Applicant: Teva Pharmaceuticals (Pty) Ltd	**Product name:** PAZOTEV 200 & PAZOTEV 400 **Dosage form & strength:** Each film-coated tablet contains pazopanib hydrochloride equivalent to 400 mg pazopanib

APPROVED PROFESSIONAL INFORMATION:

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

PAZOTEV 200, film-coated tablets

PAZOTEV 400, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each film-coated tablet contains pazopanib hydrochloride equivalent to 200 mg or 400 mg pazopanib.

PAZOTEV is sugar free.

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

3. PHARMACEUTICAL FORM:

Film-coated tablets.

PAZOTEV 200: Capsule-shaped, pink, film-coated tablet with ‘200’ debossed on one side, with dimensions 14,3 mm x 5,7 mm ± 5 %.

PAZOTEV 400: Capsule-shaped, white, film-coated tablet with ‘400’ debossed on one side, with dimensions 18,0 mm x 7,1 mm ± 5 %.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

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

4.2 Posology and method of administration:

Posology:

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

Dose modifications:

Dose modification should be in 200 mg increments in a stepwise fashion based on individual tolerability in order to manage adverse reactions. The dose of PAZOTEV should not exceed 800 mg.

CYP3A4 inhibitor: The concomitant use of strong CYP3A4 inhibitors may increase pazopanib concentrations and should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). If co-administration of a strong CYP3A4 inhibitor is warranted, a dose reduction to 400 mg of PAZOTEV is recommended based on pharmacokinetic studies. This dose is predicted to adjust the pazopanib AUC to the range observed without inhibitors (see **section 4.5**). However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors.

Special populations:

Elderly:

No alteration of dosage, dosing frequency or route of administration is required in patients over 65 years.

Renal impairment:

There is no experience of PAZOTEV in patients with severe renal impairment or in patients undergoing peritoneal dialysis or haemodialysis. Renal impairment is unlikely to have a clinically relevant effect on pazopanib pharmacokinetics given the low renal excretion of pazopanib and metabolites (see **section 5.2**, Elimination).

Hepatic impairment:

The safety and pharmacokinetics of PAZOTEV in patients with hepatic impairment have not been fully established (see **section 4.4**).

Paediatric population:

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

Method of administration:

For oral use.

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

4.3 Contraindications:

- Known hypersensitivity to pazopanib, or any of the excipients of PAZOTEV listed in **section 6.1**.

4.4 Special warnings and precautions for use:

Hepatic effects:

Cases of hepatic failure (including fatalities) have been reported during use of PAZOTEV. Administration of PAZOTEV to patients with mild or moderate hepatic impairment should be undertaken with caution and close monitoring. 800 mg pazopanib once daily is the recommended dose in patients with mild abnormalities in serum liver tests (either normal

bilirubin and any degree of ALT elevation or elevation of bilirubin up to 1,5 x ULN regardless of the ALT value). A reduced pazopanib dose of 200 mg once daily is recommended in patients with moderate hepatic impairment (elevation of bilirubin >1,5 to 3 x ULN regardless of the ALT value) (see **sections 4.2** and **5.2**). PAZOTEV is not recommended in patients with severe hepatic impairment (total bilirubin >3 x ULN regardless of the ALT value) (see **sections 4.2** and **5.2**). Exposure at a 200 mg dose is markedly reduced, though highly variable, in these patients, with values considered insufficient to obtain a clinically relevant effect.

Reports from clinical studies 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 of age may be at greater risk for mild (>3 x ULN) to severe (>8 x ULN) elevation of ALT. Patients who carry the HLA-B*57:01 allele have an increased risk of pazopanib-associated ALT elevations. Liver function should be monitored in all patients receiving pazopanib, regardless of genotype or age (see **section 5.1**).

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.

See Table 1 for dose modification guidance for patients with baseline values of total bilirubin ≤1,5 x ULN and AST and ALT ≤ 2 x ULN:

Table 1 Dose modifications for drug-induced hepatotoxicity:

Liver test values	Dose modification
Transaminase elevation between 3 and 8 x ULN	Continue on PAZOTEV with weekly monitoring of liver function until transaminases return to Grade 1 or baseline.

