

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PAZITORZ 200 mg film-coated tablets

PAZITORZ 400 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PAZITORZ 200 mg:

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

PAZITORZ 400 mg:

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

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

PAZITORZ 200 mg:

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

PAZITORZ 400 mg:

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PAZITORZ is indicated for the treatment of:

- advanced and/or metastatic renal cell carcinoma (RCC) in adults.
- 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.

4.2 Posology and method of administration

Posology

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

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

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

Special Populations:

Paediatric population (below 18 years):

The safety and efficacy of PAZITORZ 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 influence pazopanib exposure, and dose adjustment is not necessary in patients with creatinine clearance ≥ 30 ml/min. There is no experience of PAZITORZ in patients with severe renal impairment or in patients undergoing peritoneal dialysis or haemodialysis, therefore, use of PAZITORZ is not recommended in these patients.

Hepatic impairment:

The safety and pharmacokinetics of PAZITORZ in patients with pre-existing hepatic impairment have not been fully established (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 Pharmacological Properties- Pharmacokinetic properties: special populations).

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

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

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

Method of administration

PAZITORZ is for oral use.

PAZITORZ should be taken whole with water and must not be broken or crushed.

PAZITORZ 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 substance or to any of the excipients listed in section 6.1.

- Pre-clinical studies in animals have shown reproductive toxicity. Based on animal reproduction studies and its mechanism of action, pazopanib, as contained in PAZITORZ, can cause foetal harm when administered to a pregnant woman.

4.4 Special warnings and precautions for use

Class effects of Tyrosine Kinase Inhibitors (TKIs) such as contained in PAZITORZ

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 PAZITORZ should be carefully monitored, and relevant risk factors managed to reduce the risk for these class related cerebrovascular adverse events.

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

Hepatic effects

Cases of hepatic failure (including fatalities) have been reported during use of pazopanib.

PAZITORZ has not been studied in patients with pre-existing hepatic impairment and so should be used with caution in these patients.

In clinical trials with pazopanib, increase in serum transaminases (ALT, 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

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in all patients 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).

Monitor serum liver tests before initiation of treatment with PAZITORZ and at weeks 3, 5, 7 and 9, then at months 3 and 4 with additional tests as clinically indicated. Periodic monitoring should then continue after month 4.

- Patients with isolated ALT elevations between 3 x ULN and \leq 8 x ULN may be continued on PAZITORZ with weekly monitoring of liver function until ALT return to Grade 1 (NCI CTCAE) or baseline.
- Patients with transaminases of $>$ 8 x ULN should have PAZITORZ interrupted until they return to Grade 1 (NCI CTCAE) or baseline.

If the potential benefit for re-initiating PAZITORZ treatment is considered to outweigh the risk for hepatotoxicity, then re-introduce PAZITORZ at a reduced dose and measure serum liver tests weekly for 8 weeks (see section 4.2). Following re-introduction of PAZITORZ, if ALT elevations $>$ 3 x ULN recur, then PAZITORZ should be permanently discontinued.

- If ALT elevations $>$ 3 x ULN occur concurrently with bilirubin elevations $>$ 2 x ULN, PAZITORZ should be permanently discontinued. Patients should be monitored until return to Grade 1 (NCI CTCAE) or baseline. PAZITORZ 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.

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Concomitant use of PAZITORZ 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 PAZITORZ 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 newly diagnosed symptomatic episodes of elevated blood pressure (hypertensive crisis) have occurred.

Blood pressure should be well controlled prior to initiating PAZITORZ.

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.

Elevated blood pressure levels (systolic blood pressure \geq 150 mm Hg or diastolic blood pressure \geq 100 mm Hg) occurred early in the course of treatment (approximately 40 % of cases occurred by day 9 and approximately 90 % of cases occurred in the first 18 weeks). Patients should be monitored for hypertension and treated as needed with standard antihypertensive therapy (see section 4.8). In the case of persistent hypertension despite antihypertensive therapy, the PAZITORZ dose may be reduced (see section 4.2).

PAZITORZ should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persists despite anti-hypertensive therapy and PAZITORZ 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

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neurological disturbances, and can be fatal. Patients developing PRES/RPLS should permanently discontinue treatment with PAZITORZ.

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 PAZITORZ should be discontinued in patients developing ILD or pneumonitis.

Cardiac dysfunction/Heart failure

The risks and benefits of PAZITORZ 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.

In clinical studies with pazopanib, events of cardiac dysfunction such as congestive heart failure and decreased LVEF have occurred (see section 4.8).

Management

Interruption of PAZITORZ and/or dose reduction should be combined with treatment of hypertension (if present, refer to hypertension warning section above) in patients with significant reductions in LVEF, as clinically indicated.

