Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ZIBOVO 200

ZIBOVO 400

2. QUALITATIVE AND QUANTITAIVE COMPOSITION

ZIBOVO 200 mg

Each film coated tablet contains:

Pazopanib hydrochloride equivalent to 200 mg pazopanib free base.

Sugar Free

ZIBOVO 400 mg

Each film coated tablet contains:

Pazopanib hydrochloride equivalent to 400 mg pazopanib free base.

Sugar Free

For full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Film coated tablet

ZIBOVO 200

Grey coloured, capsule shaped, film coated tablets debossed with 'S7' on one side and plain on other side

ZIBOVO 400

White coloured, capsule shaped, film coated tablets plain on both the sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

ZIBOVO is indicated for the treatment of adult patients with selective subtypes of advanced soft tissue sarcoma (STS) who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo) adjuvant therapy.

Efficacy and safety have only been established in certain STS histological tumour subtypes. (see **section 5.1**).

4.2. Posology and method of administration

Posology:

ZIBOVO is for the use as a single chemotherapeutic medicine and is not for concurrent administration with other chemotherapeutic medicines

The recommended dose of **ZIBOVO** for the treatment of RCC or STS is

800 mg orally once daily.

ZIBOVO should be taken whole with water and must not be broken or crushed. (see **section 5.2**).

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

Dose Modifications:

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

Special Populations

Paediatric Populations:(below 18 years)

The safety and efficacy of pazopanib in children have not been established. (see **section 4.4**).

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 **section 5.2**).

Renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary in patients with creatinine 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**).

No dose adjustment is required in patients with mild hepatic impairment as defined by alanine aminotransferase (ALT) and bilirubin (see **section 5.2**).

The dose of pazopanib should be reduced to 200 mg per day in patients with moderate hepatic impairment (see **section 5.2**).

Pazopanib is not recommended in patients with severe hepatic impairment (defined as total bilirubin >3 x ULN regardless of the ALT value).

Cases of hepatic failure including fatal outcome have occurred in patients treated with pazopanib (see **section 4.8**).

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active component and other ingredients contained in the product (see **section 6.1**).

Pre-clinical studies in animals have shown reproductive toxicity. Based on animal reproduction studies and its mechanism of action, pazapanib can cause foetal harm when administered to a pregnant woman (see **section 4.6**).

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**). 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

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 (over 90 %) of all transaminase elevations of any grade occurred in the first 18 weeks.

Grades are based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3 (NCI CTCAE).

Serum liver tests should be performed before initiation of treatment with pazopanib, at weeks 3, 5, 7 and 9, then at months 3 and 4 with additional tests as clinically indicated. Periodic testing should then continue after month 4.

- Patients with isolated ALT elevations between 3 X ULN and 8 X ULN may be continued on pazopanib with weekly monitoring of liver function until ALT return to Grade 1 (NCI CTCAE) or baseline.

- Patients with ALT of > 8 X ULN should have pazopanib interrupted until they return to Grade 1 (NCI CTCAE) or baseline. If the potential benefit of re-initiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then re-introduce pazopanib at a reduced dose of 400 mg once daily and perform serum liver tests weekly for 8 weeks (see **section 4.2)**. Following re-introduction of pazopanib, if ALT elevations > 3 X ULN recur, then pazopanib should be permanently discontinued.
- If ALT elevations > 3 X ULN occur concurrently with bilirubin elevations > 2 X ULN, pazopanib should be permanently discontinued. Patients should be monitored until return to Grade 1 (NCI CTCAE) or baseline pazopanib is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect

hyperbilirubinemia, known or suspected Gilbert's syndrome, and elevation in ALT > 3 X ULN should be managed as per the recommendations outlined for isolated ALT elevations.

Concomitant use of pazopanib and simvastatin increases the risk of ALT elevations (see **section 4.5**) 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 s tarting 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**). Hypertension (systolic blood pressure ≥ 150 mm Hg 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). In the case of persistent hypertension despite antihypertensive therapy, pazopanib dose may be reduced (see **section 4.2**). 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**). Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis and pazopanib should be discontinued in patients developing ILD or pneumonitis.

Cardiac dysfunction

Clinical studies of pazopanib have identified a risk of cardiac dysfunction, including decreased left ventricular ejection fraction (LVEF) and congestive heart failure. Findings across studies indicate that reductions in LVEF occurred more frequently in patients receiving pazopanib compared with control groups, while cases of congestive heart failure were reported infrequently.

