency Classification	
	RCC VEG105192 , VEG108844, VEG113078 n=844	**STS VEG110727 n=240**
Hepatobiliary disorders		
Alanine amino transferase increased*	Very common	Common
Aspartate amino transferase increased*	Very common	Common
Hepatic function abnormal*	Common	♦
Hyperbilirubinaemia*	Common	Uncommon
Skin and subcutaneous tissue disorders		
Alopecia	Very common	Very common
Dry Skin	Common	Common
Exfoliative rash	Common	Very common
Hair depigmentation	Very common	Very common
Nail disorder	Common	Common
Palmar-plantar erythrodysaesthesia syndrome	Very common	Very common
Rash	Very common	Uncommon
Skin depigmentation	Common	Very common
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	Common	Very common
Myalgia	Common	Very common
Renal urinary disorders		
Proteinuria*	Very common	Uncommon
General disorders and administration site disorders		
Asthenia	Very common	Uncommon
Chest pain*	Common	Very common
Chills	Common	Common
Fatigue	Very common	Very common
Oedema peripheral	Common	Very common
Vision blurred	Common	Common

[*] *See Precautions for additional information.*

♦ *- Adverse event was not considered causally related to pazopanib 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

[†] *See below for further information*

‡ *- For RCC, the frequency category is based on data from the supportive single-arm study VEG102616.*

Bradycardia: In clinical studies with VOTRIENT, bradycardia has been experienced very commonly based on heart rate measurement. In a randomised, double-blind study in renal cell carcinoma patients (see CLINICAL TRIALS), at least one episode of heart rate < 60 bpm was experienced in 33/280 patients (11.8 %) in the VOTRIENT arm and 11/144 patients (7.6 %) in the placebo arm. Bradycardia has also been reported commonly as an adverse event. In the same

study, bradycardia or sinus bradycardia were reported as adverse events in 7/290 patients (2.4 %) in the VOTRIENT arm, and 1/145 patients (0.7 %) in the placebo arm. Most bradycardia with VOTRIENT has been asymptomatic, however syncope due to bradycardia has been reported.

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

Table 5 presents the incidence of very common (>10 %) treatment-related adverse events in RCC for patients receiving VOTRIENT versus those on placebo.

Table 5: Treatment-related Adverse Events Reported for at least 10 % of patients who received VOTRIENT or Placebo in RCC (VEG105192)

Adverse Event, n (%)	Number (% of patients)					
	VOTRIENT (n = 290)			Placebo (n = 145)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any	270 (93)	103(36)	25 (9)	107 (74)	24 (17)	8 (6)
Diarrhoea	152 (52)	11 (4)	2 (<1)	13 (9)	1 (<1)	0
Hair colour changes	109 (38)	1 (<1)	0	4 (3)	0	0
Hypertension	116 (40)	13 (4)	0	15 (10)	1 (<1)	0
Nausea	74 (26)	2 (<1)	0	13 (9)	0	0
Decreased appetite	70 (24)	6 (2)	0	17 (12)	1 (<1)	0
Vomiting	62 (21)	7 (2)	1 (<1)	13 (9)	3 (2)	0
Fatigue	57 (20)	7 (2)	0	14 (10)	2 (1)	2 (1)
ALT increased	55 (19)	18 (6)	3 (1)	5 (3)	1 (<1)	0
AST increase	45 (16)	14 (5)	1 (<1)	5 (3)	0	0
Asthenia	42 (14)	8 (3)	0	13 (9)	0	0
Abdominal pain	32 (11)	7 (2)	0	2 (1)	0	0
Headache	31 (11)	0	0	7 (5)	0	0
Proteinuria	30 (10)	6 (2)	1 (<1)	0	0	0
Weight decreased	30 (10)	2 (<1)	0	5 (3)	1 (<1)	0

Table 6 presents the incidence of very common (>10 %) treatment-related adverse events in STS for patients receiving VOTRIENT versus those on placebo.

