NEW ZEALAND DATA SHEET

VOTRIENT® 200 mg and 400 mg film coated tablets

1. PRODUCT NAME

VOTRIENT® 200 mg film coated tablets

VOTRIENT® 400 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VOTRIENT 200 mg film-coated tablets

Each immediate release film-coated tablet contains pazopanib hydrochloride equivalent to 200 mg of pazopanib free base.

VOTRIENT 400 mg film-coated tablets

Each immediate release film-coated tablet contains pazopanib hydrochloride equivalent to 400 mg of pazopanib free base.

Excipients with known effect

For the full list of VOTRIENT tablet excipients, see section 6.1. This product does not contain lactose, sucrose, tartrazine, azo dyes, or other known allergens.

3. PHARMACEUTICAL FORM

Film-coated tablets.

VOTRIENT 200 mg film coated tablets

Modified capsule-shaped, pink, unscored, film-coated with ‘GS JT’ debossed on one side.

VOTRIENT 400 mg film-coated tablets

Modified capsule-shaped, white, unscored, film-coated with ‘GS UHL’ debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Renal cell carcinoma (RCC)

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

Soft tissue sarcoma (STS)

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 (see section 5.1 Pharmacodynamic properties).

4.2 Dose and method of administration

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

Dose

Adults

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.

Table 1 Dose modifications for drug induced hepatotoxicity

Liver function values	Recommended dose modification
Isolated ALT elevations between 3 x ULN and 8 x ULN	Continue on VOTRIENT with weekly monitoring of liver function until ALT returns to Grade 1 (NCI CTCAE) or baseline.
ALT > 8 x ULN	Interrupt VOTRIENT until ALT returns to Grade 1 (NCI CTCAE) or baseline. If the potential benefit of reinitiating VOTRIENT treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce VOTRIENT at a reduced dose of 400 mg daily and measure serum liver tests weekly for 8 weeks. Following reintroduction of VOTRIENT, if ALT elevations > 3 x ULN recur, then VOTRIENT should be permanently discontinued.
ALT > 3 x ULN concurrent with bilirubin > 2 x ULN	Permanently discontinue VOTRIENT. Monitor patients until return to Grade 1 (NCI CTCAE) or baseline. *Note: 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.*

Special Populations

Paediatric population

VOTRIENT is not recommended for use in children and adolescents below 18 years of age, due to insufficient data on safety and efficacy (see section 4.4 Special warnings and precautions for use and section 5.3 Preclinical safety data).

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 VOTRIENT and metabolites (see sections 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties).

Renal impairment is not expected to influence VOTRIENT exposure, and dose adjustment is not necessary in patients with creatine clearance ≥ 30 mL/min. There is no experience of VOTRIENT in patients with severe renal impairment or in patients undergoing peritoneal dialysis or haemodialysis; therefore, use of VOTRIENT is not recommended in these patients.

Hepatic Impairment

The safety and pharmacokinetics of VOTRIENT in patients with pre-existing hepatic impairment have not been fully established (see section 4.4 Special warnings and precautions for use).

No dose adjustment is required in patients with mild hepatic impairment as defined by alanine aminotransferase (ALT) and bilirubin (see sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties).

The dose of VOTRIENT should be reduced to 200 mg per day in patients with moderate hepatic impairment (see section 5.2). There are insufficient data in patients with severe hepatic impairment (total bilirubin > 3 x ULN regardless of any level of ALT value); therefore, use of VOTRIENT is not recommended in these patients.

Method of administration

VOTRIENT should be taken without food (at least one hour before or two hours after a meal) (see section 5.2 Pharmacokinetic properties).

VOTRIENT should be taken whole with water and must not be broken or crushed (see section 5.2 Pharmacokinetic properties). If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.

4.3 Contraindications

VOTRIENT is contraindicated in patients with hypersensitivity to the active substance pazopanib hydrochloride or to any of the excipients listed in section 6.1. List of excipients.

4.4 Special warnings and precautions for use

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 section 4.8 Undesirable 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 >3 X ULN. Patients who carry the HLA-B*57:01 allele also have an increased risk of VOTRIENT-associated ALT elevations. Liver function should be monitored in all subjects receiving VOTRIENT, regardless of genotype or age (see section 5.1). 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. Then monitor at months 3 and 4, with additional tests as clinically indicated. Periodic testing should then continue after month 4.

See Table 1 for dose modifications in patients with baseline values of total bilirubin ≤ 1.5 x ULN and AST and ALT ≤ 2 x ULN.

Concomitant use of VOTRIENT and simvastatin increases the risk of ALT elevations (see section 4.5 Interaction with other medicines and other forms of interaction) and should be undertaken with caution and close monitoring.