Patients who developed cardiac dysfunction often had concurrent hypertension, suggesting that elevated blood pressure may contribute to or worsen cardiac impairment in susceptible individuals, particularly those with pre-existing cardiac risk factors or prior cardiotoxic treatments.

These findings support the importance of regular blood pressure monitoring and appropriate management during pazopanib treatment. Patients should also be monitored for signs and symptoms of heart failure, and baseline as well as periodic assessment of cardiac function (including LVEF) is recommended for individuals at increased risk of cardiac dysfunction.

QT Prolongation and Torsade de Pointes

In reported clinical studies with pazopanib, events of QT prolongation or Torsade de Pointes have occurred (see **section 4.8**).

Pazopanib should be used with caution in patients with a history of QT interval prolongation, patients taking anti-arrhythmics or other medications that may potentially prolong QT interval, or those 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 reported clinical studies with pazopanib, myocardial infarctions, angina, ischemic stroke and transient ischemic attack were observed (see **section 4.8**). Fatal events have been reported. Pazopanib should be used with caution in patients who are at increased risk for 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)

TMA has been reported in clinical studies of pazopanib as monotherapy, in combination with bevacizumab, and in combination with topotecan (see **section 4.8**). Patients developing TMA should permanently discontinue treatment with pazopanib. Reversal of effects of TMA has been reported after treatment was discontinued. Pazopanib is not indicated for use in combination with other medicine.

Haemorrhagic Events

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

Gastrointestinal Perforations and Fistula

In clinical studies with pazopanib, events of gastrointestinal (GI) perforation or fistula have been reported (see **section 4.8**). Fatal perforation events have been reported. 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 been reported (see **section 4.8**). Proactive monitoring of thyroid function tests is recommended.

Proteinuria

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

Tumour lysis syndrome (TLS)

The occurrence of TLS, including fatal TLS, has been reported to be associated with the use of pazopanib (see **section 4.8**). Patients at increased 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 outcome, have been reported.

Combination with other systemic anti-cancer therapies

Clinical trials of pazopanib in combination with pemetrexed (non-small cell lung cancer (NSCLC)) and lapatinib (cervical cancer) were terminated early due to concerns over increased toxicity and/or mortality, and a safe and effective combination dose has not been established with these regimens. Pazopanib is not indicated for use in combination with other anti-cancer medicine.

Juvenile animal toxicity:

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

Pregnancy

Pre-clinical studies in animals have shown reproductive toxicity (see **section 4.6**).

Based on animal reproduction studies and its mechanism of action, pazopanib can cause foetal harm when administered to a pregnant woman. Pregnant women 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 (see **section 4.6**).

Class effects

Class effects of Tyrosine Kinase Inhibitors (TKIs) such as contained in pazopanib**.**

Although TKIs may have different kinase inhibition profiles and/or off target binding profiles, there is some evidence that the TKIs share to a variable degree, class related cerebrovascular adverse events (e.g. cerebrovascular accident, transient ischaemic attack, ischaemic stroke, and cerebral infarction).

These cerebrovascular adverse events may occur in patients on treatment with TKIs with or without risk factors for these events and may occur at any time during treatment with TKIs.

Patients on treatment with pazopanib should be carefully monitored, and relevant risk factors managed to reduce the risk for these class related cerebrovascular adverse events.

Treatment with pazopanib should be discontinued, and alternative treatment options be considered in patients who developed these class related cerebrovascular adverse events.

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**). Selection of alternative concomitant medicines with no or minimal potential to inhibit CYP3A4, P-gp or BCRP should be considered.

Grapefruit juice should be avoided as it also inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib.

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

4.5. Interaction with other medicines and other forms of interaction

Medicines that Inhibit or Induce Cytochrome P450 3A4 Enzymes

Reported *In vitro* studies suggested that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1 A2 and CYP2C8. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib.

CYP3A4 *P-gp, BCRP* Inhibitors

Pazopanib is a substrate for CYP3, P-gp and BCRP. Concurrent administration of pazopanib (400 mg once daily) with the strong CYP3A4 and P gp inhibitor, ketoconazole (400 mg once daily) for 5 consecutive days, resulted in a 66 % and 45 % increase in mean pazopanib $AUC_{(0-24)}$ and C_{max}, respectively, relative to administration of pazopanib alone (400 mg once daily for 7 days). Pazopanib C_{max} and AUC increase in a less than dose proportional fashion with increasing dose over the range of 50 mg to 2000 mg. 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 strong inhibitors of the CYP3A4 family (e.g. itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin,

voriconazole) may increase pazopanib concentrations. Grapefruit juice should be avoided as it also inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib.

