PROFESSIONAL INFORMATION FOR

PAZOPANIB 200 CIPLA, 200 mg FILM-COATED TABLETS

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PAZOPANIB 200 CIPLA, 200 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Sugar free.

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

3. PHARMACEUTICAL FORM

Pink, film-coated, capsule-shaped tablets, with a length of 14,5 mm and a width of 5,6 mm, debossed with “173” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

PAZOPANIB 200 CIPLA 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 PAZOPANIB 200 CIPLA is 800 mg orally once daily.

Dose modification

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 PAZOPANIB 200 CIPLA should not exceed 800 mg.

CYP3A4 inhibitor

The concomitant use of strong CYP3A4 inhibitors may increase PAZOPANIB 200 CIPLA 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 PAZOPANIB 200 CIPLA 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 is no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors.

Special Populations

Renal Impairment

There is no experience of PAZOPANIB 200 CIPLA 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**).

Hepatic Impairment

The safety and pharmacokinetics of PAZOPANIB 200 CIPLA in patients with hepatic impairment have not been fully established.

Elderly population

No alteration of dosing, dosage frequency, or route of administration is required in patients over 65 years, but greater sensitivity of some elderly patients cannot be ruled out.

Paediatric Population

The safety and efficacy of PAZOPANIB 200 CIPLA in children have not yet been established.

Method of administration

PAZOPANIB 200 CIPLA should be taken orally without food (at least one hour before or two hours after a meal). (See **section 4.5** and **5.2**)

4.3. Contraindications

Hypersensitivity to pazopanib or to any of the excipients (see **section 6.1**).

4.4. Special warnings and precautions for use

Class effects of Tyrosine Kinase Inhibitors (TKIs) such as contained in PAZOPANIB 200 CIPLA:

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

Treatment with PAZOPANIB 200 CIPLA 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 the use of pazopanib. Pazopanib has not been studied in patients with pre-existing hepatic impairment (mild or moderate hepatic impairment) and so should be used with caution and close monitoring.

PAZOPANIB 200 CIPLA 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.

In 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 subjects receiving pazopanib, regardless of genotype or age (see **section 4.4 and 4.8**).

Monitor serum liver tests before initiation of treatment with PAZOPANIB 200 CIPLA at least once every 4 weeks for the first 4 months of treatment, and as clinically indicated. Periodic monitoring should then continue after this time period.

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 modification for drug-induced hepatotoxicity

Liver test values	Dose modifications
Transaminase elevation between 3 and 8 x ULN	Continue on PAZOPANIB 200 CIPLA with weekly monitoring of liver function until transaminases return to Grade 1 or baseline.
Transaminase elevation of > 8 x ULN	Interrupt PAZOPANIB 200 CIPLA until transaminases return to Grade 1 or baseline. If the potential benefit of reinitiating PAZOPANIB 200 CIPLA treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce PAZOPANIB 200 CIPLA at a reduced dose of 400 mg daily and perform serum liver tests weekly for 8 weeks. Following reintroduction of PAZOPANIB 200 CIPLA, if transaminase elevations > 3 x ULN recur, then PAZOPANIB 200 CIPLA should be permanently discontinued.
Transaminase elevations > 3 x ULN concurrently with bilirubin elevations > 2 x ULN	Bilirubin fractionation should be performed. If direct (conjugated) bilirubin is > 35 % of total bilirubin, PAZOPANIB 200 CIPLA should be discontinued.

	Patients should be monitored until return to Grade 1 or baseline. PAZOPANIB 200 CIPLA 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 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 PAZOPANIB 200 CIPLA. 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. Blood pressure should be monitored and managed promptly using a combination of antihypertensive therapy and dose modification of PAZOPANIB 200 CIPLA (interruption and re-initiation at a reduced dose (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 PAZOPANIB 200 CIPLA dose may be reduced (see **section 4.2**). PAZOPANIB 200 CIPLA should be discontinued if hypertension is severe and persists despite antihypertensive therapy and PAZOPANIB 200 CIPLA dose reduction.

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 PAZOPANIB 200 CIPLA, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

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 200 CIPLA 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**). Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis and discontinue PAZOPANIB 200 CIPLA in patients developing ILD or pneumonitis.

Cardiac dysfunction/Heart failure

The risks and benefits of PAZOPANIB 200 CIPLA 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**).

Studies indicate concurrent hypertension may have exacerbated cardiac dysfunction in patients at risk by increasing cardiac after-load.

Prior anthracycline therapy may be a risk factor for cardiac dysfunction.

Interruption of pazopanib 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. Patients should be carefully monitored for clinical signs or symptoms of congestive heart failure. Baseline and periodic evaluation of LVEF is recommended in patients at risk of cardiac dysfunction.