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

Hypertension

In clinical studies with VOTRIENT, events of hypertension including hypertensive crisis have occurred. Blood pressure should be well controlled prior to initiating VOTRIENT. Patients should be monitored for hypertension early after starting treatment (no longer than one week after starting VOTRIENT) and frequently thereafter to ensure blood pressure control, and treated promptly with a combination of standard anti-hypertensive therapy and VOTRIENT dose reduction or interruption as clinically warranted (see section 4.2 Dose and method of administration and 4.8 Undesirable effects). 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. P

Posterior reversible encephalopathy syndrome (PRES)/Reversible posterior leukoencephalopathy syndrome (RPLS)

PRES/RPLS has been reported in association with VOTRIENT. PRES/RPLS can present with headache, hypertension, seizure, lethargy, confusion, blindness and other visual and neurological disturbances, and can be fatal. Permanently discontinue VOTRIENT in patients developing PRES/RPLS.

Interstitial Lung Disease (ILD)/Pneumonitis

ILD, which can be fatal, has been reported in association with VOTRIENT (see section 4.8 Undesirable effects). Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis and VOTRIENT should be discontinued in patients developing ILD or pneumonitis.

Cardiac Dysfunction

The risks and benefits of pazopanib should be considered before beginning therapy in patients who have pre-existing cardiac dysfunction. The safety and pharmacokinetics of pazopanib in patients with moderate to severe heart failure or those with a below normal LVEF has not been studied.

In Clinical trials with 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.

Risk factors

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.

Management

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 section 4.8 Undesirable effects). VOTRIENT should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmic or other medications that may potentially prolong QT interval, or in patients with relevant pre-existing cardiac disease. When using VOTRIENT, baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (calcium, magnesium, potassium) within normal range is recommended.

Arterial Thrombotic Events

In clinical studies with VOTRIENT, myocardial infarctions, angina, ischemic stroke and transient ischemic attack were observed (see section 4.8 Undesirable 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 (TMA)

Thrombotic microangiopathy has been reported in clinical trials of VOTRIENT as monotherapy, in combination with bevacizumab, and in combination with topotecan (see section 4.8). 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 section 4.8). 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.

Aneurysms and artery dissections

Artery dissections and aneurysms have been reported in association with VEGF pathway inhibitors, including VOTRIENT (see section 4.8, Undesirable effects). The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating VOTRIENT, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Gastrointestinal Perforations and Fistula

In clinical studies with VOTRIENT, events of gastrointestinal (GI) perforation or fistula have occurred (see section 4.8 Undesirable 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 section 4.8 Undesirable effects). Proactive monitoring of thyroid function tests is recommended.

Proteinuria

In clinical studies with VOTRIENT, proteinuria has been reported (see section 4.8). 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.

Tumour lysis syndrome (TLS)

Cases of TLS, including fatal cases, have been reported in patients treated with Votrient (see Section 4.8 Undesirable effects). Patients generally at risk of TLS are those with rapidly growing tumours, a high tumour burden, renal dysfunction, or dehydration. Preventative measures such as treatment of high uric acid levels and intravenous hydration should be considered prior to initiation of Votrient. Patients at risk should be closely monitored and treated as clinically indicated.

Infections

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

Combination with other systemic anti-cancer therapies

VOTRIENT is not indicated for use in combination with other anti-cancer agents.

Clinical trials of VOTRIENT in combination with pemetrexed (non-small cell lung cancer (NSCLC)),lapatinib (cervical cancer), or pembrolizumab (advanced renal cell carcinoma) were terminated early due to concerns over increased toxicity and/or mortality, and a safe and effective combination dose have not been established with these regimens.

Interactions

Concomitant treatment with strong inhibitors of CYP3A4, P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) should be avoided due to risk of increased exposure to VOTRIENT (see section 4.5 Interaction with other medicines and other forms of interaction). Selection of alternative concomitant medicinal products with no or minimal potential to inhibit CYP3A4, P-gp or BCRP should be considered.

Paediatric Toxicity

VOTRIENT is not recommended for use in children and adolescents below 18 years of age.

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

4.5 Interaction with other medicines and other forms of interaction

Medicines that Inhibit or Induce Cytochrome P450 3A4 Enzymes

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

CYP3A4, P-gp, BCRP Inhibitors

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

Concurrent administration of VOTRIENT (400 mg once daily) with the strong CYP3A4 and P-gp inhibitor, ketoconazole (400 mg once daily) for 5 consecutive days, resulted in a 66 % and 45 % increase in mean VOTRIENT $AUC_{(0-24)}$ and Cmax, respectively, relative to administration of VOTRIENT alone (400 mg once daily for 7 days). VOTRIENT Cmax and AUC increase in a less than dose proportional fashion with increasing dose over the range of 50 mg to 2000 mg. Therefore, a dose reduction to 400 mg VOTRIENT once daily in the presence of strong CYP3A4 inhibitors will, in the majority of patients, result in systemic exposure similar to that observed after administration of 800 mg VOTRIENT once daily alone. Some patients however may have systemic VOTRIENT exposure greater than what has been observed after administration of 800 mg VOTRIENT alone.