Transaminase elevation of >8 x ULN	Interrupt PAZOTEV until transaminases return to Grade 1 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 daily and perform serum liver tests weekly for 8 weeks. Following re-introduction of PAZOTEV, if transaminase elevations >3 x ULN recur, then PAZOTEV should be permanently discontinued.
Transaminase elevations >3 x ULN concurrently with bilirubin elevations >2 x ULN	Permanently discontinue PAZOTEV. Patients should be monitored until return to Grade 1 or baseline. PAZOTEV is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinaemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinaemia, known or suspected Gilbert's syndrome, and elevation in ALT >3 x ULN should be managed as per the recommendations outlined for isolated ALT elevations.

Concomitant use of pazopanib (e.g., PAZOTEV) and simvastatin increases the risk of ALT elevations (see **section 4.5**) and should be undertaken with caution and close monitoring.

Hypertension:

Blood pressure should be well controlled prior to initiating PAZOTEV. Patients should be monitored for hypertension and treated as needed with standard antihypertensive therapy (see **section 4.8**). Hypertension occurs early in the course of treatment (88 % occurring in first 18 weeks). In the case of persistent hypertension despite antihypertensive therapy, the PAZOTEV dose may be reduced (see **section 4.2**). PAZOTEV should be discontinued if

hypertension is severe and persists despite antihypertensive therapy and PAZOTEV 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. Patients developing PRES/RPLS should permanently discontinue treatment with PAZOTEV.

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 PAZOTEV should be discontinued in patients developing ILD or pneumonitis.

Cardiac dysfunction/Heart failure:

The risks and benefits of PAZOTEV 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 left ventricular ejection fraction (LVEF) have not been studied.

QT prolongation and torsade de pointes:

In clinical studies with pazopanib, events of QT prolongation and *torsade de pointes* have occurred (see **section 4.8**). Pazopanib should be used with caution in patients with a history of QT interval prolongation, in patients taking antidysrhythmics or other medicines that may prolong QT interval and in patients with relevant pre-existing cardiac disease. When using pazopanib, baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g. calcium, magnesium, potassium) within normal range is recommended.

Arterial thrombotic events:

It has been reported that in clinical studies with pazopanib, myocardial infarction, myocardial ischaemia, ischaemic stroke and transient ischaemic attack were observed (see **section 4.8**). Fatal events have been observed. PAZOTEV 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 on the assessment of individual patient's benefit/risk.

Venous thromboembolic events:

It has been reported that in clinical studies with pazopanib, venous thromboembolic events including venous thrombosis and fatal pulmonary embolus have occurred. While observed in both RCC and STS studies, 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 PAZOTEV. Reversal of effects of TMA has been observed after treatment was discontinued. PAZOTEV is not indicated for use in combination with other medicines.

Haemorrhagic events:

Reports from 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 haemorrhage or clinically significant gastrointestinal (GI) haemorrhage in the past 6 months. PAZOTEV should be used with caution in patients with significant risk of haemorrhage.

Aneurysms and artery dissections:

The use of vascular endothelial growth factor (VEGF) pathway inhibitors in patients with or without hypertension may promote the formation of aneurysm and/or artery dissections. Before initiating PAZOTEV, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Gastrointestinal (GI) perforations and fistula:

It has been reported that in clinical studies with pazopanib, events of GI perforation or fistula have occurred (see **section 4.8**). Fatal perforation events have occurred. PAZOTEV 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 PAZOTEV should be stopped at least 7 days prior to scheduled surgery. The decision to resume PAZOTEV after surgery should be based on clinical judgement of adequate wound healing. PAZOTEV should be discontinued in patients with wound dehiscence.