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 and Torsade de Pointes have

occurred (see section 4.8).

PAZITORZ should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medicines that may potentially prolong QT interval and in patients with relevant pre-existing cardiac disease. When using PAZITORZ, baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g., calcium, magnesium, potassium) within normal range is recommended.

Arterial thrombotic events

In clinical studies with pazopanib, myocardial infarction, angina, myocardial ischaemia, ischaemic stroke and transient ischaemic attack were observed (see section 4.8). Fatal events have been observed. PAZITORZ 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

In clinical studies with pazopanib, venous thromboembolic events including venous thrombosis and fatal pulmonary embolus have occurred.

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 PAZITORZ.

Reversal of effects of TMA has been observed after treatment was discontinued. PAZITORZ 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. PAZITORZ is not recommended in patients who had

a history of haemoptysis, cerebral haemorrhage or clinically significant gastrointestinal (GI) haemorrhage in the past 6 months. PAZITORZ should be used with caution in patients with significant risk of haemorrhage.

Aneurysms and artery dissections

The use of VEGF (Vascular Endothelial Growth Factor) pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating PAZITORZ, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysms.

Gastrointestinal (GI) perforations and fistula

In clinical studies with pazopanib, events of GI perforation or fistula have occurred (see section 4.8). Fatal perforation events have occurred. PAZITORZ should be used with caution in patients at risk for GI perforation or fistula.

Wound healing

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

Hypothyroidism

In clinical studies with pazopanib, 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 PAZITORZ treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction on PAZITORZ treatment. Laboratory monitoring of thyroid function should be performed periodically and managed as per standard medical practice.

Proteinuria

In clinical studies with pazopanib, proteinuria has been reported. Baseline and periodic urinalysis during treatment is recommended and patients should be monitored for worsening proteinuria. PAZITORZ 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 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 PAZITORZ. Patients at risk should be closely monitored and treated as clinically indicated.

Pneumothorax

Patients on PAZITORZ 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

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 PAZITORZ 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 PAZITORZ (see section 4.5).

Juvenile animal toxicity:

Because the mechanism of action of pazopanib can severely affect organ growth and maturation during early post-natal development, PAZITORZ 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 PAZITORZ (see section 4.6).

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

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

Concurrent administration of pazopanib (400 mg once daily) with the strong CYP3A4 and P-gp inhibitor ketoconazole (400 mg once daily) for 5 consecutive days resulted in a 66 % and 45 % increase in mean pazopanib $AUC_{(0-24)}$ and C_{max} , respectively, relative to administration of pazopanib alone (400 mg once daily for 7 days). Pharmacokinetic parameter comparisons of pazopanib C_{max} (range of means 27.5 to 58.1 $\mu\text{g/ml}$) and $AUC_{(0-24)}$ (range of means 48.7 to 1040 $\mu\text{g}\cdot\text{h/ml}$) after administration of pazopanib 800 mg alone and after administration of pazopanib 400 mg plus ketoconazole 400 mg (mean C_{max} 59.2 $\mu\text{g/ml}$, mean $AUC_{(0-24)}$ 1300 $\mu\text{g}\cdot\text{h/ml}$) indicated that, in the presence of a strong CYP3A4 and P-gp inhibitor a dose reduction to pazopanib 400 mg once daily 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 PAZITORZ 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 should be avoided as it contains an inhibitor of CYP3A4 and may also increase plasma concentrations of pazopanib.

Administration of 1500 mg lapatinib (a substrate for and weak inhibitor of CYP3A4 and P-gp and a potent inhibitor of 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. Inhibition of P-gp and/or BCRP by lapatinib likely contributed to the increased exposure to pazopanib.

Co-administration of pazopanib with a CYP3A4, P-gp, and BCRP inhibitor, such as lapatinib, will result in an increase in plasma pazopanib concentrations. Co-administration with potent P-gp or

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BCRP inhibitors may also alter the exposure and distribution of pazopanib, including distribution into the central nervous systems (CNS).

Combination of PAZITORZ with a strong CYP3A4 inhibitors should be avoided (see section 4.4), or selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended. A dose reduction of PAZITORZ should be considered when it must be co-administered with strong CYP3A4 inhibitors (see section 4.2). In such cases there should be close attention to adverse drug reaction, and 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 medicine with no or minimal potential to inhibit P-gp or BCRP is recommended.

CYP3A4, P-gp, BCRP inducers

CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. Co-administration of PAZITORZ with potent P-gp or BCRP inducers may alter the exposure and distribution of pazopanib, including distribution into the CNS. Selection of an alternative concomitant medication with no or minimal enzyme or transporter induction potential is recommended.