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

Administration of 1500 mg lapatinib (TYKERB®), a substrate and weak inhibitor of CYP3A4, Pgp and BCRP with 800 mg VOTRIENT resulted in an approximately 50 % to 60 % increase in mean VOTRIENT $AUC_{(0-24)}$ and Cmax 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 VOTRIENT concentrations.

Concomitant use of VOTRIENT with a strong CYP3A4 inhibitor should be avoided. If no medically acceptable alternative to a strong CYP34A inhibitor is available, the dose of VOTRIENT should be reduced to 400 mg daily during concomitant administration (see section 4.4 Special warnings and precautions for use). 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 VOTRIENT 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/m^2 (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 26 % and 31 % in paclitaxel AUC and C_{max}, respectively.

Effects of VOTRIENT on Other Enzymes and Transporters

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

Effect of concomitant use of VOTRIENT and Simvastatin

Concomitant use of VOTRIENT and simvastatin increases the incidence of ALT elevations. Across monotherapy studies with VOTRIENT, ALT > 3 x ULN was reported in 126 / 895 (14 %) of patients who did not use statins, compared with 11/41 (27 %) of patients who had concomitant use of simvastatin (p = 0.038). If a patient receiving concomitant simvastatin develops ALT elevations, follow guidelines for VOTRIENT posology and discontinue simvastatin (see section 4.4 Special warnings and precautions for use). Insufficient data are available to assess the risk of concomitant administration of alternative statins and VOTRIENT.

Effect of Food on VOTRIENT

Administration of VOTRIENT with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C_{max}. Therefore, VOTRIENT should be administered at least 1 hour before or 2 hours after a meal (see section 4.2 Dose and method of administration).

Medicines that raise gastric pH

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

4.6 Fertility, pregnancy and lactation

Effects on Fertility

Based on findings from animal studies, VOTRIENT may impair human fertility in males and females of reproductive potential whilst receiving treatment. 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.

VOTRIENT 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 cribriform change in the epididymis of male rats given doses ≥ 30 mg/kg/day (approximately 0.6 times the human clinical exposure based on AUC).

Contraception in males and females

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

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

Infertility

Based on findings from animal studies, VOTRIENT may impair fertility in males and females of reproductive potential while receiving treatment (see section 5.3 Preclinical safety data).

Pregnancy (Category D)

Risk Summary

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

Females of reproductive potential should be advised to avoid becoming pregnant while receiving treatment with VOTRIENT.

Breast-feeding

Risk summary

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

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable Effects

Summary of the safety profile

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

Tabulated summary of adverse drug reactions from clinical trials

Treatment related adverse reactions from clinical trials in RCC and STS subjects are listed below by MedDRA body system organ class. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III):

Very common	≥ 1 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

Table 2 Treatment-related adverse drug reactions, by organ class and frequency, reported in RCC study (VEG105192) and STS study (VEG110727)

Adverse drug reactions	**Frequency classification**	
	RCC N=290	**STS N=240**
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		
Tumour pain	♦	Very common
Blood and lymphatic system disorders		
Neutropenia	Common	♦
Thrombocytopenia	Common	♦
Endocrine disorders		
Hypothyroidism*	Common	Common
Metabolism and nutrition disorders		
Decreased appetite	Very common	Very common
Nervous system disorders		
Dizziness	♦	Very common
Dysgeusia	Common	Very common
Headache	Very common	Very common
Ischaemic stroke*	Uncommon	Uncommon
Transient ischaemic attack*	Common	♦
Cerebral haemorrhage*	Uncommon	Uncommon
Psychiatric disorders		
Insomnia	♦	Common

Adverse drug reactions	Frequency classification RCC N=290	Frequency classification STS N=240
Cardiac disorders		
Cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure)*	Uncommon	Common
Bradycardia (asymptomatic)	Very common†	Very common†
Myocardial infarction*	Uncommon	Common
Myocardial ischaemia*	Common	♦
Torsade de Pointes*	Uncommon	♦
Vascular disorders		
Hypertension*	Very common	Very common
Venous emolism	Common	Common
Respiratory, thoracic and mediastinal disorders		
Cough	♦	Very common
Dysphonia	Common	Common
Dyspnoea	♦	Very common
Pneumothorax	♦	Common
Epistaxis	Common	Common
Pulmonary haemorrhage*	Uncommon	Common
Gastrointestinal disorders		
Abdominal pain	Very common	Very common
Diarrhoea	Very common	Very common
Dyspepsia	Common	Common
Gastrointestinal perforation*	Uncommon	♦
Gastrointestinal fistula*	Uncommon	Uncommon
Gastrointestinal haemorrhage*	Common	Common
Nausea	Very common	Very common
Stomatitis	♦	Very common
Vomiting	Very common	Very common
Hepatobiliary disorders		
Hepatic function abnormal*	Common	♦
Hyperbilirubinaemia*	Common	Uncommon
Skin and subcutaneous tissue disorders		
Alopecia	Common	Very common
Dry skin	♦	Common
Exfoliative rash	♦	Very common
Hair colour changes	Very common	Very common
Nail disorder	♦	Common
Palmar-plantar erythrodysaesthesia syndrome	Common	Very common
Rash	Common	Uncommon
Skin depigmentation	Common	Very common
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	♦	Very common
Myalgia	♦	Very common
Renal and urinary disorders		
Proteinuria*	Common	Uncommon
Haematuria	Common	Uncommon
Eye disorders		
Vision blurred	Common	Common
General disorders and administration site conditions		
Asthenia	Very common	Uncommon