Hypothyroidism:

Reports from clinical studies with pazopanib showed events of hypothyroidism have occurred (see **section 4.8**). Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism should be treated as per standard medical practice prior to the start of PAZOTEV treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction on PAZOTEV treatment. Laboratory monitoring of thyroid function should be performed periodically and managed as per standard medical practice.

Proteinuria:

Reports from clinical studies reported proteinuria. Baseline and periodic urine analysis during treatment is recommended and patients should be monitored for worsening proteinuria. PAZOTEV should be discontinued if the patient develops nephrotic syndrome.

Tumour lysis syndrome (TLS):

The occurrence of TLS, including fatal TLS, has been associated with the use of PAZOTEV (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 PAZOTEV. Patients at risk should be closely monitored and treated as clinically indicated.

Pneumothorax:

Reports from clinical studies with pazopanib in advanced soft tissue sarcoma, have shown events of pneumothorax have occurred (see **section 4.8**). Patients on PAZOTEV treatment should be observed closely for signs and symptoms of pneumothorax.

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:

It has been reported from clinical studies of pazopanib in combination with a number of other anti-cancer therapies (including for example pemetrexed, lapatinib or pembrolizumab) 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.

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.

Concomitant treatment with inducers of CYP3A4 should be avoided due to risk of decreased exposure to pazopanib (see **section 4.5**).

Cases of hyperglycaemia have been observed during concomitant treatment with ketoconazole.

Concomitant administration of PAZOTEV with uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) substrates (e.g. irinotecan) should be undertaken with caution since pazopanib is an inhibitor of UGT1A1 (see **section 4.5**).

Grapefruit juice should be avoided during treatment with PAZOTEV (see **section 4.5**).

Paediatric population:

Because the mechanism of action of pazopanib as contained in PAZOTEV can severely affect organ growth and maturation during early post-natal development in rodents (see **section 5.3**), PAZOTEV should not be given to paediatric patients younger than 2 years of age.

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction:

Effects of other medicines on PAZOTEV:

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:

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

Co-administration of PAZOTEV with strong inhibitors of the CYP3A4 family (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase pazopanib concentrations. Grapefruit juice 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, P-gp and BCRP with 800 mg PAZOTEV resulted in an approximately 50 % to 60 % increase in mean pazopanib AUC(0-24) and C_{max} compared to administration of 800 mg PAZOTEV alone. Co-administration of PAZOTEV with a CYP3A4, P-gp, and BCRP inhibitor, such as lapatinib, will result in an increase in plasma pazopanib concentrations.

Combination with strong CYP3A4 inhibitors should therefore be avoided, or selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended. A dose reduction of PAZOTEV should be considered when it must be co-administered with strong CYP3A4 inhibitors (see **section 4.2**).

CYP3A4, P-gp, BCRP inducers:

CYP3A4 inducers such as rifampicin may decrease plasma pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended.

Effects of pazopanib on CYP substrates:

In vitro studies with human liver microsomes showed that pazopanib inhibited CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, and 2E1. Potential induction of human CYP3A4 was demonstrated in an *in vitro* human PXR assay. Clinical pharmacology studies, using PAZOTEV 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 PAZOTEV 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.

Effect of concomitant use of pazopanib (e.g. PAZOTEV) and simvastatin:

Concomitant use of pazopanib as contained in PAZOTEV and simvastatin increases the incidence of ALT elevations. If a patient receiving concomitant simvastatin develops ALT elevations, follow guidelines for pazopanib posology and discontinue simvastatin (see **section 4.4**). In addition, concomitant use of PAZOTEV and other statins should be undertaken with caution as there are insufficient data available to assess their impact on ALT levels. It cannot be excluded that pazopanib as contained in PAZOTEV will affect the pharmacokinetics of other statins (e.g. atorvastatin, fluvastatin, pravastatin, rosuvastatin).

