NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Pazopanib, film-coated tablets, 200 mg (Teva)
Pazopanib, film-coated tablets, 400 mg (Teva)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg or 400 mg of pazopanib (as hydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets, 200 mg: Capsule-shaped, pink, film-coated tablet with "200" debossed on one side.

Tablets, 400 mg: Capsule-shaped, white, film-coated tablet with "400" debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Renal cell carcinoma (RCC)

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

Soft tissue sarcoma (STS)

Pazopanib (Teva) 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

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

<u>Dose</u>
Adults

The recommended dose of pazopanib 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 pazopanib 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 pazopanib with weekly monitoring of liver function until ALT returns to Grade 1 (NCI CTCAE) or baseline.
ALT > 8 x ULN	Interrupt pazopanib until ALT returns to Grade 1 (NCI CTCAE) or baseline. If the potential benefit of reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce pazopanib at a reduced dose of 400 mg daily and measure serum liver tests weekly for 8 weeks. Following reintroduction of pazopanib, if ALT elevations > 3 x ULN recur, then pazopanib should be permanently discontinued.

ALT > 3 x ULN concurrent with bilirubin > 2 x ULN	Permanently discontinue pazopanib. Monitor patients until return to Grade 1 (NCI CTCAE) or baseline. *Note: Pazopanib 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

Pazopanib 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 pazopanib pharmacokinetics given the low renal excretion of pazopanib and metabolites (see sections 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties).

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

Hepatic Impairment

The safety and pharmacokinetics of pazopanib 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 pazopanib 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 pazopanib is not recommended in these patients.

Method of administration

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

Pazopanib 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

Pazopanib 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 pazopanib. In clinical trials with pazopanib, 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 pazopanib -associated ALT elevations. Liver function should be monitored in all subjects receiving pazopanib, 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 pazopanib, 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 pazopanib 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 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 pazopanib. Patients should be monitored for hypertension early after starting treatment (no longer than one week after starting pazopanib) and frequently thereafter to ensure blood pressure control, and treated promptly with a combination of standard anti-hypertensive therapy and   pazopanib 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 pazopanib treatment (approximately 40 of cases occurred by Day 9 and approximately 90 of cases occurred in the first 18 weeks). Pazopanib should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persists despite anti-hypertensive therapy and pazopanib dose reduction.

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

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

Interstitial Lung Disease (ILD)/Pneumonitis

ILD, which can be fatal, has been reported in association with pazopanib (see section 4.8 Undesirable effects). Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis and pazopanib 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 pazopanib, 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 pazopanib arm compared with 5% (2/40) in the placebo arm.

Risk factors

Fourteen of the 16 patients in the PAZOPANIB 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 PAZOPANIB (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 pazopanib, events of QT prolongation or Torsade de Pointes have occurred (see section 4.8 Undesirable effects). Pazopanib 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 pazopanib, 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 pazopanib, myocardial infarctions, angina, ischemic stroke and transient ischemic attack were observed (see section 4.8 Undesirable effects). Fatal events have been observed. pazopanib should be used with caution in patients who are at increased risk of thrombotic events or who have had a history of thrombotic events. Pazopanib 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 PAZOPANIB, venous thromboembolic events including venous thrombosis and fatal pulmonary embolus have occurred. The incidence was higher in the STS population (5 %) than in the RCC population (2%).

Thrombotic Microangiopathy (TMA)

Thrombotic microangiopathy has been reported in clinical trials of pazopanib as monotherapy, in combination with bevacizumab, and in combination with topotecan (see section 4.8). Permanently discontinue pazopanib in patients developing TMA. Reversal of effects of TMA has been observed after treatment was discontinued. Pazopanib is not indicated for use in combination with other agents.

Haemorrhagic Events

In clinical studies with pazopanib haemorrhagic events have been reported (see section 4.8). Fatal haemorrhagic events have occurred. Pazopanib has not been studied in patients who had a history of haemoptysis, cerebral, or clinically significant gastrointestinal haemorrhage in the past 6 months. Pazopanib 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 pazopanib (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 pazopanib, 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 pazopanib, events of gastrointestinal (GI) perforation or fistula have occurred (see section 4.8 Undesirable effects). Fatal perforation events have occurred. Pazopanib should be used with caution in patients at risk for GI perforation or fistula.