QT Prolongation and Torsade de Pointes

In clinical studies with pazopanib, events of QT prolongation or Torsade de Pointes have occurred (see **section 4.8**). PAZOPANIB 200 CIPLA should be used with caution in patients with a history of QT interval prolongation, patients taking anti-dysrhythmics or other medications that may potentially prolong QT interval or those with relevant pre-existing cardiac disease. When using PAZOPANIB 200 CIPLA, periodic monitoring of electrocardiograms and maintenance of electrolytes (calcium, magnesium, potassium) within normal range is recommended.

Arterial Thrombotic Events

In clinical studies with pazopanib, myocardial infarctions, angina, ischemic stroke, cerebrovascular accident, transient ischemic attack and cerebral infarction were observed (see **section 4.8**). Fatal events have been observed. PAZOPANIB 200 CIPLA should be used with caution in patients who are at increased risk for these events. 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.

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 200 CIPLA. Reversal of effects of TMA has been observed after treatment was discontinued. PAZOPANIB 200 CIPLA is not indicated for use in combination with other medicines.

Haemorrhagic Events

In clinical studies with pazopanib, haemorrhagic events have been reported (see **section 4.8**).

Fatal haemorrhagic events have occurred. PAZOPANIB 200 CIPLA is not recommended in patients who had a history of haemoptysis, cerebral or clinically significant gastrointestinal haemorrhage in the past 6 months. PAZOPANIB 200 CIPLA 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 occurred (see **section 4.8**). Fatal perforation events have occurred. PAZOPANIB 200 CIPLA 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 VEGF inhibitors may impair wound healing, treatment with PAZOPANIB 200 CIPLA should be stopped at least 7 days prior to scheduled surgery. The decision to resume PAZOPANIB 200 CIPLA after surgery should be based on clinical judgement of

adequate wound healing. PAZOPANIB 200 CIPLA should be discontinued in patients with wound dehiscence.

Hypothyroidism

In clinical studies with pazopanib, events of hypothyroidism have occurred (see **section 4.8**). Proactive monitoring of thyroid function tests is recommended and should be initiated prior to PAZOPANIB 200 CIPLA treatment.

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 PAZOPANIB 200 CIPLA treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction.

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. PAZOPANIB 200 CIPLA 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 PAZOPANIB 200 CIPLA. Patients at risk should be closely monitored and treated as clinically indicated.

Pneumothorax

In clinical studies with pazopanib in advanced soft tissue sarcoma, events of pneumothorax have occurred (see **section 4.8**). Patients on PAZOPANIB 200 CIPLA 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.

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 pazopanib 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 as it also inhibits CYP3A4 activity and may also increase plasma concentrations of PAZOPANIB 200 CIPLA (see **section 4.8**).

Combination with other systemic anti-cancer therapies

Clinical studies 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 (see **section 4.5**).

Pregnancy

Pre-clinical studies in animals have shown reproductive toxicity. If PAZOPANIB 200 CIPLA is used during pregnancy, or if the patient becomes pregnant whilst receiving PAZOPANIB 200 CIPLA, the potential hazard to the foetus should be explained to the patient. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with PAZOPANIB 200 CIPLA (see **section 4.6**).

Paediatric population

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

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 200 CIPLA 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 200 CIPLA.

CYP3A4, P-gp, BCRP inhibitors

PAZOPANIB 200 CIPLA is a substrate for CYP3A4, P-gp and BCRP.

Concurrent administration of pazopanib (400 mg once daily) with the strong CYP3A4 inhibitor, ketoconazole (400 mg once daily), resulted in increases in mean AUC $(_{0\text{-}24})$ and C_{max}, values, relative to administration of pazopanib alone.

Co-administration of PAZOPANIB 200 CIPLA with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase PAZOPANIB 200 CIPLA concentrations.

Grapefruit juice should be avoided as it also inhibits CYP3A4 activity and may also increase plasma concentrations of PAZOPANIB 200 CIPLA.

Administration of 1500 mg lapatinib, a substrate for and weak inhibitor of CYP3A4, P-gp and BCRP with 800 mg pazopanib resulted in an approximately 50 % to 60 % increase in mean pazopanib $AUC_{(0\text{-}24)}$ 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 200 CIPLA with a CYP3A4, P-gp, and BCRP inhibitor, such as lapatinib, will result in an increase in plasma PAZOPANIB 200 CIPLA concentrations. Co-administration with potent P-gp or BCRP inhibitors may also alter the exposure and distribution of pazopanib, including distribution into the central nervous systems (CNS).

Combination with strong CYP3A4 inhibitors should therefore be avoided (see **section 4.4**), or selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended.

If no medically acceptable alternative to a strong CYP34A inhibitor is available, a dose reduction of PAZOPANIB 200 CIPLA to 400 mg 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 reactions and further dose reduction may be considered if possible, medicine related adverse events are observed.