Effect of food on PAZOTEV:

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

Medicines that raise gastric pH:

Concomitant administration of pazopanib as contained in PAZOTEV with esomeprazole decreases the bioavailability of pazopanib by approximately 40 % (AUC and C_{max}), and co-administration of PAZOTEV with medicines that increase gastric pH should be avoided. If the concomitant use of a proton-pump inhibitor (PPI) is medically necessary, it is recommended that the dose of PAZOTEV be taken without food once daily in the evening concomitantly with the PPI. If the concomitant administration of an H_2-receptor antagonist is medically necessary, PAZOTEV should be taken without food at least 2 hours before or at least 10 hours after a dose of an H_2-receptor antagonist. PAZOTEV should be administered at least 1 hour before or 2 hours after administration of short-acting antacids. The recommendations for how PPIs and H_2-receptor antagonists are co-administered are based on physiological considerations.

4.6 Fertility, pregnancy and lactation:

Women of childbearing potential/Contraception in males and females:

Women of childbearing potential should be advised to use adequate contraception during treatment and for at least 2 weeks after the last dose of PAZOTEV and to avoid becoming pregnant while receiving treatment with PAZOTEV.

Male patients (including those who have had vasectomies) should use condoms during sexual intercourse while taking PAZOTEV and for at least 2 weeks after the last dose of PAZOTEV to avoid potential exposure to the medicine for pregnant partners and female partners of reproductive potential.

Pregnancy:

PAZOTEV should not be used during pregnancy.

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.

Breastfeeding:

The safe use of PAZOTEV during lactation has not been established. Breastfeeding should be discontinued during treatment with PAZOTEV.

Fertility:

PAZOTEV may impair fertility in human males and females. In female reproductive toxicity studies in rats, reduced female fertility has been observed.

4.7 Effects on ability to drive and use machines:

PAZOTEV has no or negligible influence on the ability to drive and use machines. 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 PAZOTEV should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills. Patients should avoid driving or using machines if they feel dizzy, tired or weak.

4.8 Undesirable effects:

a. Summary of the safety profile:

The safety and efficacy of PAZOTEV 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 PAZOTEV 800 mg once daily or placebo. The median duration of treatment was 7,4 months for the PAZOTEV arm and 3,8 months for the placebo arm.

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

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

b. Tabulated list of adverse reactions:

Table 2: Treatment-related adverse reactions reported in RCC studies or during post-marketing period

(MedDRA) System Organ Class	Frequency	Adverse reactions
Infections and infestations	Frequent	Infections (with or without neutropenia)†
	Less frequent	Gingival infection, infectious peritonitis
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Less frequent	Tumour pain
Blood and lymphatic system disorders	Frequent	Thrombocytopenia, neutropenia, leukopenia
	Less frequent	Polycythaemia, thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome)†
Endocrine disorders	Frequent	Hypothyroidism
Metabolism and nutrition disorders	Frequent	Decreased appetite[e], hypophosphataemia, dehydration, anorexia
	Less frequent	Hypomagnesaemia, tumour lysis syndrome*
Psychiatric disorders	Frequent	Insomnia
Nervous system disorders	Frequent	Dysgeusia[c], headache, dizziness, lethargy, paraesthesia, peripheral sensory neuropathy
	Less frequent	Hypoaesthesia, transient ischaemic attack, somnolence, cerebrovascular accident,

		ischaemic stroke, posterior reversible encephalopathy/ reversible posterior leukoencephalopathy syndrome†
Eye disorders	Frequent	Blurred vision
	Less frequent	Retinal detachment†, retinal tear†, eyelash discolouration
Cardiac disorders	Frequent	Myocardial ischaemia, QT prolongation
	Less frequent	Bradycardia, myocardial infarction, cardiac dysfunction[f], *Torsades de Pointes*
Vascular disorders	Frequent	Hypertension, hot flush, venous thromboembolic event[g], flushing
	Less frequent	Hypertensive crisis, haemorrhage
	Frequency unknown	Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders	Frequent	Epistaxes, dysphonia, dyspnoea, haemoptysis, chest pain
	Less frequent	Rhinorrhoea, pulmonary haemorrhage, pneumothorax, interstitial lung disease/pneumonitis†
Gastrointestinal disorders	Frequent	Diarrhoea, vomiting, nausea, abdominal pain[a], stomatitis, dyspepsia, flatulence, abdominal distension, mouth ulceration, dry mouth