Wound Healing

No formal studies on the effect of pazopanib on wound healing have been conducted. Since Vascular Endothelial Growth Factor (VEGF) inhibitors may impair wound healing, treatment with pazopanib should be stopped at least 7 days prior to scheduled surgery. The decision to resume pazopanib after surgery should be based on clinical judgement of adequate wound healing. Pazopanib should be discontinued in patients with wound dehiscence.

Hypothyroidism

In clinical studies with pazopanib, events of hypothyroidism have occurred (see section 4.8 Undesirable effects). Proactive monitoring of thyroid function tests is recommended.

Proteinuria

In clinical studies with pazopanib, proteinuria has been reported (see section 4.8). Baseline and periodic urinalyses during treatment are recommended and patients should be monitored for worsening proteinuria. Pazopanib 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 pazopanib (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 pazopanib. 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

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

Clinical trials of pazopanib 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 pazopanib (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
Pazopanib is not recommended for use in children and adolescents below 18 years of age.

Pazopanib should not be given to human paediatric patients younger than 2 years of age because the mechanism of action of pazopanib 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 pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib.

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

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

Co-administration of 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 (TYKERB®), a substrate and weak inhibitor of CYP3A4, Pgp and BCRP with 800 mg pazopanib resulted in an approximately 50 % to 60 % increase in mean pazopanib $AUC_{(0-24)}$ and Cmax 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. If no medically acceptable alternative to a strong CYP34A inhibitor is available, the dose of pazopanib should be reduced to 400 mg daily during concomitant administration (see 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.

<u>CYP3A4 Inducers</u>
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.

<u>Effects of pazopanib on CYP Substrates</u>
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. Pazopanib 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 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.

<u>Effects of pazopanib on Other Enzymes and Transporters</u>
In vitro studies also showed that pazopanib is a potent inhibitor of UGT1A1 and OATP1B1 with IC_{50} of 1.2 and 0.79 microM, respectively. Pazopanib may increase concentrations of drugs primarily eliminated through UGT1A1 (e.g. irinotecan) and OATP1B1 (e.g. rosuvastatin).

<u>Effect of concomitant use of pazopanib and Simvastatin</u>
Concomitant use of pazopanib and simvastatin increases the incidence of ALT elevations. Across monotherapy studies with pazopanib, 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 pazopanib 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 pazopanib.

<u>Effect of Food on pazopanib</u>
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 section 4.2 Dose and method of administration).

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

4.6   Fertility, pregnancy and lactation
Use in Pregnancy
Pregnancy Category D

Risk Summary

Based on animal reproduction studies and its mechanism of action, pazopanib can cause foetal harm when administered to a pregnant woman. There are no adequate data from the use of pazopanib 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). Pazopanib should not be used during pregnancy unless the clinical condition

of the woman requires treatment with pazopanib. Pregnant women or females of reproductive potential should be advised of the potential risk to a foetus.

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

Fertility
Based on findings from animal studies, pazopanib 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.

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 $\geq$ 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 $\geq$ 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 pazopanib 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 pazopanib treatment and for at least 2 weeks after the last dose.

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

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 pazopanib, a lactating woman should be advised not to breastfeed during treatment with pazopanib.

4.7   Effects on ability to drive and use machines
There have been no studies to investigate the effect of pazopanib on driving performance or the ability to operate machinery. A detrimental effect on such activities cannot be predicted from the pharmacology of pazopanib. The clinical status of the patient and the adverse event profile of pazopanib 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 pazopanib 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 pazopanib 800 mg once daily (N=290) or placebo (N=145). The median duration of treatment was 7.4 months for the pazopanib arm and 3.8 months for the placebo arm.

The safety and efficacy of pazopanib 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 pazopanib 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.

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 $\geq$ 1 in 10
Common $\geq$ 1 in 100 and < 1 in 10
Uncommon $\geq$ 1 in 1,000 and < 1 in 100
Rare $\geq$ 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)

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
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 embolism	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	Commone
General disorders and administration site conditions		
Asthenia	Very common	Uncommon
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 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

† - Frequency based on heart rate measurement (< 60 beats per minute) rather than adverse event reports. Symptomatic bradycardia has been identified rarely based on a review of the pazopanib safety database
‡ - 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 pazopanib and with a frequency greater than placebo in study VEG105192

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

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

	Pazopanib (N = 290)			Placebo (N = 145)		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Parameters						
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 pazopanib. 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

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

4.9 Overdose

Pazopanib 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.

<u>Symptoms and Signs</u>

There is currently limited experience with overdosage in pazopanib.