Administration of 1 500 mg lapatinib, 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 C_{max} compared to administration of 800 mg pazopanib alone. Co-administration of pazopanib with a CYP3A4, Pgp, and BCRP inhibitor, such as lapatinib, will result in an increase in plasma pazopanib concentrations. Concomitant use of pazopanib with a strong CYP3A4 inhibitor should be avoided. 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)**. 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.

CYP3A Inducers: CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. Selection of an alternative concomitant medication with no or minimal enzyme induction potential is recommended.

Effects of Pazopanib on CYP Substrates

In vitro studies with human liver microsomes showed that pazopanib inhibited CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, and 2E1. Potential induction of human CYP3A4 was demonstrated in an *in vitro* human PXR assay. Clinical pharmacology studies, using pazopanib 800 mg once daily, have demonstrated that pazopanib does not have a clinically relevant effect on the pharmacokinetics of caffeine (CYP1A2 probe substrate), warfarin (CYP2C9 probe substrate), or omeprazole (CYP2C19 probe substrate) in cancer patients. 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 dextrometrophan to dextrorphan concentrations in the urine after oral administration of dextromethorphan

(CYP2D6 probe substrate). Co-administration of pazopanib 800 mg once daily and paclitaxel 80 mg/m^2 (CYP3A4 and CYP2C8 substrate) once weekly, resulted in a mean increase of 26 % and 31 % in paclitaxel AUC and C_{max}, respectively.

Effects of Pazopanib on other enzymes and transporters:

In vitro studies also showed that pazopanib is a potent inhibitor of UGT1A1 and OATP1B1 with IC_{50} of 1,2 and 0,79 µM, respectively. Pazopanib may increase concentrations of medicines primarily eliminated through UGT1A1 and OATP1B1.

Effect of concomitant use of pazopanib and simvastatin

Concomitant use of pazopanib patient and simvastatin increases the incidence of ALT elevations. Across monotherapy studies with pazopanib, ALT > 3 X ULN was reported in 14 % of patients who did not use statins, compared with 27 % of with 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**)

Effect of Food on pazopanib

Administration of pazopanib with a high fat or low-fat meal reported 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**).

Medicines that raise gastric pH

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 breastfeeding

Women of childbearing potential /Contraception in males and females

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

Pregnancy

Pazopanib should not be used during pregnancy (See section 4.3)

There are no adequate data from the use of pazopanib in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Women of childbearing potential should use adequate contraception and should not become pregnant while receiving treatment with pazopanib

Breastfeeding

Because of the potential for serious adverse reactions in breastfed infants from pazopanib, breastfeeding should be discontinued during treatment with pazopanib (see **section 4.6**).

Fertility

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

4.7 Effects on ability to drive and use machines

The clinical status of the patient and the adverse event profile especially fatigue and possible blurred vision 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

The safety and efficacy of pazopanib in renal cell carcinoma (RCC) have been reported to be evaluated in a randomised, double blind, placebo-controlled multi-centre study. Patients with locally advanced and/or metastatic RCC have been reported to be randomised to receive pazopanib 800 mg once daily or placebo. 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 randomized, double- blind, placebo-controlled multi-center study. Patients with advanced STS who had received prior anthracycline treatment, or were unsuited for such therapy, were randomized to receive pazopanib 800 mg once daily or placebo. The median duration of treatment was 4,5 months for the pazopanib arm and 1,9 months for the placebo arm.

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

Adverse drug reactions	**Frequency classification**	
	RCC	**STS**
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		
Tumour pain	♦	Frequent
Blood and lymphatic system disorders		
Neutropenia	Frequent	♦
Thrombocytopenia	Frequent	♦

Endocrine disorders		
Hypothyroidism*	Frequent	Frequent
Metabolism and nutrition disorders		
Anorexia	Frequent	Frequent
Weight decreased	Frequent	Frequent
Nervous system disorders		
Dizziness	♦	Frequent
Dysgeusia	Frequent	Frequent
Headache	Frequent	Frequent
Insomnia	♦	Frequent
Ischaemic stroke*	Less Frequent	Less Frequent
Transient ischaemic attack*	Frequent	♦
Cardiac disorders		
Cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure)*	Less Frequent	Frequent
Bradycardia (asymptomatic)	Frequent †	Frequent †