	Less frequent	Pancreatitis, rectal haemorrhage, haematochezia, gastrointestinal haemorrhage, melaena, frequent bowel movements, anal haemorrhage, large intestine perforation, mouth haemorrhage, upper gastrointestinal haemorrhage, enterocutaneous fistula, haematemesis, haemorrhoidal haemorrhage, ileal perforation, oesophageal haemorrhage, retroperitoneal haemorrhage
Hepato-biliary disorders	Frequent	Hyperbilirubinaemia, hepatic function abnormal, hepatotoxity
	Less frequent	Jaundice, drug induced liver injury, hepatic failure†
Skin and subcutaneous disorders	Frequent	Hair colour change, palmar-plantar erythrodysaesthesia syndrome, alopecia, rash, skin hypopigmentation, dry skin, pruritis, erythema, skin depigmentation, hyperhidrosis
	Less frequent	Nail disorders, skin exfoliation, photosensitivity reaction, rash erythematous,skin disorder, macular rash, pruritic rash, vesicular rash, generalised

		pruritus, generalised rash, papular rash, plantar erythema
Musculoskeletal and connective tissue disorder	Frequent	Arthralgia, myalgia, muscle spasms
	Less frequent	Musculoskeletal pain
Renal and urinary disorders	Frequent	Proteinuria
	Less frequent	Haemorrhage urinary tract
Reproductive system and breast disorders	Frequent	Menorrhagia, vaginal haemorrhage, metrorrhagia
General disorders and administration site conditions	Frequent	Fatigue, mucosal inflammation, asthenia, oedema[b]
	Less frequent	Chills, mucous membrane disorder
Investigations	Frequent	Increased alanine aminotransferase, increased aspartate aminotransferase, decreased weight, increased blood bilirubin, increased blood creatinine, increased lipase, decreased white blood cell count[d], increased blood thyroid stimulating hormone, increased amylase, increased gamma-glutamyl transferase, increased blood pressure, increased blood urea, abnormal liver function test
	Less frequent	Increased hepatic enzyme, decreased blood glucose, prolonged electrocardiogram QT, increased transaminase,

		abnormal thyroid function test, increased diastolic blood pressure, increased systolic blood pressure

†Treatment-related adverse reaction reported during post-marketing period (spontaneous case reports and serious adverse reactions from all pazopanib clinical studies).
*Treatment-related adverse reaction reported only during the post-marketing period. Frequency cannot be estimated from the available data.
The following terms have been combined:
a Abdominal pain, abdominal pain upper and abdominal pain lower
b Oedema, oedema peripheral, eye oedema, localised oedema and face oedema
c Dysgeusia, ageusia and hypogeusia
d White cell count decreased, neutrophil count decreased and leukocyte count decreased
e Decreased appetite and anorexia
f Cardiac dysfunction, left ventricular dysfunction, cardiac failure and restrictive cardiomyopathy
g Venous thromboembolic event, deep vein thrombosis, pulmonary embolism and thrombosis

Table 1 presents laboratory abnormalities occurring in ≥ 15 % of patients who received pazopanib.

Table 1. Selected laboratory abnormalities in ≥ 15 % of patients who received PAZOTEV and more commonly than placebo arm

	Pazopanib (N = 290)			**Placebo (N = 145)**		
Parameters	**All grades %**	**Grade 3 %**	**Grade 4 %**	**All grades %**	**Grade 3 %**	**Grade 4 %**
Haematologic						

Leukopenia	37	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

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 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 the SAHPRA website.

4.9 Overdose:

PAZOTEV doses up to 2 000 mg have been evaluated in clinical trials without dose-limiting toxicity.

Symptoms and signs:

There is currently limited experience with overdosage in PAZOTEV.

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

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 26 Cytostatic agents.