<u>Treatment</u>

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

For information on the management of overdose, contact the Poison Information Centre on 0800 764 766 (New Zealand).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent protein kinase inhibitor, ATC code: L01XE03

<u>Mechanism of Action</u>

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

<u>Pharmacogenomics</u>

In a pharmacogenetic meta-analysis of data from 31 clinical studies of pazopanib 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).

<u>Clinical Trials</u>
Renal Cell Carcinoma (RCC)

The safety and efficacy of pazopanib 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 pazopanib 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 pazopanib 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 pazopanib 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 pazopanib and placebo arms, respectively) and/or prior radiotherapy (22 % and 15 % in the pazopanib 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	Pazopanib	Placebo	HR (95% CI)	P value
PFS	**Median (months)**			**(one-sided)**
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)
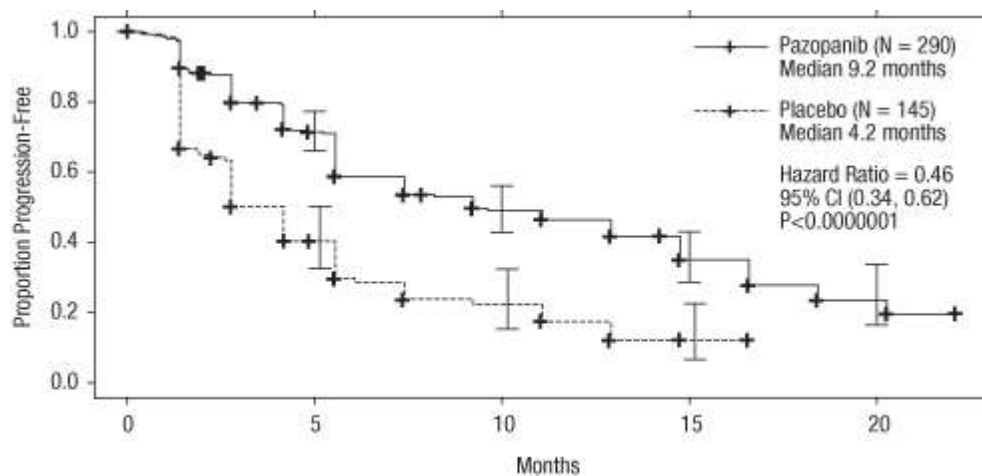
Figure 2   Kaplan-Meier Curve for Progression-Free Survival by Independent Assessment for the Treatment-Naïve Population
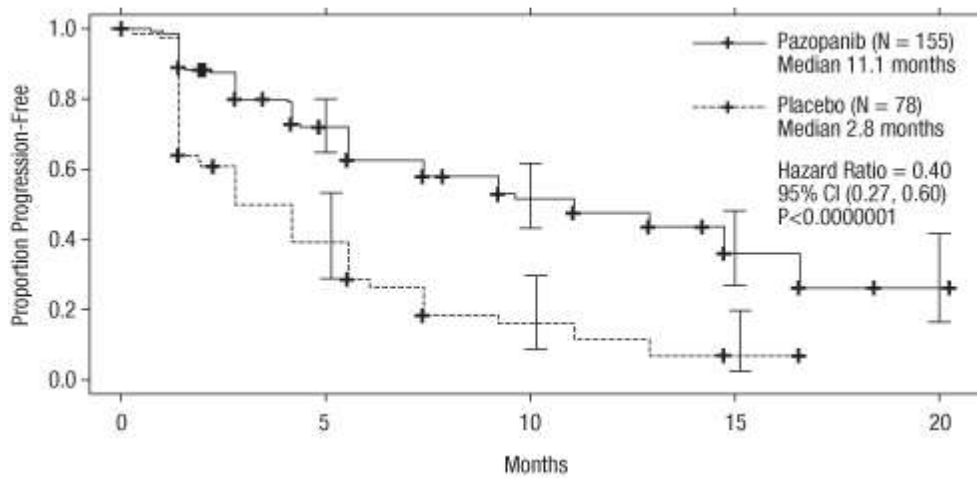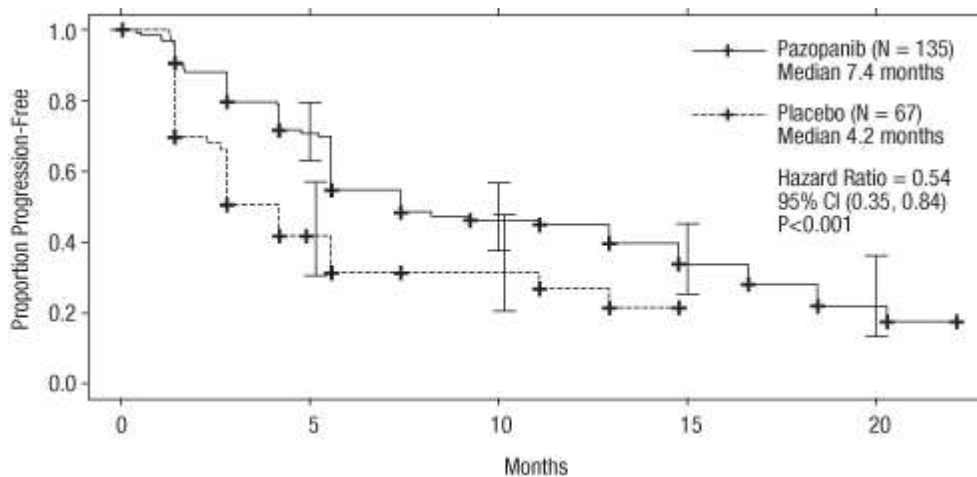