Myocardial infarction*	Less Frequent	Frequent
Myocardial ischaemia*	Frequent	♦
QT prolongation*	Frequent	Frequent
Torsade de Pointes*	Less Frequent	♦
Vascular disorders		
Cerebral haemorrhage*	Less Frequent	Less Frequent
Epistaxis	Frequent	Frequent
Gastrointestinal haemorrhage*	Frequent	Frequent
Haematuria	Frequent	Less Frequent
Hypertension*	Frequent	Frequent
Pulmonary haemorrhage*	Less Frequent	Frequent
Venous thromboembolic events*	Frequent	Frequent
Respiratory, thoracic and mediastinal disorders		
Cough	♦	Frequent
Dysphonia	Frequent	Frequent
Dyspnoea	♦	Frequent
Pneumothorax	♦	Frequent
Gastrointestinal disorders		
Abdominal pain	Frequent	Frequent
Diarrhoea	Frequent	Frequent
Dyspepsia	Frequent	Frequent

Gastrointestinal perforation*	Less frequent	♦
Gastrointestinal fistula*	Less frequent	Less frequent
Lipase elevations	Frequent‡	♦
Nausea	Frequent	Frequent
Stomatitis	♦	Frequent
Vomiting	Frequent	Frequent
Hepatobiliary disorders		
Alanine aminotransferase increased*	Frequent	Frequent
Aspartate aminotransferase increased*	Frequent	Frequent
Hepatic function abnormal*	Frequent	♦
Hyperbilirubinaemia*	Frequent	Less Frequent
Skin and subcutaneous tissue disorders		
Alopecia	Frequent	Frequent
Dry skin	♦	Frequent
Exfoliative rash	♦	Frequent
Hair depigmentation	Frequent	Frequent
Nail disorder	♦	Frequent
Palmar-plantar erythrodysaesthesia syndrome (Foot-hand syndrome)	Frequent	Frequent
Rash	Frequent	Less Frequent

Skin depigmentation	Frequent	Frequent
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	♦	Frequent
Myalgia	♦	Frequent
Renal and urinary disorders		
Proteinuria*	Frequent	Less Frequent
General disorders and administration site conditions		
Asthenia	Frequent	Less Frequent
Chest pain*	Frequent	Frequent
Chills	♦	Frequent
Fatigue	Frequent	Frequent
Oedema peripheral	♦	Frequent
Vision blurred	♦	Frequent

** - See **section 4.4** 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 erythrodysesthesia syndrome were observed more frequently in patients of East Asian descent.

Table 2 presents laboratory abnormalities occurring in ≥ 15 % of patients who received pazopanib in the pivotal RCC study. Grades are based on the NCI CTCAE.

Effect on Laboratory tests

During the clinical trials in patients with RCC (study VEG105192) and STS (study VEG110727), pazopanib caused several laboratory abnormalities but the majority were mild and did not require treatment adjustment. The changes in the following laboratory tests though still mild (grade 1-2), were greater than in the placebo group in ≥ 15 % of patients: Haematology (leukopenia, neutropenia, thrombocytopenia, lymphocytopenia and anaemia); chemistry (increased ALT, AST, glucose, total bilirubin, potassium and creatinine; and decreased phosphorus, calcium, sodium, magnesium and glucose).

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

	Pazopanib			**Placebo**		
Parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Haematologic						
Leukopenia	37	0	0	6	0	0
Neutropenia	34	1	< 1	6	0	0

Thrombocytopenia	32	< 1	< 1	5	0	< 1
Lymphocytopenia	31	4	< 1	24	1	0
Chemistry						
ALT increased	53	10	2	22	1	0
AST increased	53	7	< 1	19	< 1	0
Glucose increased	41	< 1	0	33	1	0
Total Bilirubin increased	36	3	< 1	10	1	< 1
Phosphorus decreased	34	4	0	11	0	0
Calcium decreased	33	1	1	26	1	< 1
Sodium decreased	31	4	1	24	4	1

Potassium increased	27	4	< 1	23	5	0
Creatinine increased	26	0	< 1	25	< 1	0
Magnesium decreased	26	< 1	1	14	0	0
Glucose decreased	17	0	< 1	3	0	0