Table 6: Treatment-related Adverse Events Reported for at least 10% of patients who received VOTRIENT or Placebo in STS (VEG110727)

Adverse Event, n (%)	Number (% of patients)					
	VOTRIENT (n = 240)			Placebo (n = 123)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any AE	**219 (91)**	84 (35)	17 (7)	**78 (63)**	6 (5)	3 (2)
Diarrhoea	130 (54)	11 (5)	0	14 (11)	0	0
Fatigue	126 (53)	23 (10)	1 (<1)	33 (27)	2 (2)	0
Nausea	116 (48)	7(3)	0	19 (15)	2 (2)	0
Hypertension	94 (39)	16 (7)	0	5 (4)	0	0
Hair colour changes	93 (39)	0	0	3 (2)	0	0
Decreased appetite	82 (34)	11 (5)	0	10 (8)	0	0
Weight decreased	72 (30)	5 (2)	0	8 (7)	0	0
Dysgeusia	65 (27)	0	0	4 (3)	0	0
Vomiting	61 (25)	7(3)	0	8 (7)	1 (<1)	0
Headache	38 (16)	1 (<1)	0	5 (4)	0	0
Exfoliative rash	35 (15)	2 (<1)	0	9 (7)	0	0
Gastrointestinal pain	34 (14)	3(1)	0	4 (3)	1 (<1)	0
Ear, nose and throat examination abnormal	28 (12)	4 (2)	0	1 (<1)	0	0
Myalgia	27 (11)	2 (<1)	0	3 (2)	0	0
Skin hypopigmentation	27 (11)	0	0	0	0	0
Skin disorder	26 (11)	4 (2)	0	1 (<1)	0	0
Stomatitis	26 (11)	1 (<1)	0	4 (3)	0	0
Alopecia	25 (10)	0	0	1 (<1)	0	0
Musculoskeletal pain	23 (10)	1 (<1)	0	3 (2)	0	0

Table 7 presents laboratory abnormalities occurring in ≥ 15 % of patients who received VOTRIENT in the pivotal RCC studies. Grades are based on the NCI CTCAE.

Table 7: Selected Laboratory Abnormalities in ≥ 15 % of Patients who Received VOTRIENT and More Commonly than Placebo Arm (VEG105192)

	VOTRIENT (N = 290)			Placebo (N = 145)		
Parameters	**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

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

Table 8 presents laboratory abnormalities occurring in ≥ 15 % of patients who received VOTRIENT in the pivotal STS study. Grades are based on the NCI CTCAE.

Table 8: Selected Laboratory Abnormalities in ≥ 15 % of Patients who Received VOTRIENT and More Common than Placebo Arm (VEG110727)

	Pazopanib (N = 240)			Placebo (N = 123)		
Parameters	**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

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

Common Infections (with or without neutropenia)

Blood and lymphatic system disorders

Uncommon Polycythaemia, thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome)

Nervous system disorders

Uncommon Posterior reversible encephalopathy syndrome

Gastrointestinal disorders

Common	Flatulence
Uncommon	Pancreatitis

Hepatobiliary disorders

Common	Gamma-glutamyl transpeptidase increased

Musculoskeletal and connective tissue disorders

Very common	Arthralgia
Common	Muscle spasms

Eye disorders

Uncommon	Retinal detachment/tear

Respiratory thoracic and mediastinal disorders

Rare	Interstitial lung disease/pneumonitis

DOSAGE AND ADMINISTRATION

Dosage

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

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 daily dose of VOTRIENT should not exceed 800 mg per day.

Populations

Children

VOTRIENT is not recommended for use in children and adolescents below 18 years of age, due to insufficient data on safety and efficacy (see Precautions).

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 Excretion*).

Renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary in patients with creatinine clearance ≥ 30mL/min. There is no experience of VOTRIENT 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* PHARMACOLOGY).

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 > 3x ULN regardless of any level of ALT); therefore, use of VOTRIENT is not recommended in these patients.

Administration

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

VOTRIENT tablets 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.

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 Poisons Information Centre on telephone number 131 126 (local call in all areas).

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

Presentations

Votrient tablets are modified capsule-shaped, film-coated tablets with one plain face. The tablets are supplied in high-density polyethylene (HDPE) bottles with child resistant polypropylene closures.

200 mg

The tablets are pink and debossed with ‘GS JT’ on the other side. Packs contain 30 or 90 tablets.

400 mg

The tablets are white and debossed with ‘GS UHL’ on the other side. Packs contain 30 or 60 tablets.

Storage

Store below 30°C in original container.

NAME AND ADDRESS OF THE SPONSOR

NOVARTIS Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
MACQUARIE PARK NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

30 June 2010

DATE OF MOST RECENT AMENDMENT

22 December 2017

Internal document code
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