Figure 3 Kaplan-Meier Curve for Progression-Free Survival by Independent Assessment for the Cytokine Pre-Treated Population

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 pazopanib and placebo arms, respectively. The OS results are subject to potential bias as 54 % of patients in the placebo arm also received pazopanib in the extension part of this study following disease progression. Sixty-six percent (66 %) of placebo patients received post-study therapy compared to 30 % of pazopanib patients.

In the pivotal study, the QoL assessments were based on blinded self-reported global scores from two protocol-specified questionnaires, EORTC QLQ-C30 and EuroQoL EQ-5D. Analysis was based on patients who continued on therapy in both arms, prior to progression. The assessments showed no difference between treatment with pazopanib or placebo (p > 0.05), indicating no negative impact of pazopanib 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 pazopanib 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 pazopanib 800 mg once daily continuously or sunitinib 50 mg once daily in 6-week cycles of dosing with 4 weeks on treatment followed by 2 weeks without treatment.

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

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

Table 7   Overall Efficacy Results (VEG108844)

Endpoint	Pazopanib N=557	Sunitinib N=553	HR (95 % CI)
PFS			
Overall Median (months)	8.4	9.5	1.047
(95 % CI)	(8.3, 10.9)	(8.3, 11.0)	(0.898,1.220)
Overall Survival			
Median (months)	28.4	29.3	0.908[a]
(95 % CI)	26.2, 35.6)	(25.3, 32.5)	(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 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. 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, $p < 0.001$).

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

Endpoints/study population	Pazopanib N=246	Placebo N=123	HR (95% CI)	P value (one-sided_
PFS Overall ITT median (weeks)	20.0	7.0	0.35 (0.26, 0.48)	<0.001
Leiomyosarcoma Median (weeks)	N = 109 20.1	N = 49 8.1	0.37 (0.23, 0.60)	<0.001
Synovial sarcoma subgroups median (weeks)	N = 25 17.9	N = 13 4.1	0.43 (0.19, 0.98)	0.005
'Other STS' subgroups median (weeks)	N = 122 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)
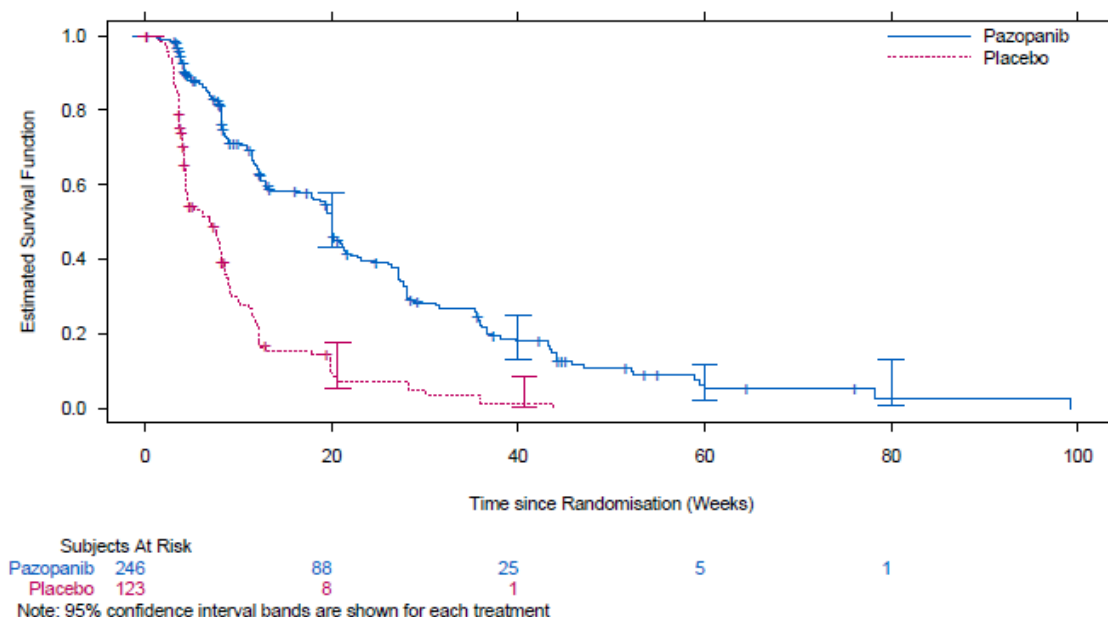
The hazard ratio (HR) at the pre-specified interim analysis for overall survival in favour of pazopanib was not statistically significant; the median overall survival in the placebo arm was 10.4 months (95 % CI 8.7 to 12.7) and was 11.9 months (95 % CI 10.7 to 15.1) in the pazopanib arm; HR = 0.82 (97.87 % 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 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 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).