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

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

	PAZOPANIB			**Placebo**		
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

Adverse reactions reported during post-approval use

Infections and infestations

Infections (with or without neutropenia -see **section 4.4**)

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

Tumour lysis syndrome (include fatal cases); (see **section 4.4**)

Blood and lymphatic system disorders

Polycythaemia, Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome see section **section 4.4**)

Nervous system disorders

Posterior reversible encephalopathy syndrome (see **section 4.4**) cerebrovascular accident, transient ischaemic attack, ischaemic stroke

Eye disorders

Retinal detachment/tear

Respiratory, thoracic and mediastinal disorders

Interstitial lung disease (ILD)/pneumonitis (see **section 4.4**)

Gastrointestinal disorders

Flatulence, Pancreatitis

Hepatobiliary disorders

Gamma-glutamyl transpeptidase increased, Hepatic Failure (Including fatal events)

Musculoskeletal and connective tissue disorders

Arthralgia, Muscle spasms

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via email: pharmacovigilance.africasme@sunpharma.com

or Tel: +27(0) 12 643 2000.

4.9 Overdose

Grade 3 fatigue (dose-limiting toxicity) and Grade 3 hypertension were observed in1 of 3 patients dosed at 2000 mg and 1000 mg daily, respectively.

Symptoms and Signs:

There is currently limited experience reported with overdosage in pazopanib.

Treatment:

Further management should be as clinically indicated or as recommended by the national poisons centre, where available. Haemodialysis is not expected to enhance the elimination of pazopanib because pazopanib is not significantly renally excreted and is highly bound to plasma proteins. Treatment should be supportive and symptomatic. Cardiovascular monitoring for dysrhythmias and hypertension is required. Hepatic function should be assessed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 26 Cytosatic agents

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, other protein kinase inhibitor**, ATC code:** L01EX03

Mechanism of Action:

Pazopanib is an oral multi-target tyrosine kinase inhibitor that potently blocks VEGF receptors, PDGF receptors, and c-KIT, which are key regulators of angiogenesis and tumor growth. In preclinical studies, it inhibited the activation of these receptors in a dose-dependent manner. Animal studies further demonstrated that pazopanib suppresses VEGF-driven signaling, inhibits the formation of new blood vessels, and reduces the growth of multiple human tumor xenografts. Overall, the findings indicate that pazopanib has significant anti-angiogenic and anti-tumor activity through the inhibition of pathways involved in cancer progression.

Pharmacogenomics

In a pharmacogenetic meta-analysis of data from 31 clinical studies of pazopanib administered either as monotherapy or in combination with other medicines, ALT > 5 X ULN (NCI CTC Grade 3) occurred in 19 % of HLA-B*57:01 allele carriers and in 10 % of non-carriers. In this dataset, 133/2235 (6 %) of the patients carried the HLA-B*57:01 allele (see **section 4.4**).

Summary of clinical studies

Renal Cell Carcinoma (RCC)

The safety and efficacy of pazopanib in renal cell carcinoma (RCC) were evaluated in a randomized, double-blind, placebo-controlled multi-center study. Patients with locally advanced and/or metastatic RCC were randomized to receive pazopanib 800 mg once daily or placebo. The primary objective of the study was to evaluate and compare the two treatment arms for progression-free survival (PFS) and the

principle secondary endpoint was overall survival (OS). The other objectives were to evaluate the overall response rate and duration of response.

From the total of patients in this study, patients were treatment naïve and were second line patients who had received one prior IL-2 or INF-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 (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 was based on disease assessment by independent radiological review in the entire study population (first line and second line).
Pazopanib demonstrated statistically significant improvement in PFS-compared with placebo treatment in the overall study population (HR 0,46 [95 % CI, 0,34 to 0,62, p<0,0000001]), the treatment-naïve (HR 0,40 [95 % CI 0,27 to 0,60, p<0,0000001]) and cytokine pre-treated (HR 0,54 [95 % CI: 0,35, 0,84, p<0,001]) subgroups. In the overall study population, the median PFS was 9,2 months in pazopanib arm

and 4,2 months in placebo arm. In treatment-naive sub-group, the median PFS was 11,1 months in pazopanib arm and 2,8 months in placebo arm. In cytokine pre-treated sub-group, the median PFS was 7,4 months in pazopanib arm and 4,2 months in placebo arm. In the overall population, the response rate was 30 % (95 % CI 25,1, 35,6) in the pazopanib arm and 3 % (95 % CI 0,5, 6,4) in placebo arm.