CYP3A4, P-gp, BCRP inducers

CYP3A4 inducers such as rifampin may decrease plasma PAZOPANIB 200 CIPLA concentrations. Co-administration of pazopanib with potent P-gp or BCRP inducers may alter the exposure and distribution of pazopanib, including distribution into the CNS. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended.

Effects of PAZOPANIB 200 CIPLA 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 dextromethorphan to dextrorphan concentrations in the urine after oral administration of dextromethorphan (CYP2D6 probe substrate). Co-administration of pazopanib 800 mg once daily and paclitaxel 80 mg/m^2 (CYP3A4 and CYP2C8 substrate) once weekly, resulted in a mean increase of 26 % and 31 % in paclitaxel AUC and C_{max}, respectively.

Based on *in vitro* IC_{50} 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 200 CIPLA 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 200 CIPLA will affect the pharmacokinetics of

substrates of OATP1B1 (e.g. statins, see “Effect of concomitant use of PAZOPANIB 200 CIPLA 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/m^2 and irinotecan 150 mg/m^2 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 200 CIPLA is co-administered with substrates of UGT1A1.

Effect of concomitant use of PAZOPANIB 200 CIPLA and simvastatin

Concomitant use of PAZOPANIB 200 CIPLA and simvastatin increases the incidence of ALT elevations. Studies with pazopanib show that ALT > 3 x ULN was reported in 14 % of patients who did not use statins, compared with 27 % of patients who had concomitant use of simvastatin (p = 0,038). If a patient receiving concomitant simvastatin develops ALT elevations, follow guidelines for pazopanib posology and discontinue simvastatin (see **section 4.4**). In addition, concomitant use of PAZOPANIB 200 CIPLA 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).

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 200 CIPLA 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 200 CIPLA 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, PAZOPANIB 200 CIPLA should be taken without food at least 2 hours before or at least 10 hours after a dose of an H_2-receptor antagonist. PAZOPANIB 200 CIPLA 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.

Effect of Food on PAZOPANIB 200 CIPLA

Administration of PAZOPANIB 200 CIPLA with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and C_{max}. Therefore, PAZOPANIB 200 CIPLA should be administered at least 1 hour before or 2 hours after a meal (see **section 4.2**).

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 PAZOPANIB 200 CIPLA and to avoid becoming pregnant while receiving treatment with PAZOPANIB 200 CIPLA.

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

Pregnancy

PAZOPANIB 200 CIPLA should not be used during pregnancy. There are no adequate data from the use of pazopanib in pregnant women. Studies in animal have shown reproductive toxicity. The potential risk for humans is unknown.

Breastfeeding

The safe use of PAZOPANIB 200 CIPLA during breastfeeding 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. Breastfeeding should be discontinued during treatment with PAZOPANIB 200 CIPLA.

Fertility

PAZOPANIB 200 CIPLA 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

There have been no studies to investigate the effect of pazopanib on driving performance or the ability to operate machinery. A. detrimental effect on such activities, cannot be anticipated from the pharmacology of pazopanib. The clinical status of the patient and the adverse event profile of pazopanib should be borne in mind when considering the patient's ability to perform 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 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 common 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.

b) Tabulated list of adverse reactions

The following undesirable effects are reported corresponding to: Frequent, Less Frequent and Frequency Unknown.

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 (including 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] Weight decreased
		Hypophosphataemia
		Dehydration
	Less Frequent	Hypomagnesaemia
	Frequency unknown	Tumour lysis syndrome
Psychiatric Disorders	*Frequent*	Insomnia
Nervous System Disorders	*Frequent*	Dysgeusia[c]
		Headache
		Dizziness
		Lethargy
		Paraesthesia
		Peripheral sensory neuropathy

System Organ Class	Frequency	Adverse reactions
		Transient ischaemic attack
	Less Frequent	Hypoaesthesia
		Somnolence
		Cerebrovascular accident
		Ischaemic stroke
		Posterior reversible encephalopathy / reversible posterior leukoencephalopathy syndrome
Eye Disorders	*Frequent*	Vision blurred
	Less Frequent	Retinal detachment, Retinal tear
		Eyelash discolouration
Cardiac Disorders	*Frequent*	QT prolongation, myocardial ischaemia
	Less Frequent	Bradycardia Myocardial infarction Cardiac dysfunction[f] Torsade de Pointes
Vascular disorders	*Frequent*	Hypertension**,** hot flush, venous thromboembolic event [g], flushing
	Less frequent	Hypertensive crisis, haemorrhage, aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders	*Frequent*	Epistaxis
		Dysphonia
		Dyspnoea
		Haemoptysis
	Less Frequent	Rhinorrhoea
		Pulmonary haemorrhage
		Pneumothorax
		Interstitial lung disease/pneumonitis
Gastrointestinal Disorders	*Frequent*	Diarrhoea
		Nausea
		Vomiting
		Abdominal pain [a]
		Stomatitis
		Dyspepsia
		Flatulence
		Abdominal distension
		Mouth ulceration
		Dry mouth
	Less Frequent	Pancreatitis
		Rectal haemorrhage
		Haematochezia