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

<u>Absorption</u>

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

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 section 4.2 Dose and method of 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 section 4.2 Dose and method of administration).

<u>Distribution</u>

Binding of pazopanib 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 pazopanib is a substrate for P-glycoprotein (Pgp) and breast cancer resistant protein (BCRP).

<u>Biotransformation</u>

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

<u>Elimination</u>

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.

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 pazopanib. Renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary in patients with creatine clearance ≥ 30 mL/min (see section 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 pazopanib 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 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 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 pazopanib 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 pazopanib 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 pazopanib, there were increased numbers of liver adenomas noted in mice and duodenal adenocarcinomas noted in rats. Based on the rodent- specific pathogenesis and mechanism for these findings, they are not considered to represent an increased carcinogenic risk for patients taking pazopanib.

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

Fertility
In a female fertility and early embryonic development study in rats, post-implantation loss, embryo lethality and decreased foetal 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-foetal development toxicity studies, pazopanib produced teratogenic effects (including cardiovascular malformations), delayed ossification, increased post-implantation loss, reduced foetal 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 foetal 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).

Pazopanib has been shown to be embryotoxic and teratogenic when administered to rats and rabbits at exposures below clinical exposure. Effects included cardiovascular malformations, delayed ossification, reduced female fertility, increased pre- and post- implantation loss, early resorptions, embryo lethality, and decreased 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, pazopanib 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
Pazopanib did not cause genetic damage when tested in genotoxicity assays (Ames assay, human peripheral lymphocyte chromosome aberration assay and rat in vivo micronucleus). A synthetic intermediate in manufacture of pazopanib, which is also present in the final drug substance, was not mutagenic but genotoxic in the mouse lymphoma assay and in vivo mouse micronucleus assay and is controlled below a daily intake of 0.1 mg.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Microcrystalline cellulose
Sodium starch glycollate
Povidone
Magnesium stearate
Film coat
Hypromellose
Titanium dioxide

Macrogol 400
Iron oxide red (200 mg only)
Polysorbate 80

6.2   Incompatibilities
Not applicable.

6.3   Shelf life
36 months.

6.4   Special precautions for storage
Store below 25°C.

6.5   Nature and contents of container
Blister pack PVC/PE/PVDC Aluminium foil. Pack size of 30 or 90 tablets (200 mg) and 30 or 60 tablets (400 mg).

HDPE bottles. Pack size of 30 or 90 tablets (200 mg) and 30 or 60 tablets (400 mg).

6.6   Special precautions for disposal
No special requirements for disposal.

7.   MEDICINE SCHEDULE
Prescription Medicine

8.   SPONSOR
Teva Pharma (New Zealand) Limited
PO Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

9.   DATE OF FIRST APPROVAL
22 June 2023

10.   DATE OF REVISION OF THE TEXT
2 November 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
6.3	Shelf life extension to 36 months