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

Mechanism of action:

Pazopanib is an orally administered, potent multi-target tyrosine kinase inhibitor (TKI) of Vascular Endothelial Growth Factor Receptors (VEGFR)-1, -2, and -3, platelet-derived growth factor (PDGFR)-α and -β, and stem cell factor receptor (c-KIT), with IC50 values of 10, 30, 47, 71, 84 and 74 nM, respectively. In preclinical experiments, pazopanib dose-dependently inhibited ligand-induced auto-phosphorylation of VEGFR-2, c-Kit and PDGFR-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.

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.

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**).

Distribution:

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

Biotransformation:

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

Elimination:

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

Special populations:

Renal impairment:

Results indicate that less than 4 % of an orally administered pazopanib dose is excreted in the urine as pazopanib and metabolites. Results from population pharmacokinetic modelling (data from participants with baseline CL_{CR} values ranging from 30,8 ml/min to 150 ml/min) indicated that renal impairment is unlikely to have a clinically relevant effect on pazopanib pharmacokinetics. No dose adjustment is required in patients with creatinine clearance above 30 ml/min. Caution is advised in patients with creatinine clearance below 30 ml/min as there is no experience of pazopanib in this patient population (see **section 4.2**).

Hepatic impairment:

Mild:

The median steady-state pazopanib C_{max} and $AUC_{(0-24)}$ in patients with mild abnormalities in hepatic parameters (defined as either normal bilirubin and any degree of ALT elevation or as an elevation of bilirubin up to 1,5 x ULN regardless of the ALT value) after administration of 800 mg once daily are similar to the median in patients with normal hepatic function (see Table 7). Pazopanib 800 mg pazopanib once daily is the recommended dose in patients with mild abnormalities of serum liver tests (see **section 4.2**).

Moderate:

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 C_{max} and $AUC_{(0-24)}$ values after administration of 200 mg pazopanib once daily in patients with moderate hepatic impairment were approximately 44 % and 39 %, of the corresponding median values after administration of 800 mg once daily in patients with normal hepatic function, respectively (see Table 7).

Based on safety and tolerability data, the dose of pazopanib should be reduced to 200 mg once daily in participants with moderate hepatic impairment (see **section 4.2**).

Severe:

The median steady-state C_{max} and $AUC_{(0-24)}$ values after administration of 200 mg pazopanib once daily in patients with severe hepatic impairment were approximately 18 % and 15 %, of the corresponding median values after administration of 800 mg once daily in patients with normal hepatic function. Based on the diminished exposure and limited hepatic reserve pazopanib is not recommended in patients with severe hepatic impairment (defined as total bilirubin > 3 X ULN regardless of any level of ALT) (see **section 4.2**).

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients

Tablet core:

Cellulose, microcrystalline

Magnesium stearate

Povidone K-30

Sodium starch glycolate (type A)

Tablet coating:

Hypromellose

Iron oxide red (E172)

Macrogol 400

Polysorbate 80

Titanium dioxide (E171).

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

30 months.

6.4 Special precautions for storage:

Store at or below 25 °C.

Store in a dry place and protect from light and moisture.

6.5 Nature and contents of container:

PAZOTEV 200 and 400 film-coated tablets are packed in aluminium-PVC/PE/PVDC blisters or in white, plastic high density polyethylene (HDPE) bottles with screwed mouth that are stoppered with a white, plastic (PP) child resistant cap.

Pack size: PAZOTEV 200 – HDPE bottles of 30 or 90 tablets.

Blisters of 30, 60, multipack of 60 (2 packs of 30), 90, multipack of 90 (3 packs of 30) tablets.

Pack size: PAZOTEV 400 – HDPE bottles of 30 or 60 tablets.

Blisters of 30, 60, multipack of 60 (2 packs of 30) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling:

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

2090

South Africa

8. REGISTRATION NUMBER(S):

PAZOTEV 200: 57/26/0150

PAZOTEV 400: 57/26/0151

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

18 March 2025

10. DATE OF REVISION OF THE TEXT:

To be allocated