System Organ Class	Frequency	Adverse reactions
		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
Hepatobiliary disorders	*Frequent*	Hyperbilirubinaemia
		Hepatic function abnormal
		Hepatotoxicity
	Less Frequent	Jaundice
		Drug induced liver injury
		Hepatic failure
Skin and Subcutaneous Tissue Disorders	*Frequent*	Hair colour change
		Palmar-plantar erythrodysaesthesia syndrome
		Alopecia
		Rash
		Skin hypopigmentation/ depigmentation
		Dry skin
		Pruritus
		Erythema
		Hyperhidrosis
	Less Frequent	Nail disorders
		Skin exfoliation
		Photosensitivity reaction
		Rash erythematous
		Skin disorders
		Rash macular
		Rash pruritic
		Rash vesicular
		Pruritus generalised
		Rash generalised
		Rash papular
		Plantar erythema
	Frequent	Arthralgia

System Organ Class	Frequency	Adverse reactions
Musculoskeletal and connective tissue Disorders		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]
		Chest Pain
	Less Frequent	Chills
		Mucous membrane disorder
Investigations	*Frequent*	Alanine aminotransferase increased
		Aspartate aminotransferase increased
		Weight decreased
		Blood bilirubin increased
		Blood creatinine increased
		Lipase increased
		White blood cell count decreased[d]
		Blood thyroid stimulating hormone increased
		Amylase increased
		Gamma-glutamyltransferase increased
		Blood pressure increased
		Blood urea increased
		Liver function test abnormal
	Less Frequent	Hepatic enzyme increased
		Blood glucose decrease
		Transaminase increased
		Thyroid function test abnormal
		Blood pressure diastolic increased
		Blood pressure systolic increased

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

System Organ Class	Frequency	Adverse reactions
[g] Venous thromboembolic event, deep vein thrombosis, pulmonary embolism and thrombosis		

Reporting of suspected adverse reactions

Suspected adverse reaction(s) are important to report as 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 "Adverse drug reaction and quality problem reporting form", found online under SAHPRA's publications:

In addition, suspected adverse reactions may also be reported by e-mail to drugsafetysa@cipla.com or by telephone to 080 222 6662 (toll free).

4.9. Overdose

Pazopanib doses up to 2000 mg have been evaluated in clinical studies without dose-limiting toxicity.

There is currently limited experience with overdosage in pazopanib. Further management should be as clinically indicated or as recommended by the national poisons centre, where applicable. Haemodialysis is not expected to enhance the elimination of PAZOPANIB 200 CIPLA because PAZOPANIB 200 CIPLA is not significantly renally excreted and is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, other protein kinase inhibitors

ATC code: L01XE11

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 IC_{50} values of 10, 30, 47, 71, 84 and 74 nM, respectively. In preclinical experiments, pazopanib dose dependently inhibited ligand-induced auto-phosphorylation of 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 to100 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. 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 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 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 indicated that renal impairment is unlikely to have 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 2**). 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 2**).

Based on safety and tolerability data, the dose of pazopanib should be reduced to 200 mg once daily in subjects 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**).

Table 2
Median steady-state pazopanib pharmacokinetics measured in subjects with hepatic impairment.

Group	**Investigated dose**	**C_{max}**	**AUC (0-24) *µ*g/mL x hr/mL**	**Recommended dose**
Normal hepatic function	800 mg OD	52,0 (17,1 - 85,7)	888,2 (345,5 - 1482)	800 mg OD

Mild HI	800 mg OD	33,5 (11,3 - 104,2)	774,2 (214,7 - 2034,4)	800 mg OD
Moderate HI	200 mg OD	22,2 (4,2 - 32,9)	256,8 (65,7 - 487,7)	200 mg OD
Severe HI	200 mg OD	9,4 (2,4 - 24,3)	130,6 (46,9 - 473,2)	Not recommended
OD – once daily				

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Magnesium stearate

Microcrystalline cellulose

Povidone K-30

Sodium starch glycolate

Opadry pink composed of:

Hypromellose (E464)

Iron oxide red (E172)

Macrogol

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 º C. This medicine does not require any special storage conditions.

6.5. Nature and contents of container

PAZOPANIB 200 CIPLA film-coated tablets is packed in HDPE containers with child-resistant PP caps (with liner), or child-resistant HDPE/PP caps (with liner), and a desiccant cylinder containing 30, 90 or 120 tablets.

Not all pack sizes are necessarily marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

56/26/0080

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 29 August 2023

Latest renewal: Not applicable

10. DATE OF REVISION OF THE TEXT