Adverse drug reactions	Frequency classification RCC N=290	STS N=240
Chest pain*	Common	Very common
Chills	♦	Common
Fatigue	Very common	Very common
Oedema peripheral	♦	Very common
Investigations		
Weight decreased	Common	Very common
Electrocardiogram QT prolonged*	Common	Common
Lipase increased	Common‡	♦
Alanine aminotransferase increased*	Very common	Common
Aspartate aminotransferase increased*	Very common	Common

**See Warnings and precautions for additional information.*

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

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

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

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

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

Table 3 and Table 4 present laboratory abnormalities occurring in ≥ 15 % of patients who received VOTRIENT in pivotal RCC study VEG105192 and pivotal STS study VEG110727 respectively. Grades in both tables are based on the NCI CTCAE.

Table 3 Selected laboratory abnormalities in ≥ 15 % of patients who received VOTRIENT and with a frequency greater than placebo in study VEG105192

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

	VOTRIENT (N=290)			Placebo (N=145)		
	All Grades	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Magnesium decreased	26	<1	1	14	0	0
Glucose decreased	17	0	<1	3	0	0

Table 4 Selected Laboratory Abnormalities in ≥15% of Patients who received VOTRIENT with a frequency greater than placebo arm in study VEG110727

	VOTRIENT (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

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

Post marketing data

Post marketing data on safety and tolerability across all pazopanib clinical trials and from spontaneous reports have also been evaluated. Within each system organ class, adverse reactions with the same frequency are presented in order of decreasing seriousness.

The adverse drug reactions in Table 5 have been identified during post-approval use of VOTRIENT. This includes spontaneous case reports as well as serious adverse events from ongoing studies, clinical pharmacology studies and exploratory studies in unapproved therapeutic indications.

Table 5 Adverse drug reactions identified during post-approval use

Infections and infestations	
Common	Infections (with or without neutropenia); see section 4.4 Special warnings and precautions for use
Metabolism and nutrition disorders	
Unknown	Tumour lysis syndrome (including fatal cases); see section 4.4 Special warnings and precautions for use
Blood and lymphatic system disorders	
Uncommon	Polycythaemia, thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome)
Nervous system disorders	
Rare	Posterior reversible encephalopathy syndrome
Gastrointestinal disorders	
Common	Flatulence

Uncommon	Pancreatitis
Hepatobiliary disorders	
Not Known	Hepatic failure
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia
Common	Muscle spasms
Vascular disorders	
Rare	Aneurysms and artery dissections
Eye disorders	
Uncommon	Retinal detachment/retinal tear
Respiratory thoracic and mediastinal disorders	
Rare	Interstitial lung disease/pneumonitis.
Investigations	
Common	Gamma-glutamyl transpeptidase increased
Skin and subcutaneous tissue disorders	
Uncommon	Skin ulcer

Special Populations

Paediatric patients (below 18 years)

The safety profile in paediatric patients was similar to that reported with pazopanib in adults in the approved indications based on data from 44 paediatric patients from Phase I study ADVL0815 and 57 paediatric patients from Phase II study PZP034X2203 (see sections 4.2 Dose and method of administration and 5.1 Pharmacodynamic properties, Clinical studies).

Reporting of suspected adverse reactions

The reporting suspected adverse reactions after the authorisation of the medicine is important. It allows for continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to Medsafe via the following web site: https//nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

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

Symptoms and Signs

There is currently limited experience with overdosage in VOTRIENT.

Treatment

Further management should be as clinically indicated or as recommended by the national poisons 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.

For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents - protein- kinase inhibitors.

ATC code: L01EX03.

Mechanism of Action

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

Pharmacogenomics

In a pharmacogenetic meta-analysis of data from 31 clinical studies of VOTRIENT administered either as monotherapy or in combination with other agents, ALT > 5 X ULN (NCI CTC Grade 3) occurred in 19% of HLA-B*57:01 allele carriers and in 10% of non-carriers. In this dataset, 133/2,235 (6 %) of the patients carried the HLA-B*57:01 allele (see Section 4.4 Special warnings and precautions for use).

Clinical Trials

Renal Cell Carcinoma (RCC)

The safety and efficacy of VOTRIENT in renal cell carcinoma (RCC) were evaluated in a randomised, double-blind, placebo-controlled multi-centre study. Patients (N= 435) with locally advanced and/or metastatic RCC were randomised 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 was overall survival (OS). The other objectives were to evaluate the overall response rate and duration of response.