Effects of PAZITORZ on other medicines

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 dextrophan

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concentrations in the urine after oral administration of dextromethorphan (CYP2D6 probe substrate). Co-administration of pazopanib 800 mg once daily and paclitaxel 80 mg/m² (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 26 % and 31 % in paclitaxel AUC and C_{max}, respectively.

Based on *in vitro* IC₅₀ and *in vivo* plasma C_{max} values, pazopanib metabolites GSK1268992 and GSK1268997 may contribute to the net inhibitory effect of pazopanib towards BCRP.

Furthermore, inhibition of BCRP and P-gp by pazopanib in the gastrointestinal tract cannot be excluded. Care should be taken when pazopanib is co-administered with other oral BCRP and P-gp substrates.

In vitro, pazopanib inhibited human organic anion transporting polypeptide (OATP1B1). It cannot be excluded that pazopanib will affect the pharmacokinetics of substrates of OATP1B1 (e.g., statins, see "Effect of concomitant use of PAZITORZ and simvastatin" below).

Pazopanib is an inhibitor of the uridine diphosphoglucuronosyl-transferase 1A1 (UGT1A1) enzyme *in vitro*. The active metabolite of irinotecan, SN-38, is a substrate for OATP1B1 and UGT1A1. Co-administration of pazopanib 400 mg once daily with cetuximab 250 mg/m² and irinotecan 150 mg/m² resulted in an approximately 20 % increase in systemic exposure to SN-38. Pazopanib may have a greater impact on SN-38 disposition in subjects with the UGT1A1*28 polymorphism relative to subjects with the wild-type allele. However, the UGT1A1 genotype was not always predictive of the effect of pazopanib on SN-38 disposition. Care should be taken when pazopanib is co-administered with substrates of UGT1A1.

Effect of concomitant use of PAZITORZ and simvastatin

Concomitant use of pazopanib and simvastatin increases the incidence of ALT elevations. If a patient receiving concomitant simvastatin develops ALT elevations, follow guidelines for pazopanib posology and discontinue simvastatin (see section 4.4). In addition, concomitant use of pazopanib 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 will affect the pharmacokinetics of other statins (e.g., atorvastatin, fluvastatin, pravastatin, rosuvastatin).

Effect of food on pazopanib

Administration of pazopanib with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C_{max} .

Therefore, PAZITORZ 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 PAZITORZ 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 pazopanib be taken without food once daily in the evening concomitantly with the PPI. If the concomitant administration of an H₂-receptor antagonist is medically necessary, PAZITORZ should be taken without food at least 2 hours before or at least 10 hours after a dose of an H₂-receptor antagonist. PAZITORZ should be administered at least 1 hour before or 2 hours after administration of short-acting antacids. The recommendations for how PPIs and H₂-receptor antagonists are co-administered are based on physiological considerations.

4.6 Fertility, pregnancy and lactation

Women of child bearing 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 PAZITORZ and to avoid becoming pregnant while receiving treatment with PAZITORZ.

Male patients (including those who have had vasectomies) should use condoms during sexual intercourse while taking PAZITORZ and for at least 2 weeks after the last dose of PAZITORZ to

avoid potential exposure to the medicine for pregnant partners and female partners of reproductive potential.

Pregnancy

PAZITORZ 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 PAZITORZ.

If the patient becomes pregnant while receiving PAZITORZ, the potential hazard to the foetus should be explained to the patient.

Breastfeeding

The safe use of PAZITORZ during breast-feeding has not been established. It is not known whether pazopanib or its metabolites are excreted in human milk. There are no animal data on the excretion of pazopanib in animal milk. A risk to the breast-fed child cannot be excluded.

Breast-feeding should be discontinued during treatment with PAZITORZ.

Fertility

PAZITORZ 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

PAZITORZ 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 PAZITORZ 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

Summary of the safety profile

The most important serious (including fatal) adverse reactions identified were transient ischaemic attack, ischaemic stroke, myocardial ischaemia, myocardial and cerebral infarction, cardiac dysfunction, gastrointestinal perforation and fistula, QT prolongation, Torsade de Pointes and pulmonary, gastrointestinal and cerebral haemorrhage.

The most frequent adverse reactions included: diarrhoea, hair colour change, skin hypopigmentation, exfoliative rash, hypertension, nausea, headache, fatigue, anorexia, vomiting, dysgeusia, stomatitis, weight decreased, pain, elevated alanine aminotransferase and elevated aspartate aminotransferase.