For patients who responded to treatment, the median duration of response was 58,7 weeks as per independent review. The median overall survival (OS) data at the protocol specified final survival analysis were 2,9 months and 20,5 months [HR=0,91 (95 % CI: 0,71, 1,16; p=0,224)] for patients randomized to the pazopanib and placebo arms, respectively. The OS results are subject to potential bias as 54 % of patients in the placebo arm also received pazopanib in the extension part of this study following disease progression. Sixty-six percent of placebo patients received post-study therapy compared to 30 % of pazopanib patients.

In the pivotal study, the QoL assessments were based on blinded self-reported global scores from two protocol-specified questionnaires, EORTC QLQ-C30 and EuroQoL EQ-5D. Analysis was based on patients who continued on therapy in both arms, prior to progression. The assessments showed no difference between treatment with pazopanib or placebo ($p > 0,05$), indicating no negative impact of pazopanib on global quality of life.

In a Phase II study of patients with locally recurrent or metastatic clear cell renal cell carcinoma, objective response rate was 35 % and median duration of response was 68 weeks, as per independent review.

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

In VEG108844, patients 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 based on independent review committee (IRC) assessment. 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 (HR of (95 % CI: 0.898; 1,220)), as the upper bound of the 95 % CI for the hazard ratio was less than the protocol-specified non-inferiority margin of 1,25. In pazopanib arm, median PFS was 8,4 months (95 % CI: 8,3, 10,9) and median OS was 28,3 months (95 % CI: 26,0, 35,5).

Soft tissue sarcoma (STS)

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

Soft-tissue sarcoma (STS)

The efficacy and safety of pazopanib in STS were evaluated in a pivotal Phase III randomised, double-blind, placebo-controlled multicentre study (VEG110727). Patients with advanced STS were randomised to receive pazopanib 800 mg once daily or placebo. Importantly, only patients with selective histological subtypes of STS were allowed to participate to the study, therefore efficacy and safety of pazopanib can only be considered established for those subgroups of STS and treatment with pazopanib should be restricted to such STS subtypes.

The following tumour types were eligible:

Fibroblastic (adult fibrosarcoma, myxofibrosarcoma, sclerosing epithelioid fibrosarcoma, malignant solitary fibrous tumours), so-called fibrohistiocytic (pleomorphic malignant fibrous histiocytoma [MFH], giant cell MFH, inflammatory MFH), leiomyosarcoma, malignant glomus tumours, skeletal muscles (pleomorphic and alveolar rhabdomyosarcoma), vascular (epithelioid hemangioendothelioma, angiosarcoma), uncertain differentiation (synovial, epithelioid, alveolar soft part, clear cell, desmoplastic small round cell, extra-renal rhabdoid, malignant mesenchymoma, PEComa, intimal sarcoma), malignant peripheral nerve sheath tumours, undifferentiated soft tissue sarcomas not otherwise specified (NOS) and other types of sarcoma (not listed as ineligible).

The following tumour types were not eligible:

Adipocytic sarcoma (all subtypes), all rhabdomyosarcoma that were not alveolar or pleomorphic, chondrosarcoma, osteosarcoma, Ewing tumours/primitive neuroectodermal tumours (PNET), GIST, dermofibromatosis sarcoma protuberans, inflammatory myofibroblastic sarcoma, malignant mesothelioma and mixed mesodermal tumours of the uterus.

Prior to randomization, eligible subjects were stratified by the factors of WHO performance status (WHO PS) (0 or 1) at baseline and the number of lines of prior systemic therapy for advanced disease (0 or 1 vs. 2+).

The median duration of follow-up of subjects (defined as date of randomization to date of last contact or death) was similar for both treatment arms (9,36 months for placebo [range 0,69 to 23,0 months] and 10,04 months for pazopanib [range 0,2 to 24,3 months].

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

In the ITT population, a statistically significant improvement in PFS was observed in the pazopanib arm compared with the placebo arm. The median PFS in the placebo arm was 7,0 weeks (95 % CI: 4,4, 8,1) and in the pazopanib arm was 20,0 weeks (95 % CI: 17,9, 21,3), with a corresponding HR of 0,35 (95 % CI: 0,26, 0,48, p<0,001) as assessed by independent radiologist. The improvement in median PFS and HR with pazopanib compared with placebo in each of the histology subgroups (leiomyosarcoma, synovial sarcoma and "other" STS) was consistent with the overall population as assessed by the independent radiologist, with HR of 0,37 (95 % CI: 0,23, 0,60, p<0,001) in leiomyosarcoma subgroup, HR of 0,43 (95 % CI: 0,19, 0,98, p=0,0005) in synovial sarcoma subgroup, and HR of 0,39 (95 % CI: 0,25, 0,60, p<0,001) in 'other' STS subgroup.