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

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

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

The primary analysis of the primary endpoint PFS is based on disease assessment by independent radiological review in the entire study population (first line and second line).

Table 6 Overall Efficacy Results 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 9.2	N=145 4.2	0.46 (0.34, 0.62)	<0.0000001
Treatment-naïve	N=155 11.1	N=78 2.8	0.40 (0.27, 0.60)	<0.0000001
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)

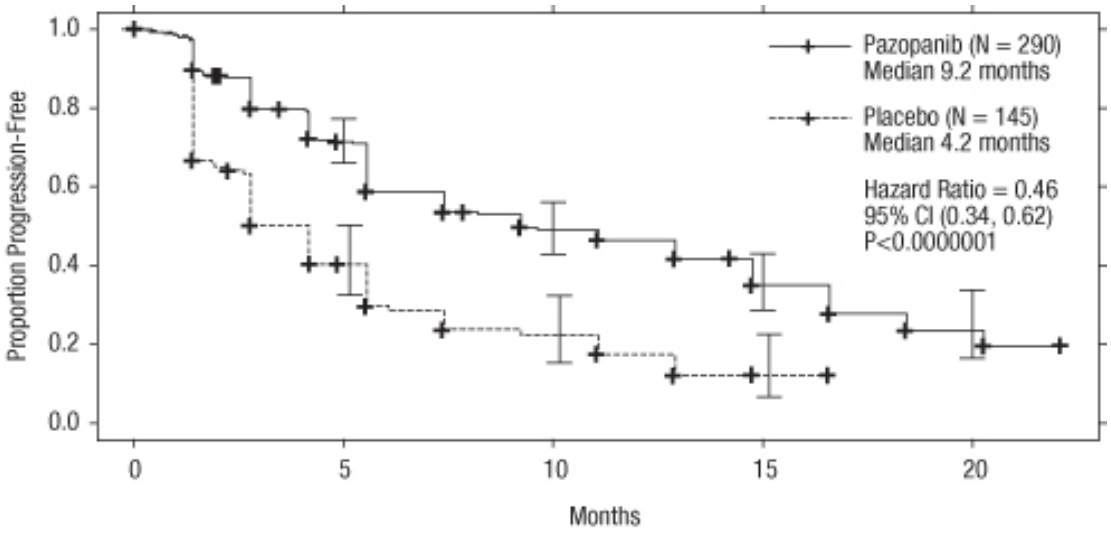


Figure 2 Kaplan-Meier Curve for Progression-Free Survival by Independent Assessment for the Treatment-Naïve Population

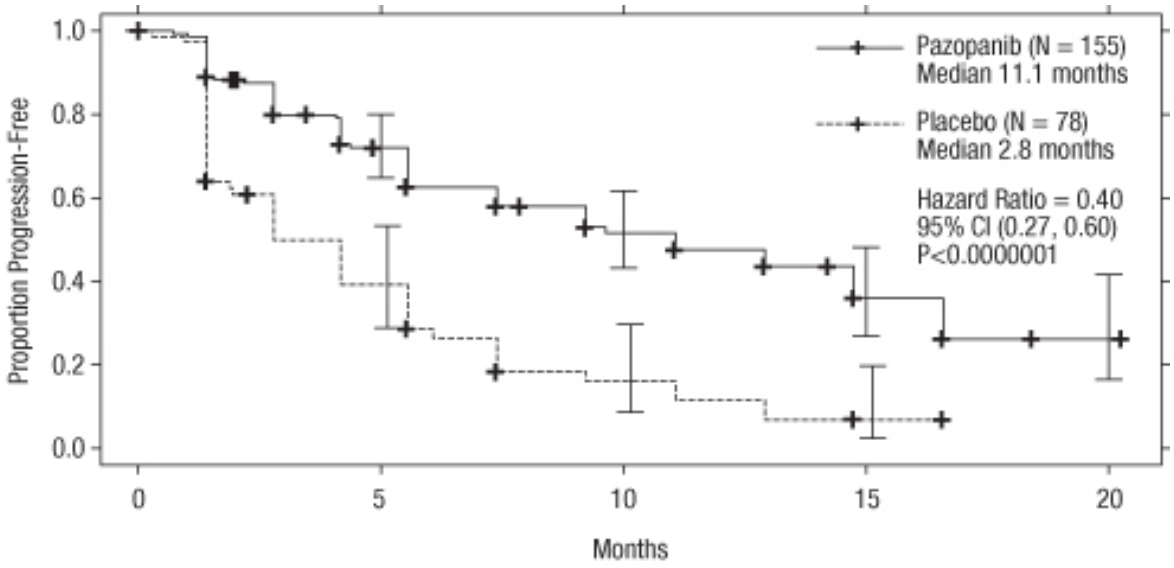
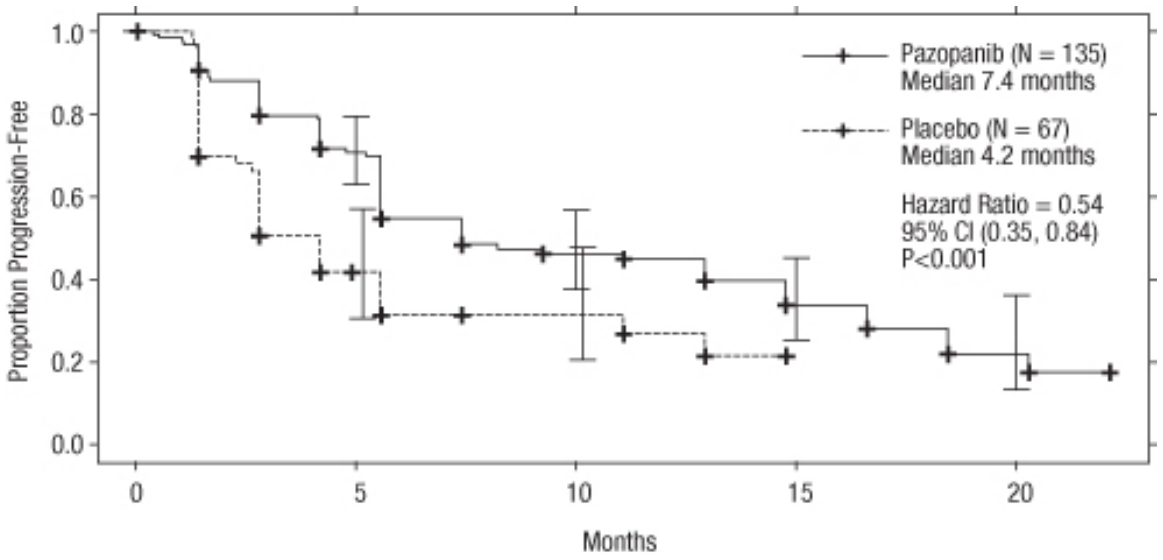