Tabulated list of adverse reactions, by system organ class and frequency, reported in RCC and STS studies

Adverse reactions/ System Organ Class	Frequency classification	
	RCC	STS
Infections and infestations		
Infections (with or without neutropenia-see section 4.4)	Frequency not known	Frequency not known
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		
Tumour pain	◆	Frequent
Tumour lysis syndrome (including fatal cases-see	Frequency not known	Frequency not known

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section 4.4)		
Blood and lymphatic system disorders		
Neutropaenia	Frequent	◆
Thrombocytopaenia	Frequent	◆
Polycythaemia , Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome-see section 4.4)	Frequency not known	Frequency not known
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	◆
Posterior reversible encephalopathy syndrome	Frequency not known	Frequency not known

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(see section 4.4), cerebrovascular accident, transient ischaemic attack, ischaemic stroke		
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
Eye disorders		

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Retinal detachment/tear	Frequency not known	Frequency not known
Respiratory, thoracic and mediastinal disorders		
Cough	◆	Less frequent
Dysphonia	Frequent	Frequent
Dyspnoea	◆	Frequent
Pneumothorax	◆	Frequent
Interstitial lung disease (ILD)/pneumonitis-see section 4.4)	Frequency not known	Frequency not known
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
Flatulence	Frequency not known	Frequency not known
Pancreatitis	Frequency not known	Frequency not known

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	known	known
Hepatobiliary disorders		
Alanine aminotransferase increased*	Frequent	Frequent
Aspartate aminotransferase increased*	Frequent	Frequent
Hepatic function abnormal*	Frequent	◆
Hyperbilirubinaemia*	Frequent	Less frequent
Gamma-glutamyl transpeptidase increased	Frequency not known	Frequency not known
Hepatic failure (including fatal events)	Frequency not known	Frequency not known
Skin and subcutaneous tissue disorders		
Alopecia	Frequent	Frequent
Dry skin	◆	Frequent
Exfoliative rash	◆	Frequent
Hair depigmentation	Frequent	Frequent
Nail disorder	◆	Frequent
Palmar-plantar erythrodysesthesia syndrome (Foot-hand syndrome)	Frequent	Frequent
Rash	Frequent	Less frequent
Skin depigmentation	Frequent	Frequent
Musculoskeletal and connective tissue disorders		

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Musculoskeletal pain	◆	Frequent
Myalgia	◆	Frequent
Arthralgia	Frequency not known	Frequency not known
Muscle spasms	Frequency not known	Frequency not known
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

Foot notes:

* - See section 4.4. "WARNINGS AND SPECIAL 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

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 asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Pazopanib doses up to 2000 mg have been evaluated in clinical studies.

Symptoms and signs:

There is currently limited experience 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: 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 or C_{max} at pazopanib doses 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, PAZITORZ 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 10-100 μ g/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 metabolism of pazopanib is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. The four principle pazopanib metabolites account for only 6 % of the exposure in plasma. One of these metabolites inhibits the proliferation of VEGF-stimulated human umbilical vein endothelial cells with a similar potency

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to that of pazopanib, the others are 10- to 20-fold less active. Therefore, activity of pazopanib is mainly dependent on parent pazopanib exposure.

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:

In a population pharmacokinetic analysis with various cancers, creatinine clearance (30 to 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 \geq 30 ml/min (see section 4.2).

Hepatic impairment:

Mild:

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 are similar to the median in patients with no hepatic impairment. 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 values of C_{max} and $AUC_{(0-24)}$ 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

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mg once daily in subjects with normal hepatic function (see section 4.2).

Severe:

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

PAZITORZ 200 mg

Tablet core

Magnesium stearate

Microcrystalline cellulose

Povidone (K-30)

Sodium starch glycolate (Type A)

Tablet coating

Hypromellose

Iron oxide red (E172)

Macrogol 400

Polysorbate 80

Titanium dioxide (E171)

PAZITORZ 400 mg

Tablet core

Magnesium stearate

Microcrystalline cellulose

Povidone (K-30)

Sodium starch glycolate (Type A)

Tablet coating

Hypromellose

Macrogol 400

Polysorbate 80

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep containers well closed.

Keep the blisters in the carton until required for use.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

PAZITORZ 200 mg

White HDPE bottles with white, polypropylene child resistant closures containing either 30 or 90 tablets.

Aluminium-PVC/PE/PVDC blisters containing either 30 or 90 tablets.

PAZITORZ 400 mg

White HDPE bottles with white polypropylene child resistant closures containing either 30 or 60 tablets.

Aluminium-PVC/PE/PVDC blisters containing either 30 or 60 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

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No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block C, Woodmead North Office Park

54 Maxwell Drive

Woodmead

Sandton

Gauteng

2191

8. REGISTRATION NUMBER(S)

PAZITORZ 200 mg: 57/26/0641

PAZITORZ 400 mg: 57/26/0642

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 April 2025

10. DATE OF REVISION OF TEXT

06 January 2026