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).

The hazard ratio at the pre-specified interim analysis for overall survival in favour of pazopanib was not statistically significant; the median overall survival in the placebo arm was 10,4 months (95 % CI 8,7 to 12,7) and was 11,9 months (95 % CI 10,7 to 15,1) in the pazopanib arm; HR=0,82 (97,87 % CI: 0,59 to 1,14, p=0,156).

5.2. Pharmacokinetic properties

Absorption

Pazopanib is absorbed orally with median time to achieve peak concentrations of 2,0 to 4,0 hours after the dose. Daily dosing results in 1,23- to 4-fold increase in AUC. There was no consistent increase in AUC and C_{max} when the pazopanib dose increased above 800 mg once daily.

Systemic exposure to pazopanib has been reported to be increased when administered with food. Administration of pazopanib with a high-fat or low-fat meal reported 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**).

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 whole tablet. Therefore, due to this potential for increased exposure, tablets should not be crushed (see **Section 4.2**).

Distribution

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

Biotransformation

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

Elimination

Pazopanib has been reported to be eliminated slowly with mean half-life of 30,9 hours after administration of the recommended dose of 800 mg. Elimination has been reported to be primarily via faeces with renal elimination accounting for < 4 % of the administered dose.

Special populations

Renal impairment

In a population pharmacokinetic analysis using subjects with various cancers, creatinine clearance (30-150 mL/min) did not influence clearance of pazopanib. Renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary in patients with creatinine clearance ≥ 30 mL/min (see **section 4.2**)

Hepatic Impairment

The median steady-state pazopanib C_{max} and $AUC_{(0-24)}$ in patients with mild hepatic impairment (defined as either normal bilirubin and any degree of ALT elevations or as an elevation of bilirubin up to 1,5 X ULN regardless of the ALT value) after a once daily dose of 800 mg/day (30,9 µg/mL, range 12,5 47,3 and 841,8 µg,hr/mL, range 600,4 1078) are similar to the median in patients with no hepatic impairment (49,4 µg/mL, range 17,1-85,7 and 888,2 µg,hr/mL, range 345,5-1482) (see **section 4.2**).

The maximally tolerated pazopanib dose (MTD) in patients with moderate hepatic impairment (defined as an elevation of bilirubin > 1,5 X to 3 X ULN regardless of the ALT values) was 200 mg once daily, The median steady-state values of C_{max} (22,4 µg/mL, range 6,4-32,9) and $AUC_{(0-24)}$ (350,0 µg,hr/mL, range 131,8-487,7) after administration of 200 mg pazopanib once daily in subjects with moderate hepatic impairment were approximately 45 % and 39 %, respectively, that of the corresponding median values after administration of 800 mg once daily in subjects with normal hepatic function (see **section 4.2**).

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Intragranular ingredients

Microcrystalline Cellulose(Avicel PH-101)

Sodium Starch Glycollate(Primojel)

Povidone(PVK K-30)

Purified Water

Extragranular ingredients

Microcrystalline Cellulose (Avicel PH-302)

Sodium Starch Glycolate (Primojel) (Type-A)

Magnesium Stearate(powder) Hyqual 2257,Vegetable Grade)

Film Coating materila

Opadry Complete Film Coating Solution

YS-1-17506-A GRAY

Opadry Complete film coating system

White YS-1-7706-G

Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at or below 30 ºC, Protect from moisture,

Do not remove the tablets from the bottle until required for use,

6.5 Nature and contents of container

200 and 400 mg

Each bottle contains 30 tablets packed in 40CC white round HDPE 33-400 Screwed neck heavy weight bottles,

6.6 Special precautions for disposal and other handling

Return all unused or expired medicines to your pharmacist for safe disposal, Do not dispose of unused medicines in drains or sewerage systems (e,g, toilets),

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill, Ext, 1

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South Africa

Tel No: 012 643-2000

8 REGISTRATION NUMBER(S)

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Zibovo 400:61/26/1849

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10 DATE OF REVISON OF THE TEXT

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