Figure 3 Kaplan-Meier Curve for Progression-Free Survival by Independent Assessment for the Cytokine Pre-Treated Population



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. The median overall survival (OS) data at the protocol specified final survival analysis were 22.9 months and 20.5 months [HR = 0.91 (95 % CI: 0.71, 1.16; p = 0.224)] for patients randomised to the VOTRIENT and placebo arms, respectively. The OS results are subject to potential bias as 54 % of patients in the placebo arm also received VOTRIENT in the extension part of this study following disease progression. Sixty-six percent (66 %) 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 II study of 225 patients with locally recurrent or metastatic clear cell renal cell carcinoma, objective response rate was 35 % and median duration of response was 68 weeks, as per independent review. Median PFS was 11.9 months.

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

In VEG108844, patients (N = 1,110) with locally advanced and/or metastatic RCC who had not received prior systemic therapy, were randomized to receive either VOTRIENT 800 mg once daily continuously or sunitinib 50 mg once daily in 6-week cycles of dosing with 4 weeks on treatment followed by 2 weeks without treatment.

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

VEG108844 achieved its primary endpoint of PFS and demonstrated that VOTRIENT was non-inferior to sunitinib, as the upper bound of the 95 % CI for the hazard ratio was less than the protocol-specified non-inferiority margin of 1.25. Overall efficacy results are summarised in Table 7.

Table 7 Overall Efficacy Results (VEG108844)

Endpoint	VOTRIENT N=557	Sunitinib N=553	HR (95 % CI)
PFS			
Overall Median (months) (95 % CI)	8.4 (8.3, 10.9)	9.5 (8.3, 11.0)	1.047 (0.898,1.220)
Overall Survival Median (months) (95 % CI)	28.4 26.2, 35.6)	29.3 (25.3, 32.5)	0.908[a] (0.762, 1.082)

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

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

Soft Tissue Sarcoma (STS)

The safety and efficacy of VOTRIENT in STS were evaluated in a randomized, double-blind, placebo-controlled multi-centre 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 VOTRIENT 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 VOTRIENT treatment arms) compared with 0 or 1 lines of prior systemic therapy (42 % and 45 % respectively for placebo and VOTRIENT treatment arms). There were slightly more 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 VOTRIENT [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. Similar to the assessments by independent radiology review, a clinically meaningful and statistically significant improvement in PFS based on investigator assessments was observed in the VOTRIENT arm compared with the placebo arm (HR: 0.39; 95 % CI, 0.30 to 0.52, $p < 0.001$).

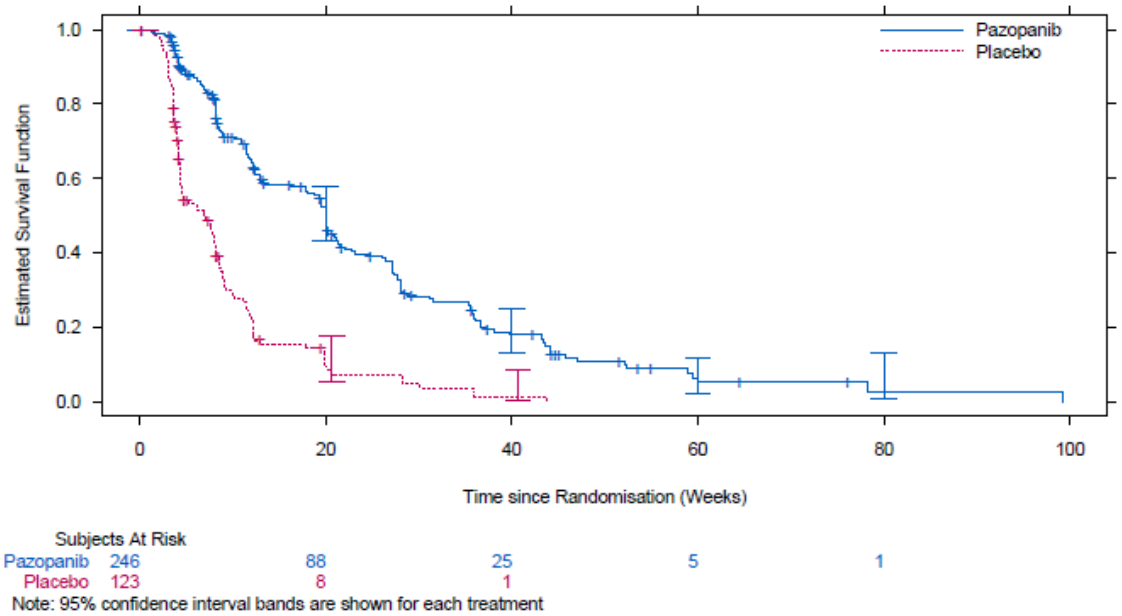
Table 8 Overall efficacy results in STS by independent assessment (VEG110727)

Endpoints/study population	VOTRIENT N = 246	Placebo N = 123	HR (95% CI)	P value (one-sided)
PFS			0.35	
Overall ITT median (weeks)	20.0	7.0	(0.26, 0.48)	< 0.001
Leiomyosarcoma	N = 109	N = 49	0.37	< 0.001
Median (weeks)	20.1	8.1	(0.23, 0.60)	
Synovial sarcoma subgroups	N = 25	N = 13	0.43	0.005
median (weeks)	17.9	4.1	(0.19, 0.98)	

Endpoints/study population	VOTRIENT N = 246	Placebo N = 123	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)	4 (2.3, 7.9)	0 (0.0, 3.0)	-	-
Duration of response Median (weeks) (95 % CI)	38.9 (16.7, 40.0)	-	-	-

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

Figure 4 Kaplan-Meier Curve for Progression-Free Survival in STS by Independent Assessment for the Overall Population (VEG110727)



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

Paediatric population

A Phase I study (ADVL0815) of pazopanib was conducted in 44 paediatric patients with various recurrent or refractory solid tumours. The primary objective was to investigate the maximum tolerated dose (MTD), the safety profile and the pharmacokinetic properties of pazopanib in children. The median duration of exposure in this study was 3 months (1-23 months).

A Phase II study (PZP034X2203) of pazopanib was conducted in 57 paediatric patients with refractory solid tumours including rhabdomyosarcoma (N=12), non-rhabdomyosarcoma soft tissue sarcoma (N=11), Ewing sarcoma/pPNET (N=10), osteosarcoma (N=10), neuroblastoma (N=8) and hepatoblastoma (N=6). The study was a single-agent, non-controlled, open-label study to determine the therapeutic activity of pazopanib in children and adolescents aged 1 to <18 years of age. Pazopanib was administered daily as a tablet at a dose of 450 mg/m^2/dose or as an oral suspension at 225 mg/m^2/dose. The maximum daily dose permitted was 800 mg for the tablet and 400 mg for the oral suspension. The median duration of exposure was 1.8 months (1 day-29 months).

Results of this study did not show any meaningful anti-tumour activity in the respective paediatric population. Pazopanib is therefore not recommended for treatment of these tumours in the paediatric population (see section 4.2 Dose and method of administration).

5.2 Pharmacokinetic Properties

Absorption

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

Systemic exposure to VOTRIENT is increased when administered with food. Administration of VOTRIENT with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C_{max}. Therefore, VOTRIENT should be administered at least 1 hour before or 2 hours after a meal (see section 4.2 Dose and method of administration).

Administration of a single VOTRIENT 400 mg crushed tablet increased $AUC_{(0-72)}$ by 46 % and C_{max} by approximately 2 fold and decreased t_{max} by approximately 1.5 hours compared to administration of the whole tablet. These results indicate that the bioavailability and the rate of VOTRIENT 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 section 4.2 Dose and method of administration).

Distribution

Binding of VOTRIENT to human plasma protein *in vivo* was greater than 99 % with no concentration dependence over the range of 10 to 100 microgram/mL. *In vitro* studies

suggest that VOTRIENT is a substrate for P-glycoprotein (Pgp) and breast cancer resistant protein (BCRP).

Biotransformation

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

Elimination

VOTRIENT 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.

Characteristics in 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 VOTRIENT. Renal impairment is not expected to influence VOTRIENT exposure, and dose adjustment is not necessary in patients with creatine clearance ≥ 30 mL/min (see section 4.2 Dose and method of administration).

Hepatic Impairment

The median steady-state 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 times the upper limit of normal [x ULN] regardless of the ALT value) after a once daily dose of 800 mg/day (30.9 microgram/mL, range 12.5 to 47.3 and 841.8 microgram.hr/mL, range 600.4 to 1078) are similar to the median in patients with no hepatic impairment (49.4 microgram/mL, range 17.1 to 85.7 and 888.2 microgram.hr/mL, range 345.5 to 1482) (see section 4.2 Dose and method of administration).

The maximally tolerated dose (MTD) of VOTRIENT 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 microgram/mL, range 6.4-32.9) and $AUC_{(0-24)}$ (350.0 microgram.hr/mL, range 131.8 to 487.7) after administration of 200 mg VOTRIENT once daily in 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 Section 4.2 Dose and method of administration).

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

Paediatric population

Upon administration of pazopanib 225 mg/m^2 (as oral suspension) in paediatric patients, the pharmacokinetic parameters (C_{max}, T_{max} and AUC) were similar to those previously reported in adult patients treated with 800 mg pazopanib. Results indicated no marked difference in the clearance of pazopanib, normalised by body surface area, between children

and adults (see sections 4.2 Dose and method of administration and 5.1 Pharmacodynamic properties, Clinical studies).

5.3 Preclinical Safety Data

The preclinical safety profile of VOTRIENT was assessed in mice, rats, rabbits and monkeys.

Safety pharmacology and repeat dose toxicity

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

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

Carcinogenicity and mutagenicity

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

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

Fertility

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

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

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

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

VOTRIENT 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 fetal body weight. The potential risk for humans is unknown.

Reproductive toxicity

Pre-clinical studies in animals have shown reproductive toxicity. See section 4.6 Fertility, pregnancy and lactation.

Juvenile animal studies

In juvenile toxicity studies, when pre-weaning rats were dosed from day 9 post-partum through day 14 postpartum, VOTRIENT caused mortalities and abnormal organ growth/maturation in kidney, lung liver and heart, at a dose approximately 0.1 times the AUC at the maximum recommended human dose (MRHD) of 800 mg/day. When post weaning rats were dosed from day 21 post-partum to day 62 post-partum, toxicological findings were similar to adult rats at comparable exposures with changes in bone, trachea, teeth, adrenal, pancreas, stomach, duodenum, lymph node, male mammary gland and reproductive organs. In rats, weaning occurs at day 21 postpartum which approximately equates to a human paediatric age of 2 years. Human paediatric patients are at increased risk for bone and teeth effects as compared to adults, as these changes, including shortened limbs, were present in juvenile rats at ≥ 10 mg/kg/day (equal to approximately 0.1-0.2 times the AUC at the MRHD of 800 mg/day) (see section 4.4 Special warnings and precautions for use).

Genotoxicity

VOTRIENT 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 VOTRIENT, 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each film-coated tablet also contains: magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycollate, hypromellose, macrogol 400, titanium dioxide, polysorbate 80, and iron oxide red CI77491 (200 mg tablet only).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months when stored at/below 30°C.

6.4 Special precautions for storage

Store in original container.

6.5 Nature and Contents of Container

VOTRIENT 200 mg film-coated tablets

Supplied in high-density polyethylene (HDPE) bottles with child resistant polypropylene (PP) closures containing 30 or *90 film coated tablets.

VOTRIENT 400 mg film-coated tablets

Supplied in high-density polyethylene (HDPE) bottles with child resistant polypropylene (PP) closures containing 30 or *60 film coated tablets.

* *Not all strengths and pack sizes may be distributed in New Zealand.*

6.6 Special precautions for disposal and other handling.

Any unused medicine or waste material should be disposed of in accordance with local requirements. Return VOTRIENT tablets to a pharmacy for safe disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Novartis New Zealand Limited
PO Box 99102 Newmarket Auckland 1149 New Zealand
Telephone number (free call within New Zealand): 0800 354 335
Fax number: (09) 361 8181
E-mail: medinfo.phauno@novartis.com

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to first distribute the medicine: 16 September 2010

10. DATE OF REVISION OF THE TEXT

10 June 2021

NEW ZEALAND DATA SHEET

SUMMARY TABLE OF CHANGES

Table 9 Summary of changes

Section	Summary of changes
4.4	• Expanded existing statement on aneurysms and artery dissections as relevant to VEGF inhibitors such as VOTRIENT.
4.8	• Revised frequency of post market AE: Aneurysms and artery dissections from "unknown" to "rare". • Addition of new post-market AE: skin ulcers with frequency "uncommon"
5.1	• ATC code updated

Internal document code: vot180621iNZ is based on CDS dated 